Recurrent Takotsubo Cardiomyopathy: Getting to the Root of the Problem

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Patient: Female, 64-year-old
Final Diagnosis: Takotsubo cardiomyopathy
Symptoms: Anxiety • retrosternal chest pain
Medication: —
Clinical Procedure: Cardiac catheterization • echocardiography
Specialty: Cardiology

Objective: Rare disease
Background: While takotsubo cardiomyopathy (TC) is a rare cardiomyopathy, recurrent takotsubo cardiomyopathy (rTC) is even more so, occurring in only 4% of patients with TC. Treatment is based on expert opinion and includes standard heart failure treatment using beta blockers (BB) and angiotensin-converting enzyme inhibitors (ACEI). We present a case of rTC demonstrating how using a selective serotonin reuptake inhibitor (SSRI) with cognitive behavioral therapy (CBT) can successfully prevent recurrence.

Case Report: A 64-year-old woman presented with ST-elevation myocardial infarction, and coronary angiography demonstrated non-obstructive coronary artery disease. Left heart catheterization showed apical hypokinesis with preserved function of the basal segments, consistent with TC. She reported having experienced multiple emotional stressors. The patient was started on BB and ACEI, and 5 months later repeat imaging showed resolution of her TC. One month after resolution, she was re-admitted for chest pressure, and imaging demonstrated rTC. This time, in addition to continued conventional therapy, she was started on an SSRI and CBT. Nearly 6 months later, her rTC had resolved.

Conclusions: Anxiety and depression are more common in patients with TC than in patients with STEMI, but there is little in the literature about the roles of SSRI and CBT in TC treatment. In fact, SSRIs are controversial since they can increase catecholamine concentration, which some experts believe contributes to TC. The positive response of our patient to combination SSRI-CBT therapy suggests that additional research is needed on the use of this approach for prevention and treatment of rTC.

MeSH Keywords: Adrenergic beta-Antagonists • Catecholamines • Cognitive Therapy • Heart Failure • Serotonin Uptake Inhibitors • Takotsubo Cardiomyopathy

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Background

Takotsubo cardiomyopathy (TC) is rare, occurring in only 1–3% of all patients presenting with STEMI [2]. The hallmark of TC is its correlation with emotionally stressful events. Anxiety and depression are more common in patients with TC than in patients with STEMI and in healthy individuals [2]. Emotional triggers, such as death, criminal arrest, divorce, suicide attempt, and uncontrolled post-traumatic stress disorder are commonly-accepted triggers for TC [2,4]. In the GEIST registry of 749 followed patients, a stressful event was documented in 70% of patients with TC [1]. TC is more prevalent in patients who exhibit Type D personality, depression, negative emotions, and social inhibition [2]. Circulating miRNAs found to be associated with neuropsychiatric conditions have also been associated with stress cardiomyopathy, suggesting there could be a genetic or epigenetic component to the pathophysiology of TC [2].

Recurrent takotsubo cardiomyopathy (rTC) is even rarer, with an estimated incidence rate of 1.8% per patient year [2] and occurring in only 4% of patients after a first episode of TC [1]. Most recurrences happen within the first 5 years of an index episode, and there is a report of several patients have had more than 1 documented recurrence [1]. In the GEIST registry analyzing 749 patients with TC, 6% of patients with recurrent TC had more than 1 episode of recurrence [1]. Treatment of TC includes using beta blockers (BB) and angiotensin-converting enzyme inhibitors (ACEI). Retrospective studies and meta-analyses have not shown a mortality benefit or reduced rate of recurrence with the use of BB, and only a few studies have shown a benefit with the use of ACEI [3]. Less is known about treatment of rTC, and current treatment is based on expert opinion.

Although emotional stress is a common trigger, there is not an accepted therapeutic plan for the management of emotional stress in the treatment and prevention of TC. In fact, use of selective serotonin reuptake inhibitors (SSRIs) is controversial given the theoretical propensity to increase catecholamine concentrations. Many experts believe that catecholamine excess, such as in patients with pheochromocytoma or recent stroke, may explain the underlying mechanism of TC [2].

