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An Emotional Stress as a Trigger for Reverse Takotsubo Cardiomyopathy: A Case Report and Literature Review

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Patient: Female, 61
Final Diagnosis: Reverse Takotsubo
Symptoms: Dyspnea • chest pain
Medication: Lisinopril • Metoprolol • Aspirin • Atorvastatin • Ticagrelor
Clinical Procedure: Cardiac catheterization
Specialty: Cardiology

Objective: Rare disease

Background: Reverse Takotsubo cardiomyopathy is one of the rarest types of stress-induced cardiomyopathy, which despite sharing similar pathogenic mechanisms with its more common counterpart, has different clinical manifestations, demographics, and laboratory values.

Case Report: We present the case of a 61-year-old woman who came to the hospital with a chief complaint of chest pain and dyspnea. She was found to have elevated troponin and severely depressed left ventricular function. Echocardiography showed normal contracting apex, with the rest of the left ventricle being hypokinetic. Cardiac catheterization revealed mild coronary artery disease and confirmed echocardiographic findings showing hyperkinetic apex and dilated base. She was discharged home on ACE inhibitor and B-blocker. A repeat echocardiogram 2 weeks after the initial presentation showed complete resolution of cardiac dysfunction.

Conclusions: Reverse Takotsubo cardiomyopathy is a rare disease mimicking acute coronary syndrome. It is essential to rule out organic coronary disease prior to attributing the presentation to Takotsubo cardiomyopathy. With supportive care, the long-term prognosis is good in the vast majority of patients.

MeSH Keywords: Catecholamines • Echocardiography, Doppler • Takotsubo Cardiomyopathy

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Background

Stress-induced cardiomyopathy (also known as apical ballooning syndrome, Takostubo cardiomyopathy, and broken heart syndrome) was first describes by Satoh et al. in 1990 in Japan. Since then it has been increasingly recognized in the Western world as transient worsening of myocardial function following emotional or physical stress [1]. We present the case of 61-year-old woman with reverse Takotsubo triggered by emotional stress and we show its similarities to and differences from the much more common classical type, which will help correctly diagnose patients with this disorder and initiate treatment in timely fashion. It was only recently described in the literature and there are only a few studies and case reports regarding its clinical characteristics, demographics, inpatient survival, and outcomes.

Case Report

A 61-year-old white woman with past medical history of chronic obstructive pulmonary disease (COPD) and a major recent psychological stressful event presented to the emergency room (ER) with chief complaint of shortness of breath and chest pain that she had been experiencing for 1 week. In the ER she was found to have elevated troponin-I of 3.088 ng/ml (normal <0.028) and her 12-lead electrocardiogram (ECG) showed sinus tachycardia with no ischemic changes. Chest X-ray showed hyperinflated lungs. The rest of her laboratory findings and vital signs were within normal limits. Physical exam showed scattered crackles in bilateral lower lobes and wheezing. No jugular venous distension (JVD) or other signs of increased filling pressures were found on exam.

She was started on heparin drip, double-antiplatelet therapy with aspirin, and ticagrelor, as well as atorvastatin and

