Takotsubo cardiomyopathy following unintentionally large subcutaneous adrenaline injection: a case report

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Introduction

Stress cardiomyopathy, also known as takotsubo syndrome, is characterized by transient left ventricular dysfunction not attributable to obstructive epicardial coronary artery disease. Several pathological mechanisms have been proposed, including multivessel coronary artery vasospasm, coronary microcirculatory dysfunction, and excess catecholamine secretion.

Case presentation

A 68-year-old male presented to our institution for elective surgical removal of a cutaneous basal cell carcinoma on the right side of his face. Within minutes following the administration of local anaesthesia, the patient developed severe hypertension, tachycardia, ST-segment elevation on the electrocardiogram, and non-sustained broad-complex tachycardia. Urgent cardiac catheterization revealed non-obstructive coronary artery disease and left ventriculography demonstrated apical hypokinesia and moderate systolic dysfunction consistent with the takotsubo syndrome. On review of the medications administered, it was noted that an unintentionally large dose of adrenaline (4mg) had been injected subcutaneously with lignocaine. He was monitored in the coronary care and recovered fully with supportive care only. Bisoprolol was initiated on day 1 post procedure. On follow-up one month later, his left ventricular function had normalized.

Discussion

Our case report provides direct evidence supporting the pathogenetic role of excess catecholamine secretion in the development of the takotsubo syndrome. A review of the literature reveals that both exogenous catecholamine administration (adrenaline injection in the context of anaphylaxis or infiltrative anaesthesia) and excess endogenous catecholamine (pheochromocytoma) secretion has been associated with the takotsubo syndrome. Local infiltrative anaesthesia with the addition of adrenaline is commonly used as a vasoconstrictor in a wide variety of surgical procedures. To reduce the risk of adverse events, the lowest effective concentration of adrenaline to provide pain control and vasoconstriction is recommended.

Keywords

Stress cardiomyopathy • Takotsubo cardiomyopathy • Takotsubo syndrome • Epinephrine • Adrenaline • Case report

Learning points

• Stress cardiomyopathy, also known as the takotsubo syndrome, is characterized by transient left ventricular dysfunction not attributable to obstructive epicardial coronary artery disease.

• The direct and immediate temporal relationship between the exogenous administration of catecholamines and the subsequent development of myocardial systolic dysfunction implicates catecholamines in the pathogenesis of this disorder.

• Local infiltrative anaesthesia with the addition of adrenaline is commonly used as a vasoconstrictor in a wide variety of surgical procedures. To reduce the risk of adverse events, the lowest effective concentration of adrenaline to provide pain control and vasoconstriction is recommended.
Introduction

Stress cardiomyopathy, also known as takotsubo syndrome, is characterized by transient left ventricular (LV) dysfunction not attributable to obstructive epicardial coronary artery disease.\(^1\,^2\) Although typically associated with acute emotional stress, triggers may also include physical stressors such as major surgery,\(^1\,^2\) major illness,\(^1\,^2\) and medical procedures.\(^3\) Takotsubo syndrome most commonly manifests with LV apical ballooning; however, mid-ventricular and basal dilatation have been also described.\(^1\,^2\) The prevalence of takotsubo syndrome is markedly higher in females compared to males (around 80–90% female prevalence in some studies).\(^1\) Patients with the takotsubo syndrome have a higher rate of neurologic or psychiatric disorders.\(^4\) Several pathological mechanisms have been proposed, including multivessel coronary artery vasospasm,\(^1\,^2\) coronary microcirculatory dysfunctions,\(^1\,^2\) and excess catecholamine secretion.\(^1\,^2\)

