

# ATYPICAL PRESENTATIONS OF HEART DISEASE

## A MEDICAL MASQUERADE

### Stress Cardiomyopathy: The Midventricular Variant



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#### INTRODUCTION

Takotsubo cardiomyopathy (TTC) is a stress cardiomyopathy that was first described in Japan in the 1980s. It is most often precipitated by severe emotional or physical stress, but other less common etiologies also exist. Several left ventricular (LV) variants have been described in the literature including the classic type (apical ballooning with hyperdynamic basal contractility), reverse Takotsubo (hypo-, a-, or dyskinesia of basal segments with a hyperdynamic apex), midventricular type (hypo-, a-, or dyskinesia of midventricular segments with hyperdynamic apical/basal segments), and localized type (focal hypo-, a-, or dyskinesia of any segment of the left ventricle [LV]).<sup>1,2</sup> The main differentiation between types is based on the area of the LV affected. One of the most rarely described variants is the midventricular TTC. A study analyzing 1,750 patients from the international Takotsubo registry noted that only 14.6% of cases had this variant.<sup>2</sup> The diagnostic criteria for TTC include (1) transient abnormal wall motion in the form of hypokinesis, akinesis, or dyskinesia of the LV segments, with the region affected extending beyond a single epicardial vascular distribution; (2) no detectable obstructive coronary disease or angiographic evidence of acute atheromatous plaque rupture; (3) newly developed electrocardiogram (ECG) abnormalities or elevation in cardiac troponin levels; and (4) absence of myocarditis.<sup>3</sup> We present a case of the uncommon midventricular variant of TTC with the aim of emphasizing the importance of considering this diagnosis in the differential of patients presenting with acute chest pain syndromes.

#### CASE PRESENTATION

A 59-year-old woman with a medical history of hyperlipidemia, tobacco use, and hypothyroidism presented to the emergency department 5 hours after a motor vehicle collision in which they were the

restrained driver. The patient described symptoms of dull chest pain that was tender to palpation. The patient denied hitting their chest on the steering wheel as well as fevers, chills, shortness of breath, orthopnea, palpitations, or other pertinent symptoms. In the emergency department, initial vital signs were stable: hypertensive (142/76 mm Hg), sinus bradycardia (58 beats per minute), no respiratory distress (16 respirations per minute), and afebrile (98.2 °F). Physical exam was entirely benign, with noted bradycardia, bilaterally clear lungs to auscultation, and the absence of jugular venous distension or lower extremity edema. The patient had a mild leukocytosis (12.9 cells/mL), elevated brain natriuretic peptide (582 pg/mL), and peak troponin I levels of 0.90 ng/mL. The ECG demonstrated sinus bradycardia and mild nonspecific T-wave changes in leads V1-V3 (Figure 1). The interTAK diagnostic score was 56 points, translating to a 37.5% chance of being TTC. All other initial obtained lab work was within normal limits, including comprehensive metabolic panel, urinalysis, and coagulation factors. The patient was admitted for observation and reported the resolution of chest pain shortly after. Fifteen hours after admission an emergency response was called to the patient's bedside for complaints of severe, substernal chest pressure with associated nausea and diaphoresis. The patient appeared in acute distress with a significant change in vital signs: hypertensive (187/90 mm Hg), sinus tachycardia (122 beats per minute), and tachypnea (28 respirations per minute). Repeat troponin I trended higher from the prior values (1.06 ng/dL), and the ECG demonstrated sinus bradycardia with ST depression suggesting myocardial ischemia in leads V3-V5 (Figure 2).

A transthoracic echocardiogram (TTE) revealed a normal-sized LV with mildly reduced systolic function and regional wall motion abnormalities (RWMA) of the midventricular segments (Figures 3-6, Videos 1 and 2). The LV ejection fraction via the three-dimensional TTE full-volume LV ejection fraction method echocardiography was 50%.

Emergent coronary angiography was pursued, which revealed mild nonobstructive coronary artery disease (CAD) with luminal irregularities of the mid left anterior descending coronary artery (Videos 3 and 4). In addition, the left ventriculogram revealed normal apical and basal contractility with abnormal midventricular motion (Video 5, Figure 7). Ultimately, in the absence of significant CAD and the presence of an RWMA in noncoronary territories, the patient was diagnosed with midventricular TTC, and the acute coronary syndrome (ACS) protocol was discontinued.