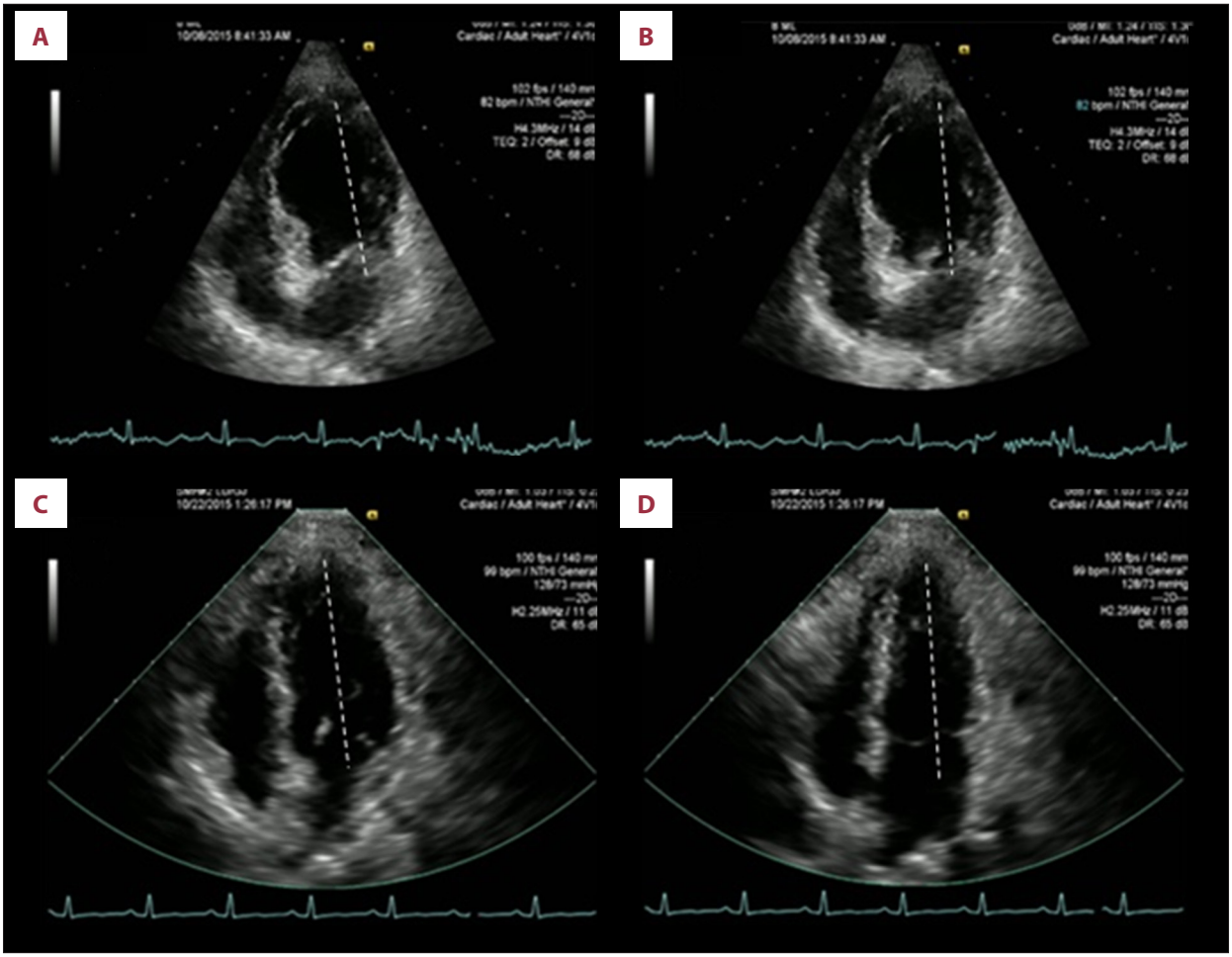

Figure 1. Transthoracic echocardiogram (apical 4-chamber view) showing apical and midventricular hypokinesis and normal contracting apex at the end of diastole (**A**) and at the end of systole (**B**). Repeat transthoracic echocardiogram 2 weeks after the initial presentation shows normalization of contraction of all segments of left ventricle. (Dotted lines to better visualize lack of shortening in **A** and **B**).

