

# “Inverted” tako-tsubo cardiomyopathy due to exogenous catecholamines

Ashwin Subramaniam, Jennifer C Cooke and David Ernest

Tako-tsubo cardiomyopathy (TTC),<sup>1</sup> or stress-related cardiomyopathy, is a recently described form of acute reversible myocardial dysfunction that is characterised by a contractile abnormality typically consisting of left ventricular (LV) apical and mid-ventricular akinesia or dyskinesia and hyperdynamic basal segments. This condition may resemble acute myocardial infarction, as electrocardiographic abnormalities and a mild rise in serum cardiac markers are common features.<sup>2-5</sup> Although serious complications (such as heart failure, cardiogenic shock and malignant arrhythmias) can occur transiently,<sup>6</sup> the in-hospital mortality rate is low, as is the risk of recurrence.<sup>7</sup> The condition has commonly been reported in postmenopausal women.<sup>7,8</sup>

Recently, a new variant of TTC, described as “inverted” TTC, has been recognised. Although this variant follows the typical clinical course, the echocardiogram (ECG) reveals an extensive basal and mid LV circumferential akinesia with a hyperdynamic apex.<sup>6</sup> In most cases of inverted TTC, a triggering acute emotional or physical stressor can be identified. The pathophysiology is believed to be mediated by endogenous catecholamines<sup>9</sup> and has been reported in related conditions, including pheochromocytoma,<sup>10</sup> traumatic brain injury (in patients requiring catecholamines)<sup>11</sup> and extreme stress (in postmenopausal women).<sup>7</sup>

We report a case of a young female patient who developed clinical and echocardiographic findings suggestive of inverted TTC after administration of an unintended bolus of noradrenaline (norepinephrine). To our knowledge, transient LV dysfunction associated with an exogenous

## ABSTRACT

Inverted tako-tsubo cardiomyopathy (TTC) is a variation of stress cardiomyopathy. It features transient myocardial dysfunction characterised by a typical contractile abnormality consisting of extensive left ventricular circumferential dyskinesia or akinesia with a hyperkinetic apex. Endogenous catecholamine surges are believed to be the mediators of this potentially life-threatening condition. We describe a patient who received an inadvertent bolus of noradrenaline and developed significant haemodynamic instability associated with electrocardiographic and cardiac biomarkers indicative of diffuse myocardial injury and echocardiography findings of an “inverted” TTC. The patient made a full recovery. Our case highlights that a reversible inverted TTC may result from an exogenous catecholamine surge.

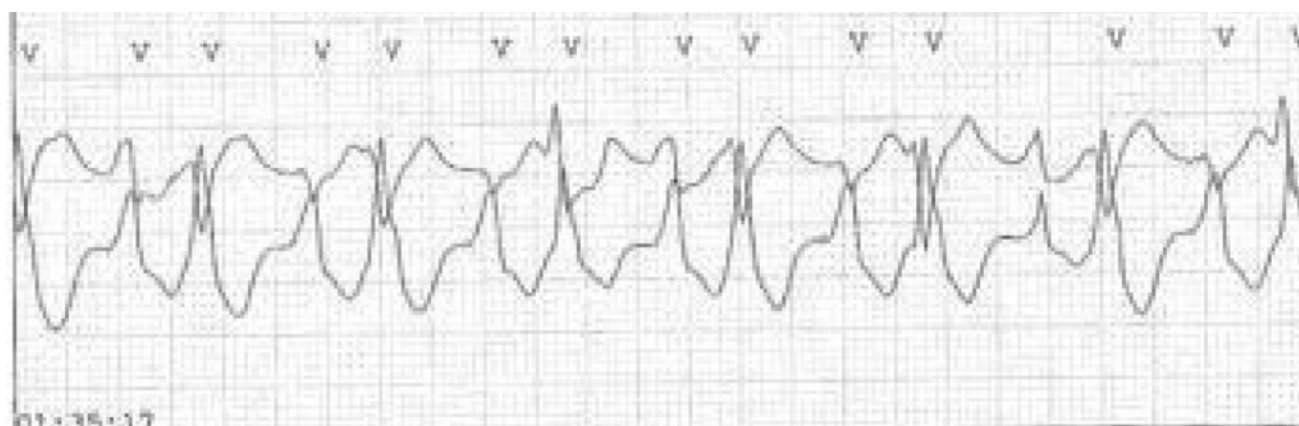
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catecholamine surge in an inverted TTC pattern has not been previously reported.

