REVIEW

Late development of Takotsubo syndrome following intensive care unit discharge

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Abstract

Takotsubo syndrome (TTS), previously called Takotsubo cardiomyopathy and stress cardiomyopathy, is an acute form of regional heart failure that usually mimics acute myocardial infarction. TTS is often precipitated by catecholamine release associated with an acute emotional and/or physical stressor such as critical illness. We describe a case of TTS following discharge from the ICU to a general ward. The medical emergency response team was called twice to the patient while on the general ward before she was readmitted to the ICU. This case indicates that the risk of developing TTS is not confined to the acute phase of a critical illness. Given that TTS may be associated with serious haemodynamic instability and/or respiratory deterioration, clinicians need to be aware that such deterioration, even following transfer from the ICU, may be due to TTS.

Case study

A 58-year-old female presented to the emergency department of a rural hospital with pyrexia, right hip pain, limited mobility and hypotension two days after a fall. Investigations revealed a fractured right acetabulum with minimal displacement and *Klebsiella* urosepsis. Past medical history included previous cigarette smoking, hypertension, osteoarthritis, hyperlipidaemia, obesity (BMI 33.02 kg/m2), bilateral total hip replacements and chronic back pain. Medication at presentation consisted of aspirin, perindopril, gemfibrozil, meloxicam, pregabalin, paroxetine, carbamazepine, sustained-release morphine and paracetamol. She was transferred to the intensive care unit (ICU) of a metropolitan hospital where her initial observations were blood pressure 88/49 mmHg, respiratory rate 16 breaths/min, oxygen saturation of 97% on 3 litres/min O_2 by nasal cannula and a temperature of 39.5°C. The admission electrocardiogram (ECG) showed sinus rhythm with first-degree heart block, low voltages consistent with the patient's obesity, a heart rate of 89 beats/min, and mild widespread P-R depression. The QTc interval was normal and there were no abnormalities of the ST segment or T wave. Electrolytes were within the normal limits. Abnormal laboratory results included creatinine 241 µmol/l and urea 10.9 mmol/l indicating acute kidney injury; arterial blood gas showed signs of metabolic acidosis with bicarbonate (HCO_3) 17 mmol/l, pH 7.15, and pCO_2 49 mmHg; C-reactive protein was 540 mg/l; white cell count 13.5 x 10^9/l. Haemoglobin was 88 g/l. An echocardiogram was performed on day 9 following admission to assess valvular function as there was some concern for endocarditis secondary to bacteraemia. The echocardiogram showed normal left ventricular (LV) systolic and valvular function. No wall motion abnormalities were reported although the test was suboptimal due to patient obesity and positioning.

The patient's index ICU admission was prolonged and complicated by multiple medical problems including septic shock (managed with antibiotics and noradrenaline infusion titrated between 0.05 µg/kg/min to 0.1 µg/kg/min to maintain the mean arterial pressure above 65 mmHg), respiratory failure (treated with non-invasive positive pressure ventilator support and diuretics), sepsis (treated with multiple antibiotics), anaemia requiring blood transfusion, acute renal failure requiring haemodialysis and functional bowel obstruction. She was found to have an infected right hip requiring multiple debridements, removal of the hip prosthesis and eventually femoral head ostectomy.

