

# Reverse Takotsubo Cardiomyopathy in a Patient With Prior Apical Takotsubo Cardiomyopathy: Challenging the Beta Receptor Gradient Theory

Ahmed Rashed, MD,<sup>1</sup> Mohamed Shokr, MD,<sup>1</sup> Ahmed Subahi, MD,<sup>2</sup> Fayeze Siddiqui, MD,<sup>1</sup> Aziz Alkatib, MD,<sup>1</sup> Luis Afonso, MD<sup>1</sup>

<sup>1</sup>Division of Cardiology, Department of Internal Medicine, Wayne State University School of Medicine/Detroit Medical Center, Detroit, MI

<sup>2</sup>Department of Internal Medicine, Wayne State University School of Medicine/Detroit Medical Center, Detroit, MI

**Background:** Classic Takotsubo cardiomyopathy has been described as transient apical dyskinesia following major stress that is believed to be related to catecholamine surges. Atypical variants have been described, including the rarer reverse Takotsubo cardiomyopathy. Discrepant gradients of the beta-2 adrenoceptors are thought to determine the different anatomic variants.

**Case Report:** A 43-year-old female presented with chest pain and a mild troponin elevation. Echocardiography and coronary angiography were consistent with stress-induced apical Takotsubo cardiomyopathy. Eight months later, the patient was admitted with a similar presentation; however, workup revealed stress-induced reverse Takotsubo cardiomyopathy.

**Conclusion:** Recurrent Takotsubo cardiomyopathy involving different anatomic regions of the left ventricle is a rare phenomenon yet appears to be similar to typical Takotsubo cardiomyopathy in presentation and hospital course. Chronic therapy with beta blockers and angiotensin-converting enzyme inhibitors did not prevent a recurrence in this patient, suggesting that optimum treatment needs to be determined. Takotsubo cardiomyopathy affecting different myocardial segments may recur in the same patient, implying that the adrenoceptor distribution theory needs further refinement.

**Keywords:** Cardiomyopathy, heart failure, receptors–adrenergic, Takotsubo cardiomyopathy

Address correspondence to Ahmed Subahi, MD, Department of Internal Medicine, Wayne State University School of Medicine/Detroit Medical Center, 4201 St Antoine St., Detroit, MI 48201. Tel: (313) 608-2515. Email: asubahi@med.wayne.edu

## INTRODUCTION

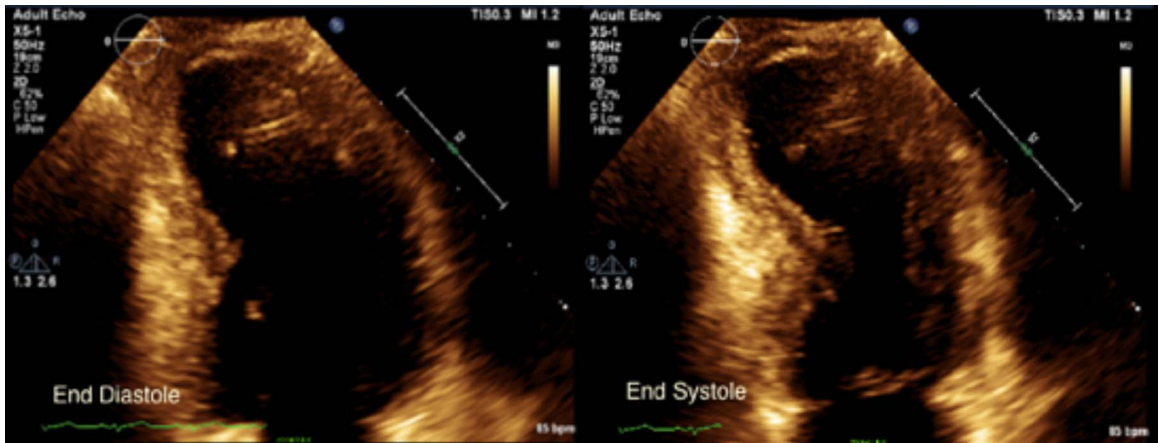
Since it was first described in Japan in 1991,<sup>1</sup> Takotsubo cardiomyopathy (also known as stress-induced cardiomyopathy) has been increasingly reported as a cause of transient focal myocardial dyskinesia following major stress.<sup>2</sup> The classic and most frequent variant of Takotsubo cardiomyopathy usually affects the left ventricular apex. However, several cases have described an atypical variant with basal ventricular ballooning (also known as reverse or inverted Takotsubo cardiomyopathy).<sup>2–4</sup> Reverse Takotsubo cardiomyopathy is a rare variant of stress-induced cardiomyopathy. Relative distributions of the beta-2 adrenoceptors are believed to determine the different anatomic variants. We report a case of apical Takotsubo cardiomyopathy followed 8 months later by basal Takotsubo cardiomyopathy.