#### DISCUSSION

Midventricular TTC is rare, with only 14.6% of patients with TTC having this variant. There are various triggers for the occurrence of all forms of TTC, with the most common being severe emotional/physical stress scenarios including motor vehicle collisions, sepsis, vaginal delivery, stroke, divorce, death of family member, and

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## VIDEO HIGHLIGHTS

**Video 1:** Two-dimensional TTE parasternal long-axis view demonstrates akinesis of the midanteroseptal and inferolateral wall segments with normal distal and basal regional wall segments.

**Video 2:** Two-dimensional TTE, apical 4-chamber view demonstrates akinesis of the midinferoseptal and anterolateral wall segments with normal apical and basal regional wall segments.

**Video 3:** Coronary angiogram (right anterior oblique cranial view) demonstrating nonobstructive CAD with a normal left main coronary artery, normal left circumflex, and mild luminal irregularities of the left anterior descending coronary artery.

**Video 4:** Coronary angiogram (left anterior oblique view) demonstrating no significant obstructive CAD in the right coronary artery.

**Video 5:** Left ventriculogram from the right anterior oblique view demonstrating normal apical and basal contractility with abnormal midventricular contractility consistent with midventricular TTC.

[View the video content online at www.cvcasejournal.com.](http://www.cvcasejournal.com)

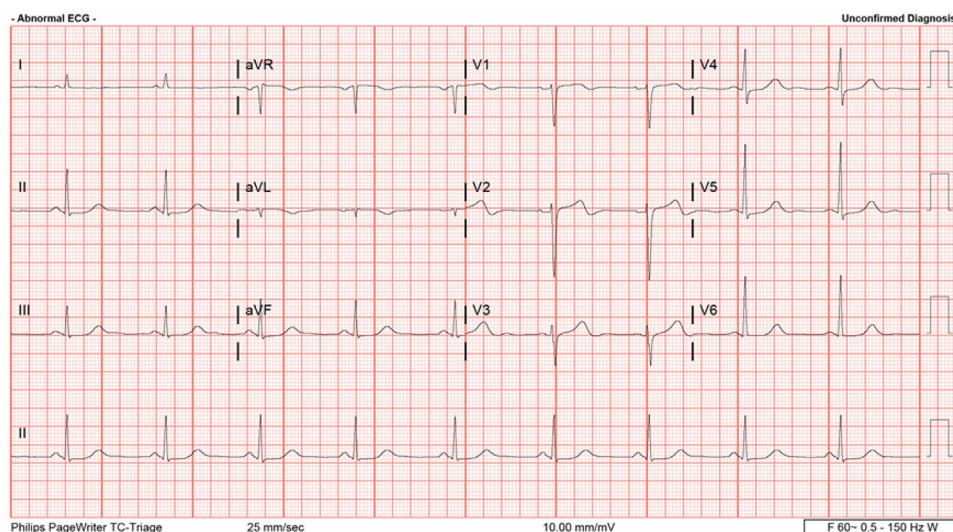
chemotherapy.<sup>4</sup> Thus, the range of associated etiologies remains broad with the pathophysiological mechanism remaining uncertain. There have been numerous potential explanatory theories proposed for RWMA in TTC including catecholamine cardiotoxicity, estrogen deficiency, and coronary artery spasm.

Excessive catecholamine stimulation is the most regarded pathophysiological theory. The belief is that high doses of epinephrine are directly toxic to the myocardial cells. The binding of epinephrine to  $\beta_2$ -adrenoreceptors results in a dramatic rise in cyclic AMP and calcium levels that then trigger the formation of free oxygen radicals and initiation of expression of stress response genes.<sup>5</sup> This molecular injury leads to profound impairment of myocardial function, which may persist for hours to days in the affected individual. A possible explanation for the different TTC types is a variation in the distribution of  $\beta_2$ -adrenoreceptors. For example, individuals with the classic type of TTC  $\beta$ -receptors may have a higher concentration of these receptors in the apex, while the reversed and midventricular variants of TTC may have a higher concentration of these receptors in the base or in the midventricular region, respectively.<sup>5</sup>