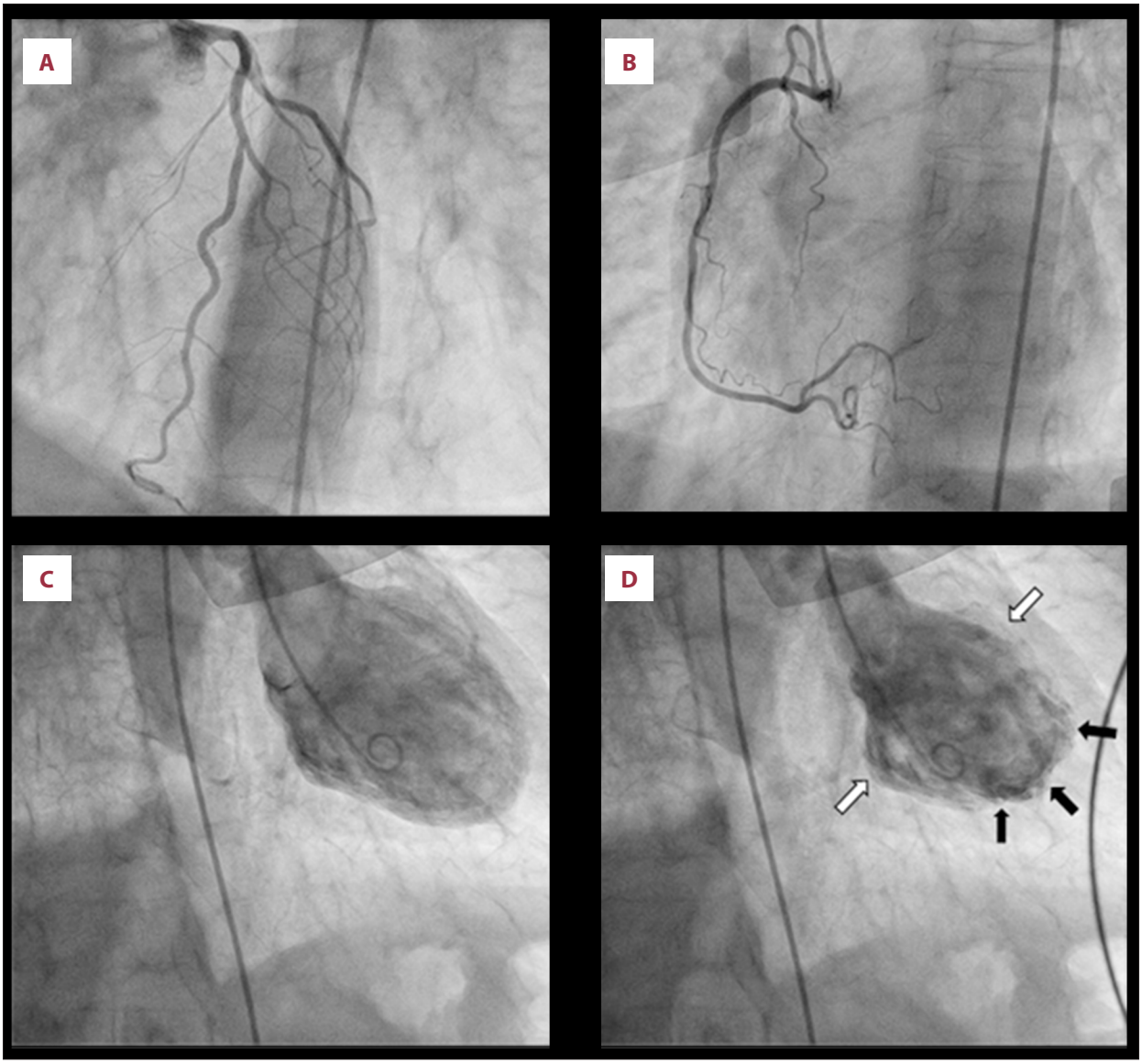

Figure 2. Coronary angiogram shows non-obstructive coronary artery disease in left (**A**) and right coronary (**B**) artery territories. Ventriculography confirms ballooning of basal and midventricular sections (white arrows) and hypercontractile apex (black arrows). (**C**) Shows end of diastole and (**D**) shows end of systole.

metoprolol. A 2-dimensional echocardiographic study with "Definity" contrast showed severely depressed left ventricular (LV) function with ejection fraction (EF) of 25%, hyperdynamic apex, and with the rest of the LV being diffusely hypokinetic (Figure 1A, 1B). The echocardiographic study also showed elevated mean left atrial pressure and mildly calcified posterior mitral annulus with no mitral regurgitation. The right ventricle size and function were normal. She was taken to the cardiac catheterization laboratory, where she underwent cardiac catheterization.