## CASE REPORT

A 43-year-old female presented with the chief complaint of acute chest pain following an emotionally stressful event. She had mildly elevated troponin I of 1 ng/mL (normal, <0.057 ng/mL). Chest x-ray was normal. Laboratory workup showed normal complete blood count, bleeding

profile, basic metabolic panel, and random blood glucose. Electrocardiogram (ECG) showed no ischemic changes. Transthoracic echocardiography (TTE) showed reduced left ventricular function (ejection fraction of 40%), with apical hypokinesis and hyperdynamic basal and mid segments (Figure 1). Cardiac catheterization revealed normal coronary arteries. The patient was diagnosed with classic stress-induced cardiomyopathy and discharged home on a beta blocker and angiotensin-converting enzyme inhibitor. Follow-up TTE showed normalization of cardiac function.

Eight months later, the patient presented with similar complaints following another stressful event. She had mildly elevated troponin I of 0.286 ng/mL (normal, <0.057 ng/mL) with no ischemic changes on ECG. TTE revealed depressed left ventricular function (ejection fraction of 30%) with hypokinetic basal to mid segments and spared apical contractility suggestive of inverted stress-induced cardiomyopathy vs acute coronary syndrome (Figures 2 and 3). Given the different echocardiographic patterns of wall motion abnormality compared to the patient's prior typical stress-induced cardiomyopathy with apical ballooning, coronary angiography was performed and revealed normal coronary



**Figure 1.** Transthoracic echocardiogram from the patient’s first presentation shows apical 2-chamber views of end diastole (left) and end systole (right) and reveals hypokinesis of left ventricular apical segments with hyperdynamic basal and mid segments.

arteries, supporting a diagnosis of reverse/inverted stress-induced cardiomyopathy. The patient was discharged on aspirin, lisinopril, and carvedilol in stable condition. Repeat TTE 2 weeks later showed complete resolution of cardiac dysfunction.

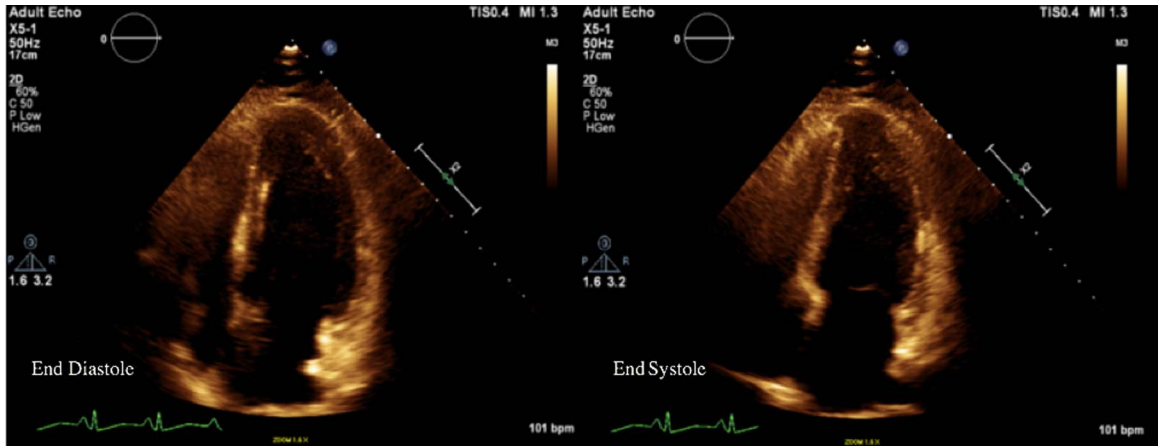
DISCUSSION

Takotsubo cardiomyopathy is characterized by transient reversible regional hypokinesia of the ventricular myocardium usually extending beyond the territory perfused by a single coronary artery.<sup>2</sup> Takotsubo cardiomyopathy can present as acute coronary syndrome or acute heart failure, usually, but not always, triggered by physically or emotionally stressful events.<sup>5</sup> Coronary angiography revealing no significant stenosis is a prerequisite for the diagnosis in almost all internationally accepted diagnostic criteria.<sup>2,5</sup> The transient myocardial hypokinesia in Takotsubo cardiomyopathy tends to affect one or more circumferential horizontal zones along the longitudinal cardiac axis. Based on this pattern, Takotsubo cardiomyopathy has 4 principal anatomic variants and a category of other rare variants (Table).<sup>2,6</sup>