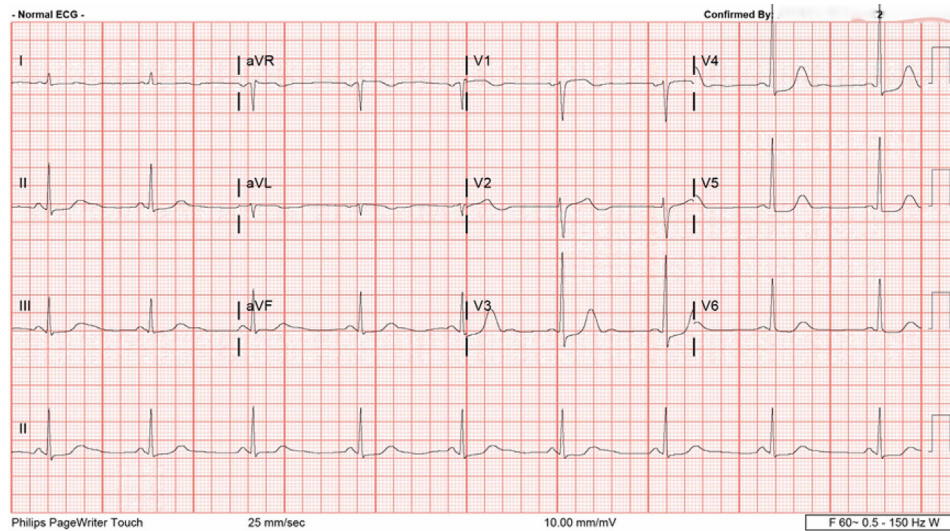
Estrogen deficiency, as most patients are postmenopausal women, is also a possible etiology as estrogen withdrawal has been associated with impaired coronary microvascular and cardiac myocyte function. For example, in studies of oophorectomized rats it was found that estrogen replacement diminished the inhibitory effects on myocardial contraction that are induced by high levels of epinephrine.<sup>6</sup> Animal models have even shown estrogen treatment to be beneficial in preventing the condition; however, human clinical trials would be needed to confirm.<sup>7</sup>

Coronary spasm resulting in blood flow disruption is another less popular theory. This theory tends to be less popular because the resulting ischemic myocardial stunning that occurs from this does not produce the typical histologic changes observed in TTC (e.g., myocardial contraction band necrosis, neutrophil infiltration, fibrosis). In addition, this mechanism would fail to account for the noncoronary distribution of the wall motion abnormality pattern that is found. Finally, an extensive case presentation literature review suspected coronary arterial spasm in 1% TTC cases, but it was never actually observed on imaging.<sup>7</sup>

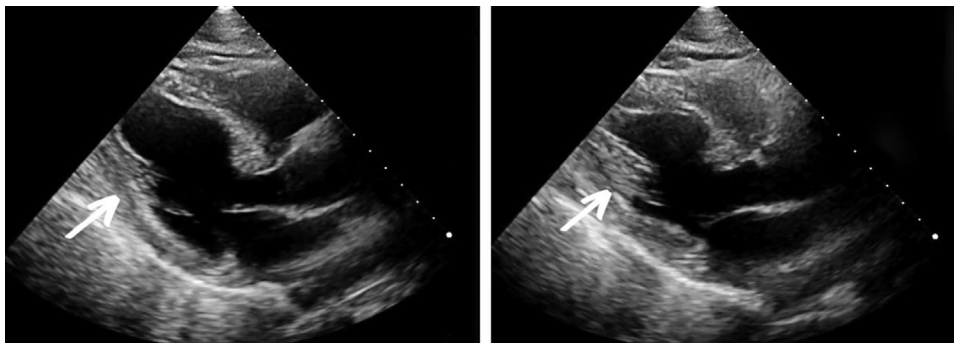
The diagnostic criteria, as described earlier, remain the same for all TTC types, and the main differentiation between the variants is the LV



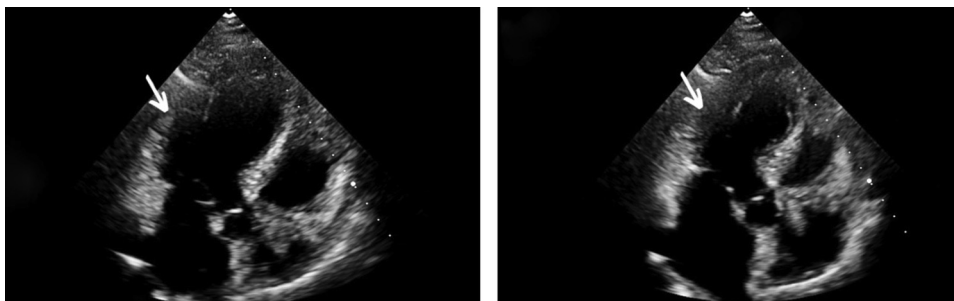
**Figure 1** Twelve-lead ECG acquired on admission (asymptomatic) demonstrates sinus bradycardia and mild nonspecific T-wave changes in leads V1-V3.