Cardiac catheterization showed nonobstructive/mild coronary artery disease (Figure 2A, 2B). Left ventriculography revealed marked hypokinesia of the inferior and the anterolateral wall, with the apex being hyperdynamic, and severely reduced ejection fraction of 25% (Figure 2C, 2D). Cardiac catheterization also showed elevated (40 mmHg) left ventricular end-diastolic pressure (LVEDP) (Figure 3).

She was subsequently started on angiotensin converting enzyme inhibitor (Lisinopril), and b-blocker (metoprolol) and was discharged home in stable condition. A repeat echocardiogram 2 weeks after the initial presentation revealed remarkably improved LV systolic function with EF of 65% (Figure 1C, 1D) and normalization of elevated filling pressure.

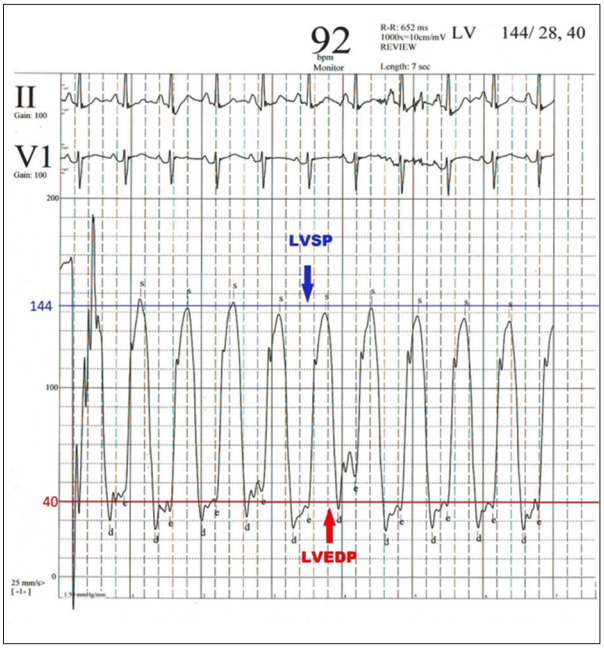

Figure 3. Left ventricle pressure tracing showing elevated left ventricular end-diastolic pressure (LVEDP-red line). Left ventricular systolic pressure (LVSP-blue line) is also shown.

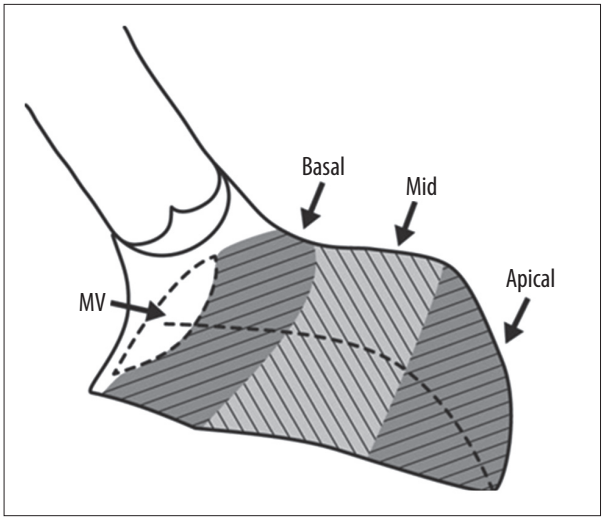

Figure 4. Schematic representation of involvement of left ventricle in different types of stress-induced cardiomyopathy. Reprinted with permission from: Angelini, Paolo. Reverse, or inverted, transient Takotsubo cardiomyopathy: Terms and status of an open discussion. Tex Heart Inst J, 2013; 40(1): 60–63. (Copyright 2013 by the Texas Heart Institute, Houston).

