

# Two Episodes of Takotsubo Cardiomyopathy in a Woman with a Bilateral Adrenalectomy

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**T**akotsubo cardiomyopathy is characterized by a reversible acute myocardial dysfunction, most typically involving the left ventricular apex and causing an apical ballooning syndrome. In the majority of cases there is full recovery of the systolic function within 1 month [1]. Triggers such as physical and emotional stress are known to precipitate a Takotsubo cardiomyopathy. Women have a higher prevalence of Takotsubo cardiomyopathy than men. A high level of catecholamines is believed to be the main pathophysiological mechanism of this disorder [2]. Other proposed mechanisms included epicardial coronary artery spasm, metabolic disturbances of the cardiac cells, and coronary microvascular impairment [1]. Acute coronary syndrome has a similar clinical presentation, electrocardiogram changes, and elevated cardiac biomarkers, and thus must be dismissed as a diagnosis. The recurrence rate is approximately 2.9% per year. We present the case of a woman with low to undetected levels of catecholamines who was diagnosed with two episodes of Takotsubo cardiomyopathy within 1 year, precipitated presumably by infection.

## PATIENT DESCRIPTION

A 60 year old woman was admitted to the hospital after experiencing chest pain

associated with dyspnea for 2 hours. She denied radiation to both arms, and had no sweating, vomiting, or nausea.

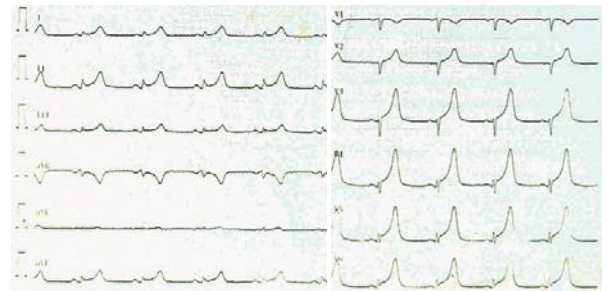
Her past history included hypertension, asthma, laparoscopic sleeve gastrectomy 5 years prior, and gastroesophageal reflux disease. Seventeen years earlier she underwent bilateral adrenalectomy due to Cushing's disease that did not respond to transsphenoidal hypophysectomy or radiation therapy.

Her relevant medical therapy included amlodipine, escitalopram and replacement hormonal therapy (levothyroxine, prednisone, and fludrocortisone). She had ST elevation in her admission electrocardiography (ECG) [Figure 1] and underwent immediate coronary angiography, which revealed normal coronary arteries [Figure 2]. Left ventriculography demonstrated hyperkinesia of the basal segments and akinesia of both midventricular and apical segments. The estimated ejection fraction was 25%.

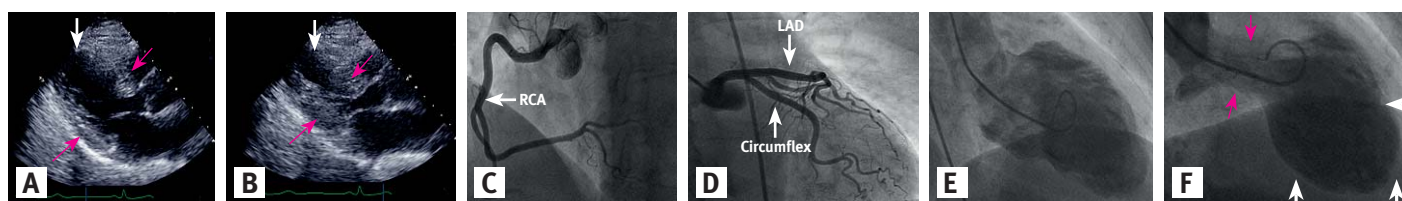
A laboratory test demonstrated elevated levels of high sensitivity troponin I of 2.64 ng/ml (normal range < 0.040), and creatine phosphokinase (CPK) of 142 U/L (normal range < 145). Echocardiography revealed wall motion abnormality with apical left

ventricular aneurysm, basal segments hyperdynamic [Figure 2] with dynamic left ventricular outflow tract obstruction (a peak gradient at rest of 21 mmHg, which increased in valsalva maneuver to 52 mmHg). The right ventricular size and function were normal. Therefore, a diagnosis of Takotsubo cardiomyopathy was made. Treatment with angiotensin converting enzyme inhibitor (ACEi) and diuretic was promptly initiated. A careful use of beta blockers along with alpha agonist in a patient with left ventricular outflow tract obstruction was suggested but due to symptomatic bradycardia and low blood pressure, a beta blocker was not given. During her hospitalization she developed fever, cough, and dyspnea. Complete blood count demonstrated white blood cells of 28000 with 84.1% neutrophils. A chest X-ray showed a diffuse infiltration in the left lung typical of pneumonia. Her systolic blood pressure was less than 60 mmHg and a diagnosis of combined septic and cardiogenic shock was made. The patient was treated with piperacillin/tazobactam for 6 days. Intravenous phenylephrine, a pure alpha agonist, was used to increase the peripheral resistance and blood pressure, which in turn caused a decrease in the left ventricular outflow