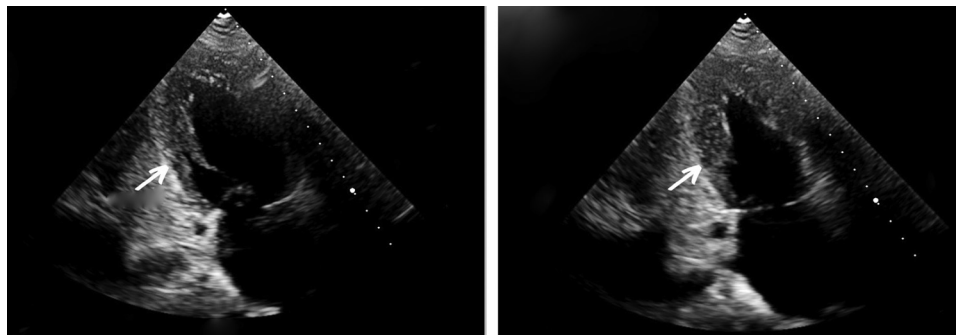
**Figure 2** Twelve-lead ECG acquired during the episode of severe chest pain demonstrates sinus bradycardia with ST depression suggesting myocardial ischemia in leads V3-V5.



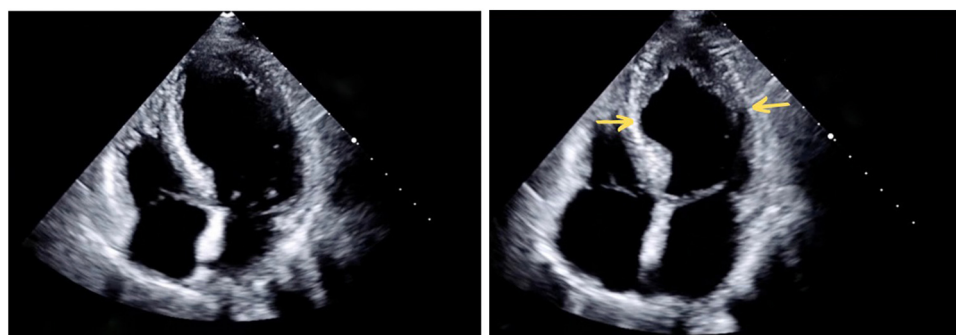
**Figure 3** Parasternal long-axis images acquired at end diastole (*left*) and end systole (*right*) demonstrate a severe, midventricular, noncoronary pattern RWMA (*arrows*).



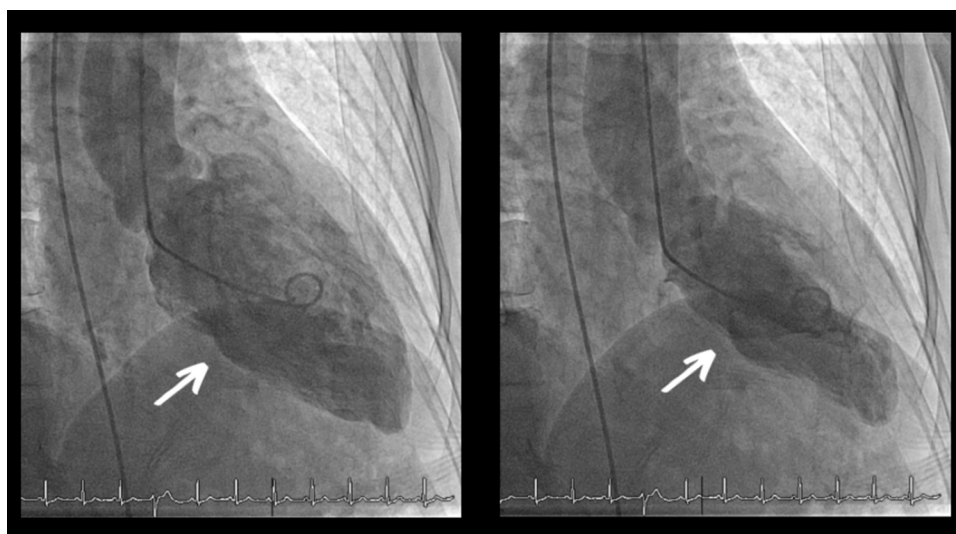
**Figure 4** Two-dimensional TTE, apical long-axis view in diastole (*left*) and systole (*right*), demonstrates RWMA at the midanteroseptal and inferolateral ventricular walls (*arrows*).