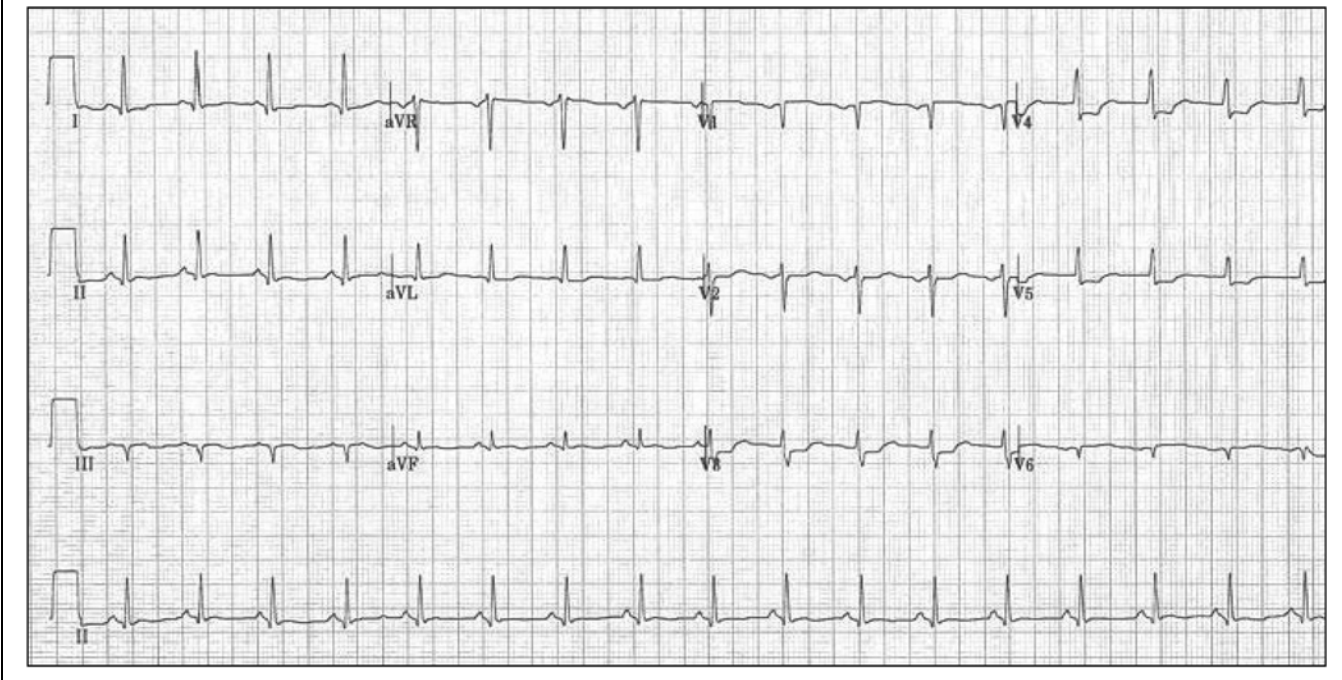
## Clinical record

A previously fit and well 26-year-old woman was referred to our emergency department by her local medical practitioner with lethargy and hyponatraemia. She had suffered from