The patient was discharged from the ICU to an orthopaedic ward on day 28 following admission and subsequently the
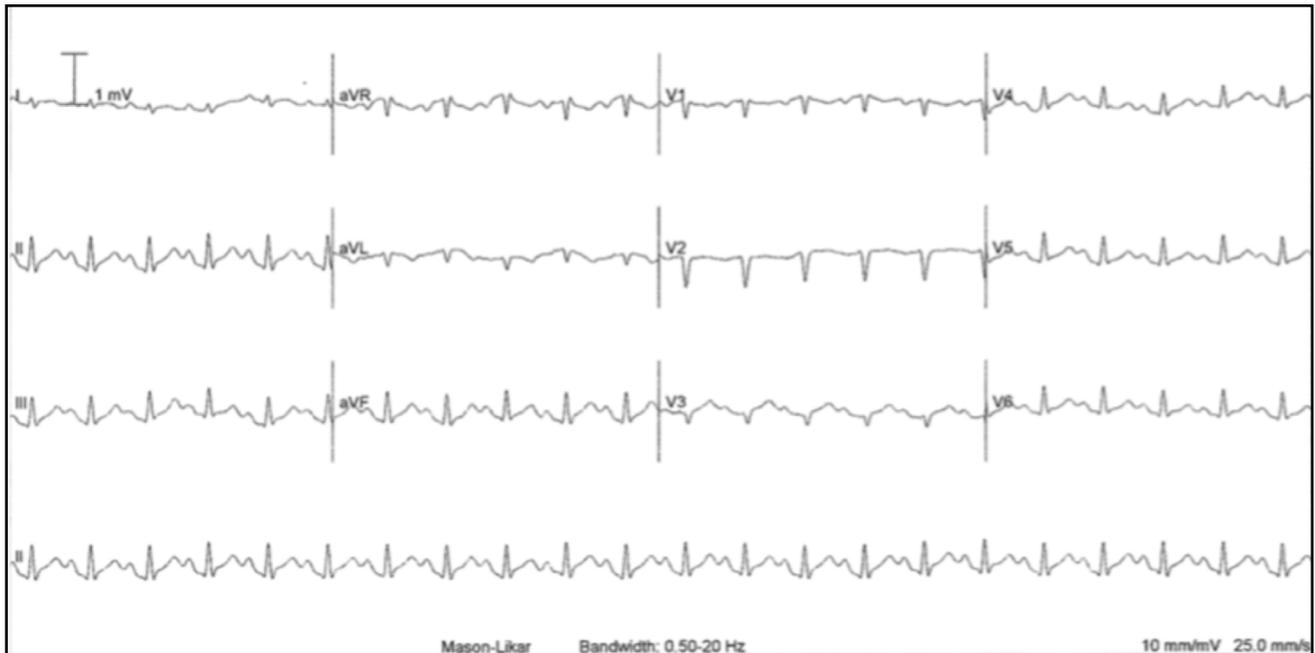
Figure 1a. 12-lead ECG (day 1 following ICU readmission)

Figure 1b. ECG showing widespread T-wave inversion and QT prolongation (day 3 following ICU readmission)

medical emergency response (MER) team was called twice in the 48 hours after ICU discharge (day 30 after admission) for acute respiratory deterioration, hypertension, tachycardia and chest pain. Table 1 shows details of precipitants of the MER calls including signs and symptoms of clinical deterioration, clinical findings and MER team management. The ECG following readmission to the ICU showed sinus tachycardia (130 beats/min) with first-degree heart block and reduced R-wave progression in precordial leads V2 and V3 *(figure 1a)* which may raise suspicion of anterior myocardial infarction, but can also transiently occur in TTS. ECGs following resolution of wall motion abnormalities showed normal R-wave progression. Serial chest X-rays showed the development of upper lobe venous congestion, increased cardiac silhouette size, linear interstitial opacities and 'bats wing' distribution of airspace opacification that developed over a few hours, strongly

suggestive of cardiogenic pulmonary oedema. Due to worsening respiratory failure, the patient was transferred to ICU for non-invasive ventilatory support. On day 1 following readmission to the ICU the troponin T was elevated at 396 ng/l and NT-proBNP was 35,000 ng/l. The ECG 3 days after readmission showed widespread T-wave inversion and QTc prolongation *(figure 1b)*. Four days after readmission, a transthoracic echocardiogram (TTE) was undertaken using contrast showing moderate to severe LV systolic impairment, LV ballooning involving mid segments *(figure 2)* and apex without LV outflow tract obstruction (LVOTO), some hypokinesis in the distal right ventricular free wall and mild to moderate mitral regurgitation with an ejection fraction (EF) of 35%. The echo was repeated two weeks later, showing a low normal LV ejection fraction (LVEF) (50-55%), mild to moderate mitral regurgitation and a dilated left atrium. No wall motion abnormalities were noted. On day 81 following first admission, the patient was transferred to a facility for ongoing rehabilitation and survived to discharge home.

Introduction

We have described the case of a 58-year-old woman who developed Takotsubo syndrome (TTS) secondary to a fall and fracture of the right acetabulum, which was complicated by urosepsis, renal failure and hypotension necessitating ICU admission. Consistent with the relatively poor prognosis of 'secondary' TTS[1] this patient had a long stay in hospital but survived to discharge. This case is also noteworthy for the late development of TTS (post discharge from ICU), the delay to diagnosis (based on ECG, biomarkers and echocardiographic appearances alone), and the lack of adjustment of therapy for the occurrence of TTS. We will review aspects of this case which are particularly relevant to the management of patients

Figure 2. Image of left ventricular apical ballooning
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with potential TTS during ICU admission and following ICU discharge in order to increase awareness of this potentially lethal inflammatory disorder.