We present the case of a patient with rTC and discuss how the use of SSRIs and cognitive behavioral therapy (CBT) added to BB and ACEI treatment successfully prevented a third recurrence of TC after guideline-directed medical therapy (GDMT) after BB and ACEI alone did not prevent recurrence.

Case Report

A 64-year-old white woman with no past medical history or history of substance abuse presented with retrosternal chest pressure. An ECG showed ST elevations in the lateral leads concerning for acute myocardial injury (Figure 1). Her troponin level was originally 0.032 (lab upper limit of normal was 0.03) and she was rushed to the catheterization lab, where emergent coronary angiography demonstrated non-obstructive coronary artery disease (Videos 1, 2). Myocardial infarction with non-obstructive coronary arteries (MINOCA) was considered as a diagnosis, but then left

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**Figure 1.** Electrocardiogram on first presentation showing sub-1-mm ST elevations in lateral leads I and aVL.
Video 1. Coronary angiogram showing the left coronary artery without plaque rupture, thrombosis, or occlusion.

Video 2. Coronary angiogram showing the right coronary artery without plaque rupture, thrombosis, or occlusion.

Video 3. Left ventriculogram at initial presentation demonstrating the classic appearance of stress cardiomyopathy with basilar hyperkinesis and “ballooning” of the apical wall segments.

Video 4. Transthoracic echocardiogram performed at initial presentation demonstrating apical hypokinesis and basilar hyperkinesis.

Video 5. Transthoracic echocardiogram 5 months after initial presentation, demonstrating transient recovery and normalization of LV function.

Heart catheterization with left ventricular image showed apical segment hypokinesis with preserved function of the basal segments, consistent with TC (Video 3). Subsequent evaluation with echocardiography demonstrated similar findings, with reduced ejection fraction of 40% (Video 4). She had reported significant emotional life stressors at home, including the death of her mother, making the diagnosis most consistent with TC. A broad differential diagnosis was considered. Aortic dissection was ruled out by the CT aorta result. Pheochromocytoma or another neuroendocrine tumor was also considered, but was not identified on CT scan of the chest, abdomen, and pelvis. The differential diagnosis also included myocarditis, but she denied infectious symptoms and sick contacts, and she had a normal c-reactive protein and erythrocyte sedimentation rate. Cardiac MRI was not performed given the extremely low pre-test probability and given she had no evidence of myocarditis. Drug-induced cardiomyopathy was also ruled out by results of a toxicology screen.
Coronary vasospasms were considered in the differential diagnosis, but her pain was not typical of a spasm and vasospasms were not seen on angiography. Lastly, her hospitalization was not complicated by arrhythmias. The patient was started on GDMT, which was ultimately increased to the maximum tolerated doses of lisinopril 5 mg 1 tablet by mouth once daily and metoprolol succinate 75 mg 1 tablet by mouth twice daily. Five months later, a repeat echocardiogram showed return of normal ejection fraction and resolution of wall motion abnormalities (Video 5).

Approximately 1 month after documented resolution, she was re-admitted for chest pressure. An electrocardiogram (ECG) showed sub-1-mm ST elevations in lateral leads, similar to her first presentation (Figure 2). Her troponin level peaked at 0.373 (lab upper limit of normal was 0.03) and quickly downtrended. She was again found to have a reduced ejection fraction (40%), along with echocardiographic evidence of apical hypokinesis with preservation of the basal segments, consistent with rTC (Video 6). During the second presentation, a second angiogram was not performed after a risk/benefit discussion with the patient and given she had undergone angiography only 6 months before. Furthermore, her ECG was very similar to her previous ECG and there was no concern for development of a new obstructive plaque rupture or erosion. Additionally, her presentation and echocardiographic imaging were again classic for stress-induced cardiomyopathy. Recurrent takotsubo cardiomyopathy was supported by the fact that she had been having severe recent stressors in the form of a domestic dispute with her sister who was attempting to deprive the patient of her inheritance from her mother who recently died, which was thought to have been the precipitating factors for her recurrent presentation. Given the recurrence, however, additional workup again ruled out a pheochromocytoma with negative fractionated free plasma metanephrines. In addition to BB and ACEI, she was started on sertraline and was referred to a clinical psychologist. A repeat echocardiogram 1 month after the recurrence was normal (Video 7). On further follow up over 1 year after her original presentation, her anxiety was greatly relieved after starting sertraline and CBT. She reports that her chest discomfort has resolved, she denies having shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea, and she states her anxiety during periods of high emotion and stress is much better controlled.