**Figure 5** Two-dimensional TTE, apical 2-chamber view in diastole (*left*) and systole (*right*), demonstrates RWMA at the midanterior and inferior ventricular level walls (*arrows*).



**Figure 6** Two-dimensional TTE, apical 4-chamber view acquired at end diastole (*left*) and end systole (*right*), demonstrates akinesis at the midventricular myocardial wall segments (*arrows*).



**Figure 7** Left ventriculogram, right anterior oblique orientation in diastole (*left*) and systole (*right*), demonstrates normal apical and basal contractility with dyskinetic midventricular motion (*arrows*).

myocardial wall segments affected. Typically, in midventricular TTC, the midventricular segments are dyskinetic with relative sparing of the apex and base. The initial diagnosis of TTC, however, remains difficult as the symptoms of TTC mimic ACS, and it is estimated that 2% of suspected ACS cases are in fact TTC.<sup>8</sup> The diagnostic challenges between TTC and ACS arise because patient symptoms

and the initial diagnostic workup results overlap. Symptoms for both conditions include anginal chest pain, nausea, diaphoresis, dyspnea, and epigastric pain. Initial diagnostic tests for patients presenting with these symptoms include troponin levels, TTE to assess for RWMA, and a 12-lead ECG. The most common ECG changes are ST-segment elevation, usually in the precordial leads but also possible

in the inferior and lateral leads. Other ECG changes associated with TTC include T-wave inversion, ST-segment depression, prolonged QT interval, and new bundle branch block.<sup>9</sup> Given the similarity in presentation between TTC and ACS, management is directed toward ACS until it is ruled out because a delay in management in patients with ACS can lead to catastrophic consequences. For example, TTC is definitively diagnosed following the exclusion of ACS.<sup>10</sup> Furthermore, coronary angiography is typically performed in patients presenting with symptoms of TTC as studies have shown that patients who did not undergo coronary angiography had a higher in-hospital mortality than those who did.<sup>10</sup> This may be in part due to the misdiagnosis or undertreatment of ACS as TTC and therefore a failure for these patients to receive prompt revascularization. Despite these challenges, there are subtle differences to be aware of in the TTC patient. In TTC, the symptoms tend to present after a preceding stressful event, as a recent trauma, like our patient's motor vehicle collision. In addition, troponins tend to peak at symptom onset then decline, unlike in ACS, where there is a gradual rise, and RWMA seen on imaging are discordant with respective ECG changes unlike in an ST-elevation myocardial infarction. Lastly, in TTC the RWMA are usually transient and resolve spontaneously, allowing for LV function to return to normal usually within a few days or weeks.

The management of TTC as per the American College of Cardiology guidelines is primarily supportive.<sup>11</sup> Common potential complications associated with TTC include pleural/pericardial effusion, LV thrombi, LV outflow tract obstruction, and cardiogenic shock. Thus, although usually a benign reversible syndrome, there are complications that can occur, and clinicians should remain aware of the myriad of manifestations and conduct their management accordingly.

The future holds promise for understanding and treating this condition as numerous investigations are ongoing. For example, long term  $\beta$ -blocker therapy has been hypothesized to reduce the likelihood of reoccurrence and improve symptoms in these patients. Despite this promising evidence, more studies are still needed.

## CONCLUSION

We present a case of the uncommon midventricular TTC. All users of echocardiography should be aware of this variant and should always consider TTC in the differential diagnosis of a patient presenting with chest pain, especially in patients at risk for TTC. In doing so, the appropriate diagnostic and management strategies can be undertaken.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2022.06.008>.

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