TTS is a cause of acute heart failure that is associated with characteristic left ventricular (LV) regional wall motion abnormalities (RWMAs) in the absence of causative occlusive coronary artery disease.[2] The vast majority of patients diagnosed with TTS are older women, but cases of TTS have been identified in both genders and in all age groups.[2,3] In most cases TTS is precipitated by endogenous (associated with emotional or physical stressors), or exogenous (pharmacological) catecholamine surges.[4,5] TTS may be triggered by other diseases and is denoted as 'secondary TTS'.[1,6] Myocardial injury is associated with diffuse inflammatory activation[7] and oedema throughout the left ventricle: this persists for at least three months, together with evidence of impaired myocardial energetics[8] and eventual diffuse, but variable fibrous scarring.

Takotsubo syndrome diagnosis

TTS signs and symptoms at onset usually mimic those of acute coronary syndrome including chest pain and dyspnoea and in some cases severe hypotension or cardiac arrest.[9] In the past, TTS has largely been diagnosed 'by accident' during emergency cardiac catheterisation for management of patients with presumptive acute myocardial infarction. Initially, the diagnosis was essentially one of exclusion: there was either no coronary stenosis, despite the advanced age of most patients, or the stenosis which was present did not account for the pattern of regional systolic dysfunction.[9] However, the problem with this method was that it relied entirely on cardiac catheterisation findings: it is theoretically possible to have a myocardial infarct without major coronary stenosis, for example on the basis of coronary artery spasm, embolic infarct in atrial fibrillation, and spontaneous coronary artery dissection. Furthermore, there are many patients, such as those who were severely ill in the ICU, who could not readily undergo immediate cardiac catheterisation because of clinical circumstances.[10] The patient in the case reported here falls into this category. In response to this dilemma, there has been progressive development of a set of criteria for presumptive (preliminary) diagnosis of TTS, based on ECG appearances, biomarkers, and echocardiographic changes.[11]

The ECG in TTS can initially show elevated, normal or non-specifically altered ST segments, left bundle brunch block and/or T-wave abnormalities.[12,13] Widespread deep T-wave inversion and QT-interval prolongation are commonly seen around 24-36 hours following onset of TTS symptoms.[12,14] Often, ECG changes in TTS are 'multi-regional,' suggesting abnormalities extending beyond the distribution of a single coronary artery.[12] The most diagnostically useful biomarkers for TTS are the combination of a small elevation in cardiac troponin concentrations, together with a very large elevation

Table 1. Patient's vital signs during medical emergency response (MER) calls

	MER call 1 (day 2 post-ICU transfer)	MER call 2 (day 3 post-ICU transfer)
Symptoms	Dyspnoea Chest tightness	Dyspnoea Chest pain Feeling lightheaded
Reasons for MER call	Tachycardia Tachypnoea Hypertension Hypoxia Chest pain	Tachycardia Tachypnoea Hypertensive Hypoxia Chest pain
Heart rate (beats/min)	100	140
Respiratory rate (breaths/min)	26	32
Systolic BP (mmHg)	166	173
Diastolic BP ((mmHg)	110	101
Temperature	38.2°C	38.1°C
SpO$_2$	80%; 4 l/min Nasal catheter	79%; 6 l/min Simple O$_2$ mask
Glasgow Coma Scale	14	14
Blood glucose (mmol/l)	5.5	7.6
12-lead ECG	Sinus tachycardia	Ventricular bigeminy
MER management	O$_2$ 10 l/min NRB GTN patch IV frusemide ABG; CXR; ECG	Transfer to ICU for BiPAP ventilation

BP = blood pressure; SpO2 = peripheral capillary oxygen saturation; ECG = electrocardiogram; NRB = non-rebreather mask; GTN = glyceryl trinitrate; IV = intravenous; ABG = arterial blood gas CXR = chest X-ray; BiPAP = bilevel positive airway pressure

in NT-proBNP and BNP concentrations[15] as was seen in the case we present here. The high ratio of natriuretic peptide to troponin may be useful in discriminating between TTS and acute coronary syndrome.[15] It is likely that the disproportionate rise in NT-proBNP reflects inflammation rather than heart failure. The performance of NT-proBNP estimation is highly recommended when evaluating the cause of any cardiac injury in the ICU setting.