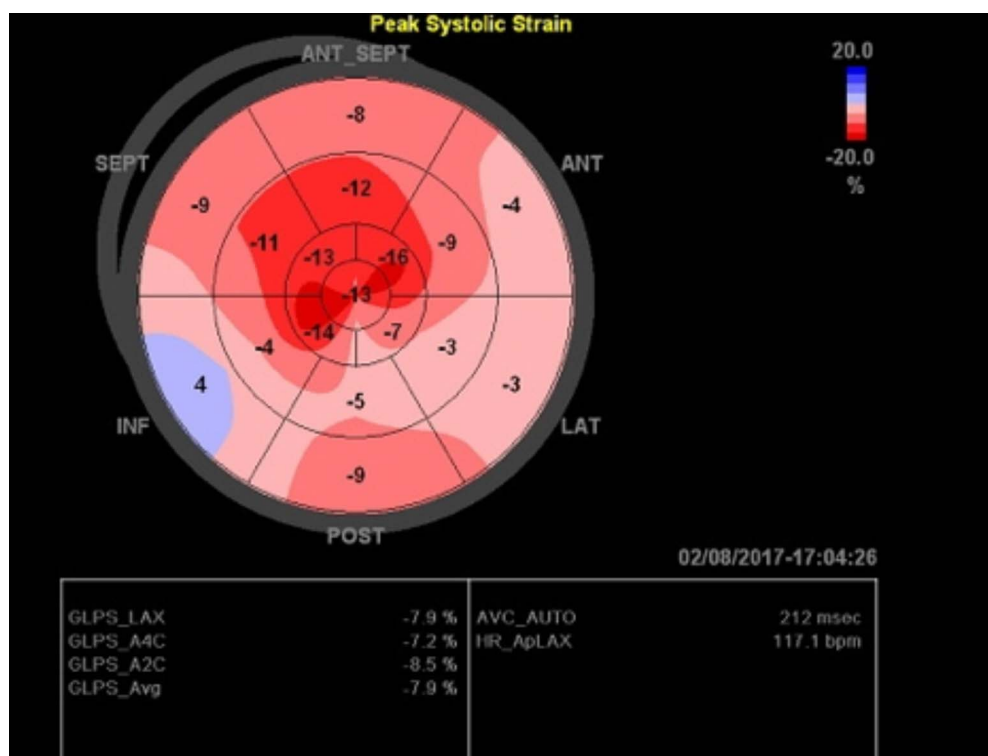
**1. Apical, typical, or classic variant:** Apical hypokinesia/dyskinesia with or without circumferential mid left ventricular hypokinesia with basal hyperkinesia. This variant is reported for 81.7% of patients in the International Takotsubo Registry.

**Table. Anatomic Variants of Takotsubo Cardiomyopathy<sup>2,6</sup>**

Variant	Estimated Incidence
Apical	75%-82%
Midventricular	10%-15%
Basal or inverted	2%-5%
Focal variant	1.5%
Other rare atypical variants:	
Biventricular apical variant	Unknown
Dysfunction sparing apical tip	Unknown
Isolated right ventricular variant	Unknown
Global variants	Unknown



**Figure 2.** Transthoracic echocardiogram from the patient’s second presentation shows apical 4-chamber views of end diastole (left) and end systole (right) and reveals hypokinesis of the basal and mid left ventricular segments with spared apical contractility.



2. **Midventricular variant:** Mid left ventricular hypokinesia with basal and apical hypercontractility. This variant is reported for 14.6% of patients in the International Takotsubo Registry.
3. **Basal, reverse, or inverted variant:** Basal left ventricular hypokinesia with apical hyperkinesia. This variant is reported for 2.2% of patients in the International Takotsubo Registry.
4. **Focal variant:** Focal left ventricular wall hypokinesia. This variant is reported for 1.5% of patients in the International Takotsubo Registry.
5. **Other rare atypical variants:** Biventricular apical variant, dysfunction sparing apical tip (possibly a form of the mid left ventricular variant), isolated right ventricular variant, and global variants.