**Figure 1.** Electrocardiogram demonstrating ST elevation in lead V2–V6, I, II, III, and AVF



**Figure 2.** Transthoracic echocardiogram (TTE) parasternal long axis in diastole **[A]** compared to systole **[B]** showing a hyperkinesia of both the basal segments and midventricular (pink arrows) with akinesia of the apical region (white arrow). Coronary angiogram depicted normal coronary arteries (LAD, circumflex, and RCA) **[C] [D]**. Ventriculography in diastole **[E]** and systole **[F]** showing left ventricular aneurysm with midventricular akinesia (big white arrow) and hyperkinesia in the basal segments (small pink arrow)



obstruction to avoid, as much as possible, a toxic effect of beta stimulation on the myocardium. Admission levels of epinephrine were disproportionally low (undetected levels in the blood) (normal range 20–40 pg/ml), norepinephrine 273 pg/ml (normal range 200–800) and dopamine 466 pg/ml (normal range 1000–2000).

A repeated echocardiography done 7 days after the prior echocardiography demonstrated improved left ventricular systolic function with estimated ejection fraction of 45–50% with no evidence of left ventricular outflow tract obstruction, albeit a mural left ventricular thrombus was seen. She was subsequently started on enoxaparin and warfarin and was discharged.

Ten months later, the patient was admitted because of acute chest pain accompanied by dyspnea. One week prior to her admission she complained of throat pain and a cough. The ECG revealed negative T wave in aVL, I, V2–V6, high sensitive troponin I was 208 ng/ml (normal range < 0.040) and, echocardiogram showed apical region hypokinesia with mild left ventricular dysfunction. Immediate coronary angiography depicted again normal coronary arteries. Hence a second episode of Takotsubo cardiomyopathy was confirmed.

**COMMENT**

Takotsubo cardiomyopathy was first coined in 1990 by researchers in Japan [1] who described a reversible heart failure with abnormal shape of the left ventricle. Takotsubo cardiomyopathy is best characterized by an acute akinesia or hypokinesia of the midventricular and apical segments

along with hyperkinesia of the basal segments. This typical type is known as apical ballooning, which is reversible within a few weeks in the majority of cases.

The prevalence of Takotsubo cardiomyopathy is estimated to be around 1–2% of all patients with acute myocardial infarction. It is more common in postmenopausal women, with relatively rare occurrence in the younger population. The majority of patients have triggers such as emotional stress, physical stress, and surgical procedures that are known to cause a Takotsubo cardiomyopathy. It is also known as stress induced cardiomyopathy [1]. The clinical presentation of chest pain, dyspnea, and occasional syncope with the associated electrocardiographic changes and elevated cardiac biomarkers (troponin) make it essentially indistinguishable from acute coronary syndrome (ACS). Hence, the best way to differentiate between Takotsubo cardiomyopathy and ACS is coronary angiography.

The pathophysiology of Takotsubo cardiomyopathy is not well understood, yet there are several proposed mechanisms.

One of the most cited mechanism is catecholamine-induced myocardial injury and catecholamine-induced coronary microvascular spasm [2]. The excess of catecholamine and the sympathetic over activity is one of the main pathophysiology of Takotsubo cardiomyopathy. Data showed that the serum catecholamine levels in Takotsubo cardiomyopathy patients are two to three times higher than in patients with myocardial infarction with similar hemodynamic compromise. Several studies support the theory of

catecholamine-induced Takotsubo cardiomyopathy and have shown that high levels of catecholamine secreted from central autonomic system and from adrenal medulla cause a myocardial injury, elevated blood pressure, and increased after load. In pheochromocytoma it was shown that high concentration of catecholamine may cause Takotsubo cardiomyopathy (stress cardiomyopathy). Administering catecholamine and beta agonists (such as dobutamin and epinephrine) have been shown to precipitate Takotsubo cardiomyopathy. The histology of myocardial injury in patients with Takotsubo cardiomyopathy has a similar specimen in disorders of catecholamine-induced contraction band necrosis. Recent evidence hypothesized that high levels of catecholamine cause a signal switch from the B2 receptor G-stimulating to B2 receptor G-inhibiting, which accounts for the negative inotropic effect on myocardial contractility. While the apical region contained the highest density of B-adrenergic receptor (compared to the basal) and the lowest sympathetic nerve density, this explained the hypokinesia of the left apical region [3]. It is worth noting that in so-called reverse Takotsubo cardiomyopathy, where the apical region is hyperdynamic and the basal segments are hypokinesia or akinesia, it is believed to be caused by the high concentration of B-receptors at the basal segments compared to the apical region, typical for the earlier age.

