Heart failure due to ‘stress cardiomyopathy’: a severe manifestation of the opioid withdrawal syndrome

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Abstract

Takotsubo cardiomyopathy (TTC) is a transient left ventricular (LV) dysfunction due to akinesia of the LV mid-apical segments (‘apical ballooning’) in the absence of critical coronary stenoses which can be complicated in the acute phase by heart failure, mitral regurgitation, life-threatening ventricular arrhythmias, or apical LV thrombosis. The syndrome is typically precipitated by intense emotional or physical stress; however, other causes of sympathetic overstimulation including administration of exogenous sympathomimetics or withdrawal of sympathetic antagonists can trigger TTC. We report the case of a patient who unexpectedly developed an ‘apical ballooning’ with severe reduction in the LV systolic function and heart failure after the withdrawal of methadone. The case supports the concept that increased sympathetic activity secondary to opioids withdrawal can trigger a stress-induced severe LV dysfunction. Physicians should be aware that the abrupt discontinuation of a long-term therapy with opioids may lead to serious cardiac complications. The administration of clonidine may be considered to prevent early clinical manifestations of addictive withdrawal, including TTC.

Keywords

Apical ballooning, heart failure, methadone, opioids, stress cardiomyopathy, Tako Tsubo

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Introduction

Takotsubo cardiomyopathy (TTC) is a transient left ventricular (LV) dysfunction due to akinesia of the LV mid-apical segments (‘apical ballooning’) which can cause severe reduction in LV systolic function. The typical clinical picture of TTC include chest pain, ECG changes consisting of mild ST-segment elevation followed by diffuse deep T-wave inversion, QTc-interval prolongation, and troponin release in the absence of significant coronary stenoses. The syndrome often affects post-menopausal women and is triggered by sympathetic overstimulation, like intense physical or emotional stress, so that it is called the ‘broken heart syndrome’. Although LV systolic dysfunction usually fully recovers within few days, heart failure can still complicate the early phase.^{1–3}

TTS, acute coronary syndrome, and sepsis-induced ventricular dysfunction are all possible causes of heart failure in critically ill patients. Therefore, differential diagnosis is essential to establish an appropriate therapy.

We report the case of a patient with a history of drug abuse who developed TTC after withdrawal of methadone.

Case presentation

A 41-year-old female presented to the emergency department for pneumococcal meningitis. She had a history of heroine abuse 20 years ago and she had been on anti-addictive therapy with methadone (100 mg/day) for 18 years. She had positive serum markers for HCV and HIV

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Figure 1. Electrocardiogram at admission.

Twelve-lead electrocardiogram performed at admission showing mild QT-interval prolongation (QTc=490 ms). Non-significant, ascending ST-segment depression in leads V3–V5 and aVF is also evident.

with normal liver function and lymphocyte count and no risk factors for coronary artery disease. At initial evaluation, the blood pressure was 120/60 mmHg; the heart rate was 61 bpm; the body temperature was 38.3°C. Laboratory investigations demonstrated white blood cell count of $17.9 \times 10^9/l$ (normal value $4.4\text{--}11 \times 10^9/l$), C-reactive protein level of 200 mg/l (normal value <6 mg/l), and procalcitonin level, which is a specific marker for bacterial infection, of 5.7 mg/l (normal value <0.5 mg/l). The ECG showed only mild QTc prolongation (490 ms, probably secondary to methadone therapy⁴) in the absence of other significant abnormalities and no signs of heart failure were present (Figure 1). An echocardiogram was performed to exclude an underlying endocarditis with no abnormalities detected.

The patient was admitted to the infectious disease unit where the haemodynamic conditions remained stable and serial ECGs showed no changes. The cerebral infection responded to standard therapy but the course was complicated with a post-meningitis inflammatory reaction causing C5–C6/C6–C7 spondylodiscitis with epidural dissemination, transient quadriparesis, and decline of the level of consciousness. In order to avoid all sedative drugs, the methadone therapy was discontinued.

Seventy-two hours later, when the neurological conditions had improved and the inflammatory biomarkers had normalized, the patient developed withdrawal signs in the form of pupillary dilatation, lacrimation, and diarrhoea. Shortly afterwards, she suffered a severe respiratory distress (SpO₂ 80% with 15 l/min O₂, blood pressure 110/60 bpm, heart rate 120 bpm) that required placement of an endotracheal tube and

admission to the intensive care unit (APACHE III score 56, SAPS II score 44, SOFA score 6). Chest X-ray showed the presence of pulmonary oedema and an urgent echocardiogram revealed severe LV systolic dysfunction (ejection fraction 20%) due to akinesia of all the mid- and apical LV segments (Figure 2A). Subsequently, diffuse T-wave inversion and QTc-interval prolongation (540 ms) were observed at the ECG; moreover, a rise in troponin I (peak value 1.8 µg/l; normal value <0.045 µg/l) was detected (Figure 2B). A stress cardiomyopathy from opioids withdrawal was suspected and the patient was treated with clonidine infusion in addition to furosemide and dobutamine. During the following days, she underwent complete respiratory, haemodynamic, and neurological recovery. Two weeks later, the ECG and the echocardiogram had completely normalized and a stress test was negative for myocardial ischaemia.