Coronary angiography with left ventriculography has in the past been considered to be the gold standard diagnostic tool for diagnosis of TTS,[3] but this is essentially a diagnosis of exclusion. Coronary angiography in TTS typically shows normal coronary arteries or mild to moderate coronary artery disease, while ventriculography will show regional wall motion abnormalities characteristic of TTS.[2] Most cases of TTS involve apical and mid-ventricular regional wall motion abnormalities (termed apical ballooning), often with hyperkinetic basal segments, although TTS may occasionally demonstrate basal (inverted TTS), localised, or even global wall motion abnormalities. Approximately one third of patients will have concomitant wall motion abnormalities of the right ventricle.[16]

For patients in whom emergency coronary angiography is not a practical option, including critically ill ICU patients,

transthoracic echocardiography (TTE) can provide a presumptive diagnosis of TTS. The key echocardiographic feature in distinguishing TTS from acute coronary syndrome is the large area of myocardial systolic dysfunction that extends beyond the territory of a single coronary artery and symmetrical regional abnormalities in TTS.[2] TTE is also used to detect potential TTS complications including left ventricular outflow obstruction (LVOTO), mitral regurgitation, right ventricular involvement, apical thrombus formation and cardiac rupture, as well as monitoring the recovery of LV function.[11,17]

In the last decade, cardiac magnetic resonance imaging (CMR) has become the key diagnostic modality for patients with suspected TTS.[18] TTS is associated with extensive myocardial oedema (a result of both myocardial inflammation and increased vascular permeability) as well as the absence of late gadolinium enhancement without evidence of acute myocardial infarction.[7,8,18] In addition to visualisation of regional wall motion abnormalities, CMR allows for precise quantification of right and left ventricular function, exclusion of myocarditis and the assessment of other abnormalities such as pericardial and pleural effusion and thrombi in the left and right ventricle.[18] Performing CMR may be extremely challenging, particularly because of severe illness, obesity and/or claustrophobia, as in the case reported here, but where possible, a patient with suspected TTS should have the diagnosis established definitively via CMR.

Significance of Takotsubo syndrome

When first described in 1990, TTS was thought to be a relatively benign condition with complete recovery within a few weeks in most cases. However, this concept of TTS being a transient disorder is incorrect.[8,19,20] With improved recognition of TTS, it has been found that in-hospital mortality is similar to that of patients with acute coronary syndrome (4-5%),[2,17] although attributable mortality remains unclear. A physical trigger for TTS (such as acute illness or medical procedures) has been found to be an independent predictor for in-hospital complications, with TTS secondary to neurological disease having the worst short- and long-term prognosis.[17] Several early complications may develop from TTS. A syndrome resembling cardiogenic shock occurs in up to 10% of TTS patients and is associated with a significant increase in 28-day mortality compared with patients without cardiogenic shock.[13] LVOTO, transient mitral regurgitation, and right ventricular involvement may theoretically contribute to shock,[17] but hypotension and shock in TTS are likely multifactorial and not purely due to impaired cardiac output.[9,21,22] Nguyen et al.[9] have demonstrated that Syndecan-1, a component of glycocalyx, is released into plasma during the acute stages of TTS. TTS patients often exhibit features of pulmonary oedema in the setting of pulmonary capillary wedge pressures that are not substantially elevated. In these cases, pulmonary oedema is not haemodynamically determined and likely results from fluid extravasation into the

pulmonary interstitium due to inflammatory changes resulting from 'shedding' of the endothelial glycocalyx[9] that in many ways is analogous to glycocalyx shedding in the setting of septic shock.[23] Pleural or small pericardial effusions may also be seen. Hypotension may result from a combination of fluid extravasation plus increased vascular sensitivity to the dilator effects of nitric oxide.[24,25] For these patients, fluid replacement may be considered, but for those who develop hypoxia, ventilatory assistance may be required for the first 2-3 days, until glycocalyx shedding ceases, and the overall inflammatory crisis which underlies TTS is attenuated.