**Discussion**

Combined psychologic-cardiac rehab has been proposed as co-treatment and is endorsed by expert consensus guidelines, but there is little evidence in the literature about the benefits (or lack thereof) of SSRIs and CBT [3]. While SSRIs are controversial because they can increase serotonin and catecholamine availability, it should be noted that most SSRIs predominantly increase serotonin concentrations, not norepinephrine and epinephrine. This is distinct from serotonin–norepinephrine reuptake inhibitors (SNRIs), which are more likely to increase catecholamine concentrations that act directly on the cardiac beta receptors. It is also interesting that despite the theory that catecholamine excess triggers TC, the use of beta blockers, which should minimize

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**Figure 2.** Electrocardiogram on second presentation showing sub-1-mm ST elevations in lateral leads I and aVL, similar to the first presentation.
the effects of excess catecholamine action on the beta receptors in the heart, have not been shown to have any benefit in retrospective and meta-analysis for treatment or for prevention of recurrence [3]. In fact, in the GEIST registry, >50% of patients who developed stress cardiomyopathy were admitted after having already been taking a beta blocker, ACE inhibitor, or AT-II antagonist. Furthermore, use of a combination of a beta blocker and ACE inhibitor or AT-II antagonist was documented in 28% of recurrence cases [1]. Like others, our patient still developed rTC despite neurohormonal blockade with BB and ACEI. In our case, a third episode of TC appears to have been prevented by the addition of SSRI and CBT to her previous GDMT. However, a limitation should also be noted – in the GEIST registry analyzing 749 patients with TC, only 6% of patients with recurrent TC had more than 1 episode of recurrence [1]. However, the fact that our patient noted significant clinical improvement in her mood, control of anxiety, and cardiac symptoms after starting CBT and SSRI, in addition to her GDMT, also shows the efficacy of this combined pharmaceutical and therapeutic regimen and how it aims to address the root of the problem.

The link between the brain and the heart desperately needs additional research to provide the best care for patients with TC and to prevent recurrence. While the relatively low rate of recurrence makes randomized controlled trials difficult, it would be helpful to compare those with TC who receive treatment with GDMT alone to those who receive GDMT with SSRIs and/or CBT. Future studies would also need to take into account the relative control of each patient’s anxiety and depression, which could be done with questionnaires and severity rating scales, as well as clinician judgment. It may simply be that uncontrolled anxiety/depression is an independent risk factor for developing TC, regardless of whether or not an SSRI is being used. It would also be important to study the distinction between SSRIs and SNRIs, as the mechanism of action is not the same, especially in the context of catecholamine excess as a possible underlying cause of TC. Additional research could also assess whether SSRIs and CBT play a role in the treatment of TC triggered primarily by physiologic stressors, especially given that anxiety and depression generally develop in patients with serious physiologic illness, as in those who experienced debilitating strokes, terminal cancer, trauma, or alcohol addiction withdrawal.

**Conclusions**

Our case of rTC suggests that the addition of CBT and SSRI to GDMT could be a novel approach to treat and prevent TC, and emphasizes that providers must address the root cause of the problem, which means, at least in the case of emotional triggers causing TC, controlling emotional stress and anxiety. This requires a combined approach with pharmaceuticals and behavioral therapy. The pathophysiology of TC is likely more complex than excess sympathetic tone or catecholamine action on the heart, and will necessitate further research to elucidate the link between the heart, brain, and adrenal axis.

**Disclaimer**

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**Conflicts of interest**

None.
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