Discussion

Stressed-induced cardiomyopathy (SIC) is a reversible dysfunction of the left ventricle (LV), which in its classical variant is characterized by akinesis of LV apical segments. Cardiac catheterization usually reveals normal coronary arteries. The annual incidence is 1–2% of all troponin-positive acute coronary syndromes [2]. Ninty percent occur in women, with average age of onset 58–75 years and only 3% in women less than 50 years of age [3]. In the International Takotsubo Registry (ITR), which includes 1750 patients with stress cardiomyopathy, the reverse type was present in 2.2% of cases [4].

The pattern of transient myocardial dysfunction in Takotsubo usually does not follow any single coronary artery territory. It rather tends to be limited to horizontal areas along the longitudinal axis of the LV. Based on this pattern, stress-induced cardiomyopathy is divided into (Figure 4) [1,4–6] 4 types:

1. Apical or classical (apical akinesia and basal hyperkinesia) – 82% in ITR.
2. Basal or reverse (basal akinesia and apical hyperkinesia) – 2.2% in ITR.
3. Midventricular – 14.6% in ITR.
4. Focal – 1.5% in ITR.

Isolated LV involvement is the most common variant of SIC but right ventricular (RV) involvement has also been recognized. It has been demonstrated that biventricular involvement is present in 25–42% of patients diagnosed with SIC [7]. It has been shown in multiple case reports that patients with biventricular SIC have significantly greater reduction in EF, longer hospitalization, more pleural effusions, and greater need for cardiopulmonary resuscitation (CPR) and hemodynamic support [7,8].

It is believed that emotional and physical stressors are the main triggers for this condition. In the ITR of 1750 patients, 36% had a physical trigger, 27.7% had emotional stressors, 7.8% had both physical and emotional triggers, and 28.5% had no triggers at all [4]. In contrast, ischemic cardiomyopathy is associated with a stressful trigger in only 3% of cases [9]. Moreover, 56% of patients in ITR had an acute episode of neurological or psychiatric disorder, but only 26% of patients with acute coronary syndrome had an antecedent neurological or psychiatric event [4].

Catecholamine-mediated myocardial and vascular dysfunction is the most widely accepted theory [8–10]. Vasospasm of coronary arteries has been demonstrated in some patients [11]. Studies also have shown that high levels of catecholamines are toxic to cells via generation of free radicals and induction of apoptosis [12].

In support of this theory is the fact that subarachnoid hemorrhage and pheochromocytoma have been found as common triggers for SIC [13]. For example, pathological findings consistent with myocyte necrosis with contraction bands were found

in a patient with reverse Takotsubo induced by subarachnoid hemorrhage. Contraction-band necrosis is a result of massive catecholamine surge and is found in patients with stress cardiomyopathy. This suggests that classical and reversed types of Takotsubo share similar pathogenic mechanisms [6].

It is not yet clear why SIC predominantly affects postmenopausal women. It is hypothesized that lack of estrogens in postmenopausal woman can play a role by actions on both the nervous system and the heart. In particular, estrogen supplementation attenuated cardiac dysfunction in rats that had immobilization-induced cardiomyopathy. Immobilization is known to cause sympathoadrenal activation in rats, mimicking SIC in adults [14].

The clinical and laboratory manifestations of SIC are similar to that of different types of acute coronary syndromes [15]. According to ITR, chest pain, shortness of breath, and syncope are the most common presenting symptoms. Some patients present with signs and symptoms of heart failure and up to 10% of patients might present with signs and symptoms characteristic of cardiogenic shock [4].

The mean level of troponin elevation is similar in both SIC and acute coronary syndromes (ACS), according to ITR data. According to the same registry, about 80% of patient with SIC presented with elevated troponin level and had ischemic changes on ECG, making cardiac catheterization a necessary step in ruling out acute coronary syndrome in these patients. Levels of brain natriuretic peptide are significantly higher in patients with SIC than in patients with acute coronary syndrome. The latter may be explained by the fact that more patients with SIC in ITR had reduced LV EF compared to patients with acute coronary syndrome (86.5% *vs.* 54.2%, respectively) [4].