The annual incidence of Takotsubo cardiomyopathy is unclear; however, 1%-2% of patients with troponin-positive acute coronary syndromes are eventually diagnosed with Takotsubo cardiomyopathy.<sup>7,8</sup> Takotsubo cardiomyopathy predominantly affects postmenopausal women (90% of all cases),<sup>2</sup> but men and younger women can be affected, with <10% of patients less than 50 years of age.<sup>5</sup>

Several diagnostic criteria have been proposed, but no criteria have been universally accepted. The European Soci-

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ety of Cardiology (ESC) diagnostic criteria released in 2016 took into consideration epidemiologic, pathophysiologic, and diagnostic updates in the last decade.<sup>2</sup> The ESC diagnostic criteria addressed two critical issues in the Mayo Clinic criteria after a review of the expanding data.<sup>9</sup> First, the classic demographic category (postmenopausal women) is no longer needed for the diagnosis.<sup>2</sup> Second, pheochromocytoma was included as a cause of Takotsubo cardiomyopathy because it can lead to the same clinicopathologic phenotype.<sup>2</sup> The pivotal role of catecholamine surges in the pathophysiology of Takotsubo cardiomyopathy is widely accepted.<sup>2</sup> However, the pathophysiology of Takotsubo cardiomyopathy is complex, and multiple mechanisms have been proposed with no proven conclusive theory. Catecholamine surges can affect the coronary macrovascular and microvascular circulation, the peripheral circulation, and the cardiac muscle. Specifically, catecholamine surges can lead to multivessel epicardial coronary spasm, cardiac microvascular dysfunction, peripheral vasoconstriction with acute increase in the afterload, acute left ventricular outflow tract obstruction, direct catecholamine-induced myocardial stunning, band necrosis, and catecholaminergic myocarditis with edema and inflammation.<sup>10</sup>

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and tendency of Takotsubo cardiomyopathy to affect the apical segment.<sup>11,12</sup> Growing evidence has pointed to a possible switch in the intracellular signaling of beta-2 adrenoceptors in ventricular cardiomyocytes from the Gs protein to the Gi protein as a result of elevated epinephrine levels in Takotsubo cardiomyopathy.<sup>11</sup> This switch to the Gi protein is proposed to have protective effects against the proapoptotic forces of intense activation of the beta-1 adrenoceptors with catecholamine surges.<sup>11</sup> However, this switch to the Gi protein is also negatively inotropic, and it exerts maximal effect at the apical region which is believed to have the highest concentration of beta-2 adrenoceptors.<sup>11</sup> As a result of this biased Gs agonism and the beta-2 adrenoceptor apical-basal gradient, Takotsubo cardiomyopathy tends to affect the apical segment of the left ventricle.<sup>12</sup> However, in our patient during the second attack, the basal segment was hypokinetic while the apical segment assumed the reverse role with hypercontractility. This recurrence with a different pattern in our patient, after complete recovery within a relatively short period of time, illustrates that the receptor gradient theory may not fully explain the pathophysiology behind Takotsubo cardiomyopathy. This recurrence affecting a different region of the myocardium may suggest a dynamic expression of beta-2 adrenoceptors where the concentration of these receptors in different segments of the myocardium changes in response to certain stimuli such as ventricular wall stress, hormones, or certain medications.

## CONCLUSION

Different anatomic variants of Takotsubo cardiomyopathy may recur in the same patient. Despite the involvement of a different myocardial region, the clinical presentation and the in-hospital course of the recurrent Takotsubo cardiomyopathy can be similar to the classic apical Takotsubo cardiomyopathy. Additionally, the adrenoceptor distribution theory does not fully explain recurrence of the Takotsubo cardiomyopathy at a different myocardial region, as in our case, and hence needs further refinement. In addition, chronic therapy with beta blockers and angiotensin-converting enzyme inhibitors did not prevent Takotsubo cardiomyopathy recurrence in our patient. Therefore, the optimum therapy after the acute phase of Takotsubo cardiomyopathy has yet to be determined.

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