Discussion

TTS is defined as a transient LV systolic dysfunction due to mid-apical akinesia ('apical ballooning') in the absence of critical coronary stenoses precipitated by intense acute emotional or physical stress.³ Atypical (mid-ventricular or 'apical sparing') variants have also been described.⁵ The syndrome usually affects post-menopausal women and presents with chest pain, ST–T-segment changes at the ECG and slightly elevated cardiac enzymes so that it is often misinterpreted as an acute myocardial infarction. However, the regional distribution of both echocardiographic and ECG abnormalities goes beyond the distribution of a single coronary artery.^{1–3} Cardiac magnetic resonance reveals myocardial

Figure 2. Electrocardiographic (A) and echocardiographic (B, C) findings at admission in the intensive care unit.

Twelve-lead electrocardiogram showing repolarization abnormalities (T-wave inversion and QTc-interval prolongation) in leads V2–V5, aVL, I, and II. Transthoracic echocardiography (TTE) performed at admission to the intensive care unit, four-chamber apical view, in systole (B) and diastole (C) showing mid-apical left ventricular segments akinesia (arrows) conferring the typical 'apical ballooning' pattern.

inflammation (oedema) in the affected LV segments which resolves at follow-up in concomitance with normalization of the LV systolic function and ECG changes.⁶ Although full recovery of the LV dysfunction is typically observed within few days, TTC is not an entirely benign condition as complications such as acute heart failure, mitral regurgitation, life-threatening ventricular arrhythmias, or apical LV thrombosis may be observed. The therapy is usually supportive but it is important to identify and correct any potential triggering factors to avoid recurrences.^{1–3,5,7}

The main hypothesis for the pathophysiology of TTS is that an increase in the level of serum catecholamines secondary to a stressful event may cause either microvascular

coronary spasm or direct myocardial toxicity and give rise to a reversible myocardial inflammation and dysfunction.² The sympathetic overstimulation can also be caused by pheochromocytoma, exogenous sympathomimetics, or withdrawal of sympathetic antagonists, such as opioids.^{8–14} Methadone is a synthetic opioid prescribed as an analgesic and anti-addictive drug. By binding to the opioids receptor, it reduces the euphoric effect of illicit drugs such as heroin and, at the same time, mitigates withdrawal symptoms. Unfortunately, methadone is also a highly addictive drug.^{15,16}

Our case supports the concept that increased sympathetic activity secondary to methadone withdrawal can trigger a

stress-induced LV dysfunction. It has to be recognized that the stress of the pneumococcal meningitis that the patient suffered may have also played a role in causing the TTS. However, the haemodynamic parameters have been normal for all the acute phase of the infection and the heart failure developed only after methadone withdrawal, when patient's conditions were improving and inflammation biomarkers had normalized and in concomitance with other withdrawal symptoms like pupillary dilatation, lacrimation, and diarrhoea.¹⁵ The onset of TTC 72 hours after the opioid discontinuation further supports this hypothesis, because plasma concentrations of methadone decrease after withdrawal with a mean half-life of around 22 hours (range of 5–130 hours, with known wide inter-individual variation) and withdrawal symptoms usually occur after 72–96 hours.^{15,16}

Although the association between methadone withdrawal and TTC has already been reported, in two previous cases the syndrome occurred soon after administration of an opioid antagonist while in our patient heart failure developed late after methadone discontinuation as a consequence of the drug pharmacokinetic.^{13,14} Furthermore, to our knowledge, this is the first report to highlight the efficacy of clonidine administration in addition to standard therapy in counteracting the causative mechanism of TTC. Clonidine is a central sympatholytic drug which decreases presynaptic alpha-2 receptors in the locus coeruleus and is an effective treatment for opioid withdrawal.^{15,17–19} Even if this treatment was safe and effective in our case, we recommend prudence before considering the option of clonidine therapy in patients suffering from LV dysfunction because it can reduce the cardiac output due to its anti-adrenergic effect. Further studies on larger groups of patients are needed to properly assess the safety and efficacy profile of clonidine in treatment of TTC due to opioid withdrawal.

Conclusions

TTC is a stress-induced reversible acute myocardial dysfunction that must be recognized as a cause of heart failure in critically ill patients. Increased sympathetic activity secondary to the withdrawal of sympathetic antagonists, such as methadone, can lead to the development of TTC. Hence, long-term opioid therapy should not be discontinued abruptly to avoid such potentially malignant complication. In patients with an 'apical ballooning' suspected to be triggered by psychotropic drugs discontinuation, the infusion of clonidine may be administered in addition to standard supportive therapy to counteract the causative mechanism.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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