Intraventricular thrombosis is reported to occur in around 3% of patients in the acute phase of TTS[26] with the attendant risk of embolic complications, including stroke. Ventricular tachyarrhythmias (monomorphic and polymorphic ventricular tachycardia and ventricular fibrillation) occur in an estimated 10% of patients with TTS and are linked to worsened survival in both acute and convalescent phases of TTS.[27] New onset of atrial arrhythmia (atrial fibrillation and atrial flutter) occurs in up to 25% of patients with TTS and is associated with a worsened short-term[28,29] and long-term prognosis.[28-30] Atrioventricular block has less frequently been described in the setting of TTS and may lead to torsade de pointes.[31] Cardiac arrest at the time of TTS presentation or during the acute phase of the syndrome is associated with increased in-hospital and long-term mortality compared with TTS patients without cardiac arrest.[32]

At long-term follow-up in the International Takotsubo Registry (InterTAK), the rate of major adverse cardiac and cerebrovascular events was 9.9% per patient-year and death (all-cause) was 5.6% per patient-year.[13] Longer-term mortality appears to occur predominantly in the first four years after TTS diagnosis and is partially related to concomitant non-cardiac illnesses including malignancy.[2,33]

Takotsubo syndrome in critically ill patients

Acute illness is a potential trigger for TTS, particularly in conditions with high sympathetic activity. TTS has been identified in patients with respiratory insufficiency, sepsis, neurological disease, major surgery,[1,34,35] and numerous other disease processes. Indeed, neurogenic stress cardiomyopathy, a form of acute reversible myocardial dysfunction associated with a variety of neurological conditions that include subarachnoid haemorrhage,[36,37] intracerebral haemorrhage,[38] acute ischaemic stroke,[39] traumatic brain injury,[40] seizure,[41] transient global amnesia,[42] electroconvulsive therapy,[43] hydrocephalus,[44,45] encephalitis,[46] multiple sclerosis,[47-50] myasthenia gravis[51] and other less common neurological conditions, has been recognised for decades. There have been conflicting views on whether neurogenic stress cardiomyopathy is in fact TTS,[52] but there now seems to be general acceptance that neurogenic stress cardiomyopathy and TTS are the same entity.[53,54]

TTS resulting from an acute illness (secondary TTS) may be common.[34,35] Estimates of incidence in ICU vary between 1.5%[55] to 28%.[56] Studies using retrospective data report a lower incidence and likely missed cases,[1,34] whereas most prospective studies using TTE to screen all ICU patients report a higher incidence.[34,57-60] A recent prospective single-centre study of 280 ICU patients who had TTE, ECG and troponin measurement performed on admission, at 24 and 48 hours following admission, at discharge and in the case of clinical deterioration, as well as measuring BNP in all patients on admission and in the case of LV failure, found a TTS incidence of 4.6% (7.6% among females only).[34] It is uncertain whether there are times when the risk of developing TTS in ICU patients is greater: for example, at ICU admission, peak severity of the primary illness, when complications (such as sepsis) occur, during catecholamine administration, during invasive procedures, or other events. In the case that we have presented, TTS occurred following resolution of acute illness and discharge from ICU to general wards suggesting that the risk of developing TTS may not be confined to the most severe phase of illness.

Chest pain and dyspnoea are the usual presenting symptoms for TTS, but ICU patients rarely exhibit or communicate symptoms of chest pain or breathlessness that may be associated with TTS onset due to intubation, sedation, analgesia, and the primary underlying illness that may obscure these symptoms in critically ill patients. The first indications of TTS may be the presence of associated complications that include acute heart failure, pulmonary oedema, stroke, cardiogenic shock, arrhythmia, or cardiac arrest manifested by symptoms of impaired consciousness, neurologic complications, and sudden respiratory or haemodynamic deterioration.[10,35,59] A reasonable approach to TTS detection includes a baseline ECG and troponin on admission to ICU, and daily ECGs throughout ICU admission to observe for pathognomonic features of TTS. In the case of ECG abnormalities or clinical deterioration suggestive of TTS, troponin and BNP should be measured and TTE performed if coronary angiogram or CMR are not possible. If clinicians do not recognise TTS as the cause of the associated cardiopulmonary or neurological deterioration, appropriate management may be delayed.