Case report

A 68-year-old male patient with a background of hypertension, chronic hepatic C, and peripheral vascular disease presented to our institution for elective surgical removal of a cutaneous basal cell carcinoma on the right side of his face. He took candesartan 16 mg daily and reported no allergies. Induction of anaesthesia with midazolam, alfentanil, propofol, and rocuronium and orotracheal intubation was followed by subcutaneous infiltration of local anaesthesia with adrenaline to the right cheek. Within minutes after the administration of local anaesthesia, the patient became markedly hypertensive (blood pressure 252/135 mmHg), tachycardic (heart rate 135 b.p.m.), and developed mild ST-segment elevation in leads V₁–V₃ on the electrocardiogram with reciprocal ST-segment depression in leads V₄–V₆ and T wave flattening/inversion in leads I and aV₆ (Figure 1). Non-sustained, broad-complex tachycardia was noticed on cardiac monitoring. The QTC interval was 404 ms. On review of the medications administered, it was noted that an unintentionally large dose of adrenaline (4 mg) had been injected subcutaneously with the lignocaine. Urgent blood pressure control was achieved with intravenous esmolol, clonidine, metoprolol, and further propofol. Profound hypotension followed (blood pressure 65/35 mmHg), necessitating multiple intravenous boluses of metaraminol and a dose of ephedrine. He was extubated and transferred to the recovery room. His ST-segment deviation persisted. Physical examination was unremarkable. Urgent bedside transthoracic echocardiography demonstrated moderate LV apical dilatation and systolic function (estimated LV ejection fraction 40%). Initial cardiac troponin T was mildly elevated at 18 ng/L (reference range 0–14 ng/L); repeat measurement was 11 ng/L. Results of the tests of renal, hepatic function were within normal limits. Full blood count was unremarkable. Serum calcium, magnesium, and phosphorus levels were normal. Urgent cardiac catheterization revealed non-obstructive coronary artery disease. Left ventriculography demonstrated apical ballooning and moderate systolic dysfunction, consistent with acute takotsubo syndrome (Figure 2, Supplementary material online, Video S1). He was observed in the coronary care unit for 24 h and bisoprolol 2.5 mg daily was initiated the following day. He recovered uneventfully and was discharged on Day 2 post-procedure. On follow-up 1 month later, his LV function had normalized on transthoracic echocardiography (Figure 3). He remained on bisoprolol and candesartan and underwent basal cell carcinoma excision under general anaesthesia uneventfully 1 month later. Subcutaneously injected adrenaline was used with infiltrative anaesthesia in the latter operative procedure, albeit at a much lower dose (1 mg). Six months following the index event, he was doing well.

Discussion

Adrenaline is a monoamine organic compound derived from the amino-acid tyrosine in the chromaffin cells of the adrenal medulla and the post-ganglionic fibres of the sympathetic nervous system. Adrenaline is used in a variety of medical settings, due to its vasoconstrictive properties (mediated by the alpha-1 receptor), and its positive inotropic effects (mediated by the beta-1 receptor). Stress cardiomyopathy occurring following exogenous adrenaline administration has been reported in the literature. We searched the PubMed

Timeline

| Time                  | Events                                                                 |
|-----------------------|------------------------------------------------------------------------|
| Initial presentation  | Admitted for elective surgical excision of basal cell carcinoma on the right side of face. |
| Procedure (Day 0)     | Local anaesthesia injection with adrenaline following induction of general anaesthesia. |
|                       | Within minutes, develops severe hypertension, tachycardia, ST-segment elevation on the electrocardiogram, and non-sustained broad-complex tachycardia. On review of the medications administered, it was noted that 4 mg of adrenaline had been inadvertently injected subcutaneously with the lignocaine. |
|                       | Urgent bedside transthoracic echocardiogram demonstrates left ventricular (LV) apical dilatation and moderate systolic dysfunction. Urgent cardiac catheterization demonstrates non-obstructive coronary artery disease. Left ventriculography reveals apical ballooning and apical systolic dysfunction. |
| Day 1                 | Monitored in coronary care, bisoprolol initiated. |
| Day 2                 | Recovers uneventfully, discharged. Repeat transthoracic echocardiogram demonstrates normalization of LV function. |
| One month post-       | Successfully undergoes basal cell carcinoma excision with 1 mg of adrenaline mixed with local anaesthesia. |
| procedure: follow-up  | Well, normal. Left ventricular function normal. |
| in cardiologist office|                                                                 |
| Eight weeks post-     |                                                                 |
| procedure, re-        |                                                                 |
| admitted to hospital  |                                                                 |
| Six months post-      |                                                                 |
| procedure: follow-up  |                                                                 |
| in cardiologist office|                                                                 |
database with terms ‘stress cardiomyopathy’, ‘takotsubo’, ‘adrenaline’, and ‘epinephrine’, restricting the search to the last 10 years, and retrieved all papers thus encountered. We also cross-checked references found in each paper. We excluded abstracts and case reports which did not contain sufficient information to conclusively diagnose takotsubo cardiomyopathy. We found 29 reports describing a total of 35 cases, and we summarized the salient features of these cases in Table 1. About half the reported cases (47.5%) described involve the use of adrenaline in the treatment of anaphylaxis due to food ingestion or hymenoptera (bee) sting, and treatment of severe asthma. Additional cases ascribe the development of stress cardiomyopathy to the infiltration of local anaesthesia, nasal packing, and intra-articular irrigation (in these settings, adrenaline is used as an adjunct to control or prevent excessive bleeding due to its potent vasoconstrictor properties). Self-injection of adrenaline has also been described. Administration routes described include

Figure 1 Twelve lead electrocardiogram demonstrating sinus rhythm and mild ST-segment elevation in leads V1–V3 on the electrocardiogram with reciprocal ST-segment depression in leads V4–V6 and T wave flattening/inversion in leads I and aVL.