**Figure 1. Rhythm strip showing runs of broad complex tachycardia (atrial fibrillation with aberrant conduction)**



**Figure 2. Electrocardiogram with global ST-T wave changes**

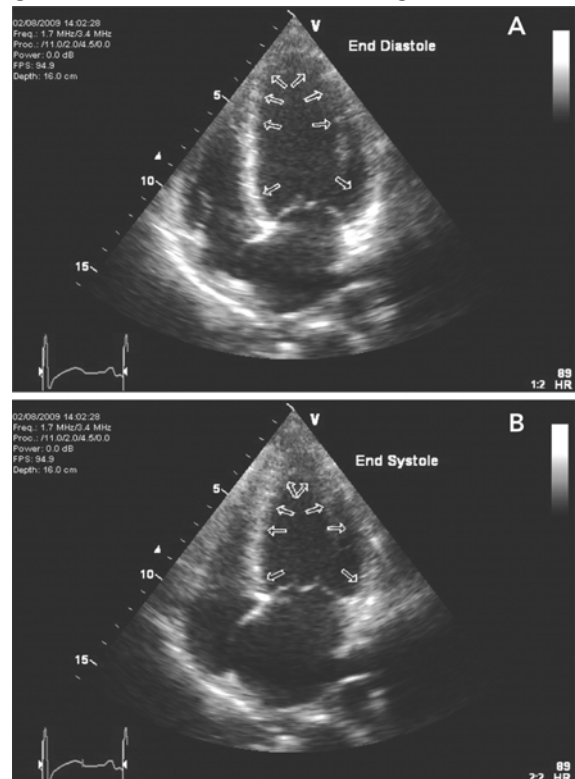


chronic constipation, for which she self-administered a sodium phosphate (Fleet) enema, and drank about 5L of water, after which she had profuse diarrhoea and vomiting. On arrival, she was alert and orientated and her initial clinical examination was unremarkable. Serum electrolyte measurements on admission confirmed her hyponatraemia: sodium 120 mmol/L (mEq/L) (reference range [RR], 135–145 mmol/L); potassium 2.7 mmol/L (mEq/L) (RR, 3.5–5.0 mmol/L); chloride 88 mmol/L (mEq/L) (RR, 95–110 mmol/L); and bicarbonate 20 mmol/L (mEq/L) (RR, 20–32 mmol/L).

Shortly after her arrival, she had a single generalised seizure complicated by aspiration, for which she was managed with midazolam, endotracheal intubation and 100 mL 3% saline followed by a 0.9% saline infusion. A computed tomography (CT) brain scan was normal. Repeat measurements of serum sodium concentration were 123 mmol/L (mEq/L) 4 hours later and 134 mmol/L (mEq/L) 11 hours later. Because of persisting hypotension following her seizure, she was managed with a low-dose noradrenaline infusion (1–3 µg/min) and admitted to the intensive care unit, where her initial progress was unremarkable.

Twenty-four hours after admission to the ICU, she suddenly developed marked hypertension (blood pressure 250/120 mmHg) and rapid atrial fibrillation with aberrant conduction (150 beats/min) (Figure 1). The noradrenaline infusion was immediately ceased and she was treated with amiodarone for heart rate control. On ceasing the noradrenaline infusion, it was noted that the noradrenaline

**Figure 3. Transthoracic echocardiogram**



*Apical four-chamber view with normal left ventricular end diastolic appearance. B: In systole there was good apical contractility but extensive akinesis of the basal and mid left ventricular segments.*

infusion bag was near empty, which indicated, based on the time of commencement of the infusion and the infusion rate, that the patient had received an inadvertent bolus of noradrenaline of about 4.5 mg, the cause of which is presently under investigation.

After stabilisation, the patient had persistent hypotension, which was managed with noradrenaline and adrenaline (epinephrine) infusions, using two replacement infusion pumps. There was evidence of myocardial damage, with electrocardiographic and biochemical cardiac marker abnormalities. The ECG study revealed significant global ST-T wave changes, with ST depression in chest leads (V3–V5) and T wave flattening in anterior leads, suggestive of diffuse myocardial injury, along with inverted P waves in V1 and V2, indicating left atrial enlargement (Figure 2). Levels of cardiac enzymes were markedly increased: creatine kinase (CK) 1016 IU/L (RR, 30–180 IU/L); CK myocardial isoenzyme (CKMB) 12 µg/L (RR, <4 µg/L); and troponin T 1.22 ng/mL (RR, <0.03 ng/mL). A subsequent transthoracic ECG at 12 hours, while the patient was receiving infusions of noradrenaline (10 µg/min) and adrenaline (2 µg/min), revealed marked LV systolic dysfunction, with an ejection fraction of 35%, associated with a contractile abnormality consistent with inverted TTC (Figure 3).

The patient made an uneventful recovery over the following 48 hours, during which she was extubated, her ECG and cardiac biomarker levels returned to normal, and her serum sodium concentration remained stable at 141 mmol/L (mEq/L).

The patient was discharged home on Day 7. At follow-up 7 weeks later, she had returned to all her normal activities without experiencing any exertional dyspnoea or other features of heart failure, and a repeat transthoracic ECG showed normalisation of LV function without residual wall motion abnormalities.

## Discussion

We report on a young woman who developed reversible marked LV dysfunction and a contractile abnormality in an inverted TTC pattern after the inadvertent administration of a bolus of noradrenaline. She made an uneventful clinical recovery, with complete resolution of her echocardiographic abnormality within 7 weeks.

We note that the serum CKMB fraction was relatively low for the corresponding serum CK concentration, suggesting a predominantly skeletal muscle source of CK, with only a relatively small cardiac contribution (Table 1). As her LV dysfunction proved reversible, we suggest that the majority of the LV dysfunction noted on initial echocardiography reflected myocardial stunning rather than irreversible damage.