Collectively these data suggest that an elevated catecholamines level is the main pathophysiology factor to cause Takotsubo cardiomyopathy. Our case is important in that it emphasizes other plausible mecha-

nisms that should be considered, such as dysfunction of coronary microvascular, coronary artery spasm of multiple vessel epicardium, and metabolic disturbances in the myocardium. In coronary microvascular dysfunction there is an abnormal increase in vascular reactivity along with decreased endothelial function causing vasoconstriction in response to acute mental stress. Multiple coronary artery spasms can lead to so-called stunned myocardium and consequently to ventricular dysfunction. A metabolic disturbance affecting the glucose or fatty acid metabolism causing an impaired metabolism of cardiac cells can lead to myocardial stunning. Another alternative possible mechanism to such cardiomyopathy is that the myocardium may be excessively stimulated by the sympathetic nerve endings, which were perfectly intact and not related to the circulating catecholamines, which are measured low in a bilateral adrenalectomy patient.

Recurrent episodes of Takotsubo cardiomyopathy are uncommon, with a prevalence of approximately 3% of patients admitted to the emergency department with acute coronary syndrome. In hemodynamic stable patients, the treatment for heart failure that is required includes angiotensin converting enzyme inhibitor, beta blockers, mineralocorticoid antagonist, and diuretics. In a cardiogenic shock patient, an intra-aortic balloon pump may be necessary; intravenous fluids and inotropic

agents should be used cautiously. It is worth noting that the prognosis of Takotsubo cardiomyopathy is not that of a benign disease as thought in previous studies. On the contrary, the large registry on Takotsubo cardiomyopathy established by Templin et al. [4] demonstrated that the mortality rate is comparable to acute coronary syndrome patients. Such cardiomyopathy is associated with a substantial risk for adverse events, with the rate of major adverse cardiac and cerebrovascular effects in the first 30 days after admission being 7.1% and the long-term follow-up demonstrated death rates of 5.6% per patient per year and rates of adverse cardiac and cerebrovascular events of 9.9% per patient year [4].

Our case is unique in that we describe a patient with recurrent Takotsubo cardiomyopathy with bilateral adrenalectomy documented low to undetected levels of catecholamines in the blood circulation. This is extremely unusual when compared to other trials in which the measured levels of plasma catecholamines were markedly elevated in Takotsubo cardiomyopathy compared to those of patients with myocardial infarction, suggesting the activation of adrenal medullary system [5]. It is thus possible that in our case other mechanisms played an important role in the pathogenesis of Takotsubo cardiomyopathy, or alternatively, the main source was from local secretion from the sympathetic nerve innervating the cardiac cell.

## CONCLUSIONS

In conclusion, we have described a patient with recurrent typical Takotsubo cardiomyopathy despite bilateral adrenalectomy. Plasma levels of catecholamine were low to undetected suggesting that either the pathophysiology of this specific patient is unrelated to catecholamines or alternatively that the syndrome was secondary to increased local secretion from sympathetic nerve endings at the myocardium.

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## Capsule

### Fine-mapping inflammatory bowel disease loci to single-variant resolution

In the quest for a functional cure or the eradication of HIV infection, it is necessary to know the sizes of the reservoirs from which infection rebounds after treatment interruption. Estes and co-authors quantified SIV and HIV tissue burdens in tissues of infected nonhuman primates and lymphoid tissue (LT) biopsies from infected humans. Before antiretroviral therapy (ART), LTs contained > 98% of the SIV RNA+ and DNA+ cells. With ART, the numbers of virus (v) RNA+ cells substantially decreased but remained detectable, and their persistence was associated with relatively lower drug concentrations in LT than in peripheral blood. Prolonged ART

also decreased the levels of SIV- and HIV-DNA+ cells, but the estimated size of the residual tissue burden of 10<sup>6</sup>vDNA+ cells potentially containing replication-competent proviruses, along with evidence of continuing virus production in LT despite ART, indicated two important sources for rebound following treatment interruption. The large sizes of these tissue reservoirs underscore challenges in developing 'HIV cure' strategies targeting multiple sources of virus production.

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