Figure 2 Left ventriculography stills in the [right anterior oblique 29°, cranial 1°] plane. (A) It depicts normal left ventricular dimensions at the end of ventricular diastole. (B) It demonstrates the typical apical ballooning of the takotsubo syndrome at the end of ventricular systole.
intravenous, intramuscular, subcutaneous, intra-articular, intra-nasal, and nebulized. Typical doses administered range between 0.3 mg and 1 mg, although much higher doses have been reported (up to 5 mg). The median and average doses reported were 1 mg and 2.9 mg, respectively. Apical ballooning is the most commonly occurring form of LV dysfunction, occurring in 60% of cases, followed by mid and basal dilatation. The temporal relationship between adrenaline exposure and the development of adverse signs and symptoms is immediate (i.e. within minutes), in almost all cases. Most reported cases (89%) were mild-to-moderate in severity requiring supportive treatment only, with ensuing complete recovery within 3–5 days. Rarely, severe cardiogenic shock necessitating extra-corporeal membrane oxygenation (3/35 cases, or 11.4%), or catastrophic cardiovascular collapse resulting in death (1/35 cases, or 2.9%) have been described. Takotsubo syndrome following excess endogenous catecholamine secretion has been described in the setting of pheochromocytoma.33,34

The direct temporal relationship between the exogenous administration of a large amount of adrenaline and the subsequent rapid onset of myocardial systolic dysfunction implicates adrenaline as the aetiological trigger in the pathogenesis of this disorder. In stress cardiomyopathy, it is hypothesized that exposure to acute emotional or physical stress leads to activation of the sympathetic nervous system, resulting in local myocardial adrenaline release and an increase in circulating plasma catecholamines. Animal studies support a role for catecholamines in the pathophysiology of the takotsubo syndrome. High-dose adrenaline injection in rats has been shown to induce the takotsubo syndrome, whereas equivalent-dose injection of noradrenaline does not.35 At a cellular level, stress cardiomyopathy in rats produces a rapid activation of protein kinases, followed by a transient up-regulation of immediate early genes in the coronary arteries and myocardium.36 Conversely, inhibition of both alpha- and beta-adrenoreceptors eliminates the stress-induced up-regulation of

![Figure 3](https://example.com/f7052545.png)

_Transthoracic echocardiogram. Four chamber view still demonstrating normal left ventricular size and systolic function._

| References | Age, gender | Clinical setting | Epinephrine dose | Administration route | Takotsubo pattern | Outcome |
|------------|-------------|------------------|-----------------|---------------------|------------------|---------|
| Spina et al. (current report) | 68, M | Inadvertently large dose (in context of infiltration of local anaesthesia) | 4 mg | SC | Apical | Complete recovery |
| Jeremy et al. | 28, M | Self-injection in context of suicide attempt | 5 mg | IV | Apical | Cardiogenic shock requiring extra-corporeal membrane oxygenation. Complete recovery |
| Nassif et al. | 35, F | Excision of leiomyomas | 0.3 mg | Intra-myometrial | Mid | Complete recovery |
| Belliveau and De | 30, F | Infiltration into perineum with local anaesthetic following vaginal delivery | 1 mg | SC | Mid, basal | Complete recovery |
| Nazir et al. | 37, F | Anaphylaxis to food (tomatoes) | 0.3 mg | IM | Apical | Complete recovery |
| Keshar et al. | 66, F | Acute airway obstruction (neck tumour) | 1 µg/mL | Nebulised | Apical | Complete recovery |
| Ghanim et al. | 37, F | Anaphylaxis to Hymenoptera sting | 0.9 mg | IM | Mid, basal | Cardiogenic shock requiring extra-corporeal membrane oxygenation. Complete recovery |
| Gicquel-Chlemmer et al. | 48, M | Elective shoulder repair | 1 mg | IA | Apical | Cardiogenic shock, fatal |