**Table 1. Cardiac biomarkers**

Day	CK (IU/L)	Troponin T (ng/mL)	CKMB (µg/L)
-1	76	< 0.03	
0	1016	1.22	12
1	1051	0.89	20
2	1522	0.49	23
3	2726	0.24	11
4	2386	0.11	1
5	844		

CK = creatine kinase. CKMB = CK myocardial isoenzyme.

Our patient had ECG changes similar to those previously reported in patients with TTC,<sup>12</sup> and additionally had runs of atrial fibrillation, most likely due to excessive catecholamine stimulation and abnormal repolarisation in the setting of stunned myocardium. The LV ejection fraction, estimated from the ECG, was 35%, which is comparable to levels reported in previous TTC studies by Haghi et al (mean, 37% [SD, 7%]; range, 25%–46%)<sup>12</sup> and Teh et al (mean, 50% [SD, 10%]).<sup>13</sup>

Inverted TTC may be associated with neurological conditions, including seizure disorders,<sup>6</sup> head trauma,<sup>11</sup> haemorrhagic stroke,<sup>6</sup> and inhalation of amphetamine (a non-catecholamine sympathomimetic amine with central nervous system stimulant activity).<sup>14</sup> Although our patient experienced a hyponatraemia-related seizure, the timing of her haemodynamic instability did not correlate with her seizure activity and we do not consider this to be a relevant association in our patient.

Reversible myocardial dysfunction in critically ill non-cardiac patients is a well recognised entity, particularly in the setting of severe sepsis.<sup>15</sup> However, given that our patient received an inadvertent exogenous noradrenaline bolus, and based on her ECG findings, we consider that a transient inverted TTC is the likely explanation for her reversible myocardial depression.

TTC, inverted TTC and the other rarer regional variants<sup>16</sup> of TTC are increasingly being recognised in critically ill patients admitted to intensive care for management of non-cardiac illnesses.<sup>12,17-21</sup> The incidence of TTC in troponin-positive acute coronary syndrome patients is estimated to be about 1.2%, of which about 40% of cases have been reported to be atypical variants.<sup>22</sup> Both TTC and inverted TTC have typical clinical presentations. However, the usual symptoms, such as angina-like chest pain<sup>13</sup> or dyspnoea, may not be recognised in ICU patients because of the use of sedative agents and mechanical ventilation. The usual clinical manifestation of TTC in intubated patients is sudden haemodynamic deterioration (unexplained hypotension,

tachycardia and reduction in stroke volume) requiring vasopressor support to maintain adequate blood pressure.<sup>12</sup> A recent study comparing the clinical characteristics of classic and inverted variants of TTC concluded that, although the two have similar clinical presentations, classic TTC is associated with more severe heart failure and a higher rate of cardiac complications.<sup>23</sup>

Enhanced sympathetic activity appears to play an important role in the pathophysiology of TTC,<sup>9,24</sup> based on the observations that excessive catecholamine levels have been reported in patients with TTC,<sup>25</sup> catecholamines have been shown to induce myocardial damage,<sup>26,27</sup> and excessive stimulation of cardiac adrenergic receptors leads to transient oxidative stress<sup>28</sup> and LV hypocontraction in animal models.<sup>29</sup> The mechanism underlying the association between catecholamines and myocardial injury remains uncertain, but direct myocyte injury has been proposed as one possible mechanism of myocardial stunning.<sup>10</sup> An alternative pathophysiological mechanism to explain TTC is that of transient vasospasm of coronary arteries, but this has not been a consistent finding and, when present, may not correlate with the region of wall motion abnormality.

The management of TTC is generally considered supportive and may require the use of inotropic agents. Patients generally recover over a period of months.

## Conclusion

We describe a patient who developed transient myocardial dysfunction in an inverted TTC pattern, consequent to the administration of an inadvertent bolus of noradrenaline. Although this syndrome has been recognised to be mediated by endogenous catecholamine surges, our case highlights that exogenous catecholamine surges may also result in a reversible “inverted” TTC.

## Author details

Ashwin Subramaniam, Intensive Care Registrar

Jennifer C Cooke, Director of Echocardiography

David Ernest, Director of Intensive Care

Box Hill Hospital, Melbourne, VIC.

**Correspondence:** catchdrash@yahoo.com

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AUTHORS' NAMES (Print)

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AUTHORS' SIGNATURES (and Date)

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