The severe inpatient complication rate for SIC is similar to that in patients with acute coronary syndrome, despite the fact that most of the patients with SIC recover their cardiac function over time. Moreover, the rate of in-hospital short-term (30 days after admission) and long-term death and major cardiac and cerebrovascular events is higher in men than in women [4].

Despite similar pathogenic mechanisms, patients with the reverse type of Takotsubo might have different clinical manifestations, demographics, and laboratory values, which can be explained partly by the different location of regional wall motion abnormalities.

In reverse or so-called inverted type of stress-induced cardiomyopathy, the apex is hypercontractile in contrast to the base, which is akinetic or hypokinetic [16–20]. Patients with reversed type present at an earlier age compared to the classical variant of Takotsubo, due to the abundance of adrenoceptors at the base compared to the apex [21]. The concentration of adrenoceptors is highest in the apex compared with the base in postmenopausal women, explaining the prevalence of classical (apical) type among older women [22].

Another difference between classical and reverse variants is in the hemodynamic changes, which can be explained by differences in the location of regional wall motion abnormality. For example, patients with reverse Takotsubo usually present with less shortness of breath, pulmonary edema, and cardiogenic shock [21]. More myocardial tissue is involved in the reversed variant than in the classical type, explaining the observation that patients with reversed type have more elevations of cardiac biomarkers (e.g., troponin-I, CK-MB, and BNP) [23].

Reverse Takotsubo patients also have higher prevalence of triggering stress, either physical or emotional, compared to their apical counterparts [23]. For example, both Ramaraj et al. and Song et al. showed that most patients with reverse Takotsubo have either physical or psychological stressors, whereas 15–23% of patients with non-reverse type do not have any stressor or trigger [21,23]. Our patient did not have any antecedent physical stressor, but she experienced a major psychological stress event in her life 1 month prior to presentation.

Apical and other variants of stress-induced cardiomyopathy tend to have more reversible functional mitral regurgitation than in the inverted variant. This is explained by the spatial relationship between mitral valve leaflets and hypercontractile base, causing dynamic LV outflow tract obstruction, which in turn can cause hemodynamic instability and exacerbation of heart failure symptoms [23].

Patients with SIC present with different ECG abnormalities. According to ITR, the 2 most common changes on ECG are ST elevation (43.7%) and ST depression (7.7%). Other ECG abnormalities include QT prolongation, T wave inversion, and abnormal Q waves. Patients with non-reverse type have significantly higher prevalence of T wave inversions [4,23].

Patients who present with clinical (e.g., chest pain and breathlessness) and laboratory (e.g., elevated troponin and abnormal ECG) findings consistent with acute coronary syndrome (ACS) tend to have normal coronary arteries and represent a heterogeneous group. LV dysfunction in these cases can be a manifestation of pathologies other than SIC. In particular, Kawecki et al. conducted a prospective multicenter observational study enrolling 75 patients with the above characteristics in whom ACS was ruled out by coronary angiogram. A cardiac magnetic resonance (CMR) imaging study was performed, which found that 49 patients (65%) had myocarditis, 3 patients (4%) had SIC, and 7 patients were reclassified to having ACS. At 6-month follow-up there were no significant echocardiographic

changes compared with the initial examination in the myocarditis group [24]. In our patient, a repeat echocardiogram at 2 weeks after the initial presentation showed complete resolution of LV dysfunction and normalization of increased filling pressures, which makes myocarditis an unlikely cause of LV dysfunction in our case.

Conclusions

Reverse Takotsubo cardiomyopathy is one of the rarest types of stress-induced cardiomyopathy, which, despite sharing similar pathogenic mechanisms with its more common counterpart, might have different clinical manifestations, demographics, laboratory values, and ECG and echocardiographic characteristics. The in-hospital complication rate for SIC is similar to that in patients with acute coronary syndrome, making timely recognition of this disorder crucial in initiating diagnostic and lifesaving treatment options.

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