Continued
Alpha- or beta-agonist stimulation leads to up-regulation of immediate early genes in the perfused rat heart. Further evidence supporting a mechanistic link between excess catecholamine secretion, and the takotsubo syndrome is provided by studies demonstrating higher plasma catecholamine levels in patients with stress cardiomyopathy compared to control patients. Findings on endomyocardial biopsy in patients with the takotsubo syndrome include contraction band necrosis, dense eosinophilic transverse

| References | Age, gender | Clinical setting | Epinephrine dose | Administration route | Takotsubo pattern | Outcome |
|------------|-------------|------------------|-----------------|---------------------|------------------|---------|
| Murthy et al. | 49, M | Bradycardia, hypotension | 0.3 mg | IV | Mid | Complete recovery |
| Alyonan et al. | 50, F | Anaphylaxis to insect bite, unspecified | 1 mg | IV | Apical | Complete recovery |
| Esnault et al. | 49, F | Hypotension during laparoscopic cholecystectomy | 1 mg | IV | Mid, basal | Cardiogenic shock requiring extra-corpoREAL membrane oxygenation. Complete recovery |
| Khoeiry et al. | 44, F | Anaphylaxis to iodine contrast | 1 mg | IM | Mid, basal | Complete recovery |
| Sundbøll et al. | 67, M | Elective biopsy of left maxillary sinus tumour (Moffat’s solution: adrenaline and cocaine packing) | 3.2 mg | IN | Mid, apical | Complete recovery |
| Kajander et al. | 31, F | Exercise-induced anaphylaxis | 0.3 mg | IV | Basal | Complete recovery |
| Patankar et al. | 44, F | Angioedema (ACE inhibitor) | 3.3 mg | SC | Apical | Complete recovery |
| Harle et al. | 39, F | Inadvertent injection (in context of adrenergic stress testing) | 1 mg | IV | Mid, basal | Complete recovery |
| Magri et al. | 26, F | Severe allergic reaction to proton-pump inhibitor | 0.5 mg | IM | Apical | Complete recovery |
| Scheiba et al. | 81, M | Anaphylaxis to Hymenoptera sting | 1 mg | IV | Apical | Complete recovery |
| Winogradow et al. | 70, F | Anaphylaxis to Hymenoptera sting | 0.3 mg | IV | Apical | Complete recovery |
| Geppert et al. | 70, F | Anaphylaxis to Hymenoptera sting | 1 mg | IV | Apical | Complete recovery |
| Subramaniam et al. | 26, F | Inadvertently large dose (in context of inotropic support) | 4.5 mg | IV | Mid, basal | Complete recovery |
| Von Knobelsdorff-Brenkendorf et al. | 31, F | Endoscopic nasal surgery | Not reported | IN | Mid | Complete recovery |
| Abraham et al. | 30, F | Attempted suicide | 40 mg | IV | Apical in three patients, basal in three patients | Complete recovery in all patients |
| Lainez et al. | 61, M | Anaphylaxis to anaesthesia | 1 mg | IV | Apical | Complete recovery |
| Litvinov et al. | 24, F | Anaphylaxis to food | 5 mg | IM | Basal | Complete recovery |
| Manivannan et al. | 41, M | Anaphylaxis to Hymenoptera (bee) sting | 1 mg | IV | Apical | Complete recovery |
| Osuori et al. | 46, F | Status asthmaticus | Not reported | IV | Apical | Complete recovery |
| Volz et al. | 27, M | Self-administration (IV drug user) | 2 mg | IV | Apical | Complete recovery |
| Zubrinich et al. | 76, F | Generalized urticarial and angioedema | 0.3 mg | IM | Apical | Complete recovery |

ACE, angiotensin converting enzyme; F, female; IM, intra-muscular; IN, intra-nasal; IV, intravenous; M, male; SC, subcutaneous.
bands and an interstitial mononuclear inflammatory response. These myocardial histological changes closely resemble those seen in local catecholamine cardiotoxicity in animal models and are distinct from the histological findings observed in myocardial infarction. Elevated catecholamine levels decrease the viability of myocytes through cyclic adenosine monophosphate (AMP)-mediated calcium overload.3,36 Catecholamines are also a potential source of oxygen-derived free radicals and, in animal models, cause myocyte injury.37 Although the base of the heart has greater density of sympathetic nerves compared to the apex, there is evidence that apical myocardium has enhanced responsiveness to sympathetic stimulation, potentially making the apex more vulnerable to sudden surges in circulating catecholamine levels.38,40 An apical–basal gradient in beta-adrenergic receptor activation at different adrenaline dosages may explain the differential regional responses seen in the takotsubo syndrome.35

Conclusion
We report a case of stress cardiomyopathy developing immediately following the subcutaneous administration of an inadvertently large dose of adrenaline. Our case report provides direct evidence supporting the pathogenetic role of excess catecholamine secretion in the development of the takotsubo syndrome. Local infiltrative anaesthesia with the addition of adrenaline is commonly used as a vasoconstrictor in a wide variety of surgical procedures. To reduce the risk of adverse events, the lowest effective concentration of adrenaline to provide pain control and vasoconstriction is recommended.

Supplementary material
Supplementary material is available at European Heart Journal – Case Reports online.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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