ICU patients with diagnosed TTS are more likely to experience shock, arrhythmias, and require ventilation more frequently than ICU patients with causes of LV dysfunction other than TTS.[35] To date, there does not appear to be convincing evidence of higher mortality for patients with TTS compared with patients with similar comorbidities without TTS,[1,34,36] but ICU patients with TTS have a more complex course of hospitalisation and incur higher healthcare costs compared with ICU patients without TTS.[1]

In the absence of evidence from randomised clinical trials to support therapeutic strategies in the TTS population, current management is based on clinical experience and expert

consensus,[2,17] and consists of supportive care and prevention of complications. Treatment algorithms have been proposed, notably the expert consensus document from the International Takotsubo (InterTAK) Registry[17] and the position statement from the Heart Failure Association of the European Society of Cardiology.[2,17] In the absence of contraindications, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended for use in patients with normal or high systemic vascular resistance and an LVEF <45% and beta blockers in patients with LVEF <45%.[2,17] It may be harmful to administer either catecholamines[61] or organic nitrates during the acute stages of TTS. Inflammatory changes found within the myocardium in TTS patients appear to stem from abnormal post-receptor signalling in response to β-adrenoceptor agonist binding[5,62] coupled with activation of nitric oxide synthase and release of the hypotensive autacoid nitric oxide, which may contribute to hypotension directly or via the formation of peroxynitrite.[25] Given the putative role of catecholamine-induced myocardial damage in the aetiology of TTS, there is general consensus that mechanical circulatory support should be considered in preference to these agents.[52-54,56] An intra-aortic balloon pump is the most commonly used device, although it is not recommended in patients with LVOTO.[2,17] There are limited reports of veno-arterial extracorporeal membrane oxygenation[63] and Impella mechanical circulatory support[64] being used successfully in TTS but these are expensive and not always available. The Ca2þ-sensitiser levosimendan has been used safely and effectively as an alternative inotrope to catecholamine agents in TTS,[60,61] but is not recommended for patients with LVOTO.[17] The role of prophylactic anticoagulation in higher risk TTS cases has not yet been determined but given the risk of stroke or arterial embolism may be considered in those at higher risk of developing thrombus in akinetic apical TTS.[2,17]

Discussion

The case study presented here illustrates some of the challenges in recognising and managing a patient with TTS in the ICU. The patient in this case experienced an index ICU admission that was prolonged and complicated by multiple medical problems including sepsis, respiratory failure, anaemia, acute renal failure and functional bowel obstruction. She was readmitted to the ICU two days later following two MER calls due to acute respiratory deterioration associated with chest pain, hypertension and tachycardia, and subsequently diagnosed with TTS.

The patient in this case was exposed to emotional and physical stressors associated with critical illness, including invasive procedures and the use of catecholamines in ICU. It is not clear why TTS developed following transfer from the ICU when the patient was purportedly in the process of recovery rather than during the ICU admission when physical stresses were likely greater. Discharge from the ICU represents a positive step in terms of physical recovery, but the transition from high acuity care in the

ICU to a general ward with less nursing presence and monitoring can be psychologically distressing for patients.[65,66] Indeed, post-traumatic stress disorder has been reported in 20-43% of patients after ICU discharge.[67,68] This patient was noted to be extremely anxious following ICU transfer. It is plausible that psychological stress may have contributed to the development of TTS in this patient, and the propensity for psychological stress to cause TTS must not be underestimated.

The exact timing of TTS onset in this patient is uncertain as TTS was not considered as a cause of the clinical deterioration, resulting in a delay in the appropriate investigations. An echocardiogram was not undertaken until four days after readmission, but the onset of chest discomfort and dyspnoea at the time of the MER calls, along with respiratory deterioration, may have been indicators of TTS onset. Troponin and NT-proBNP were taken on day 1 after readmission to the ICU and both were elevated. A definite diagnosis of TTS cannot be made without information on the status of the coronary arteries and even when the coronary anatomy is known, differentiation is difficult between post-ischaemic myocardial stunning or aborted myocardial infarction. Some of the clinical findings, such as acute heart failure and troponin and NT-proBNP elevation, could have resulted from ischaemia, but in the context of the pathognomonic patterns of LV dysfunction found on echocardiography and the ECG as well as temporal resolution of LV function and echocardiographic abnormalities, TTS is the most likely diagnosis.

Conclusion

Increasing reports of TTS in the ICU suggest that it may not be uncommon in critically ill patients, particularly in conditions associated with high sympathetic activity. TTS is associated with serious complications including arrhythmias, shock and emboli. ICU patients with TTS have a more complex course of hospitalisation and incur higher healthcare costs compared with those without TTS. Recognising TTS in ICU patients can be challenging. Clinicians should retain a high index of suspicion of TTS if patients show unexpected haemodynamic or respiratory deterioration. Increased awareness and understanding of TTS and depth of knowledge of this condition may reduce early diagnostic errors, minimise delays in onset of appropriate treatment and prevent further complications. TTS may not be limited to the ICU admission and risk following ICU discharge.

Disclosures

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