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CASE REPORT
Heart failure

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

Roberto Spina, Ning Song, Krishna Kathir, David W. M. Muller, and David Baron

Department of Interventional Cardiology, St Vincent's Hospital, Sydney, Australia

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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 (phaechromocytoma) 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.

* Corresponding author. Tel: +61 8382 2357, Fax: +61 8382 2359, Email: roberto.spina@hotmail.com. This case report was reviewed by Kyriakos Dimitriadis, Albert Galyavich, and Christian Fielder Camm.

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.[1] Several pathological mechanisms have been proposed, including multivessel coronary artery vasospasm,[1,2] coronary microcirculatory dysfunction,[3,4] and excess catecholamine secretion.[1,2]

Timeline

Time	Events
Initial presentation (elective surgery)	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 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.
One month post-procedure: follow-up in cardiologist office	Repeat transthoracic echocardiogram demonstrates normalization of LV function.
Eight weeks post-procedure, re-admitted to hospital	Successfully undergoes basal cell carcinoma excision with 1 mg of adrenaline mixed with local anaesthesia.
Six months post-procedure: follow-up in cardiologist office	Well, normal. Left ventricular function normal.

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 V_1–V_3 on the electrocardiogram with reciprocal ST-segment depression in leads V_4–V_6 and T wave flattening/inversion in leads I and aV_L (*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

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

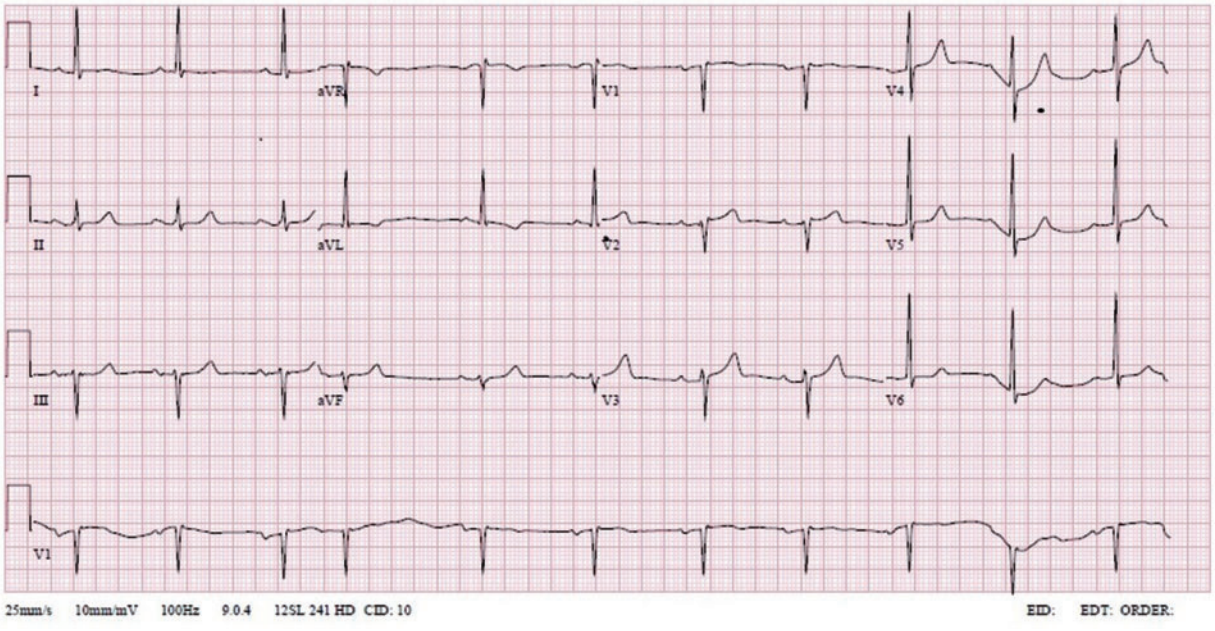

Figure 1 Twelve lead electrocardiogram demonstrating sinus rhythm and mild ST-segment elevation in leads V_1–V_3 on the electrocardiogram with reciprocal ST-segment depression in leads V_4–V_6 and T wave flattening/inversion in leads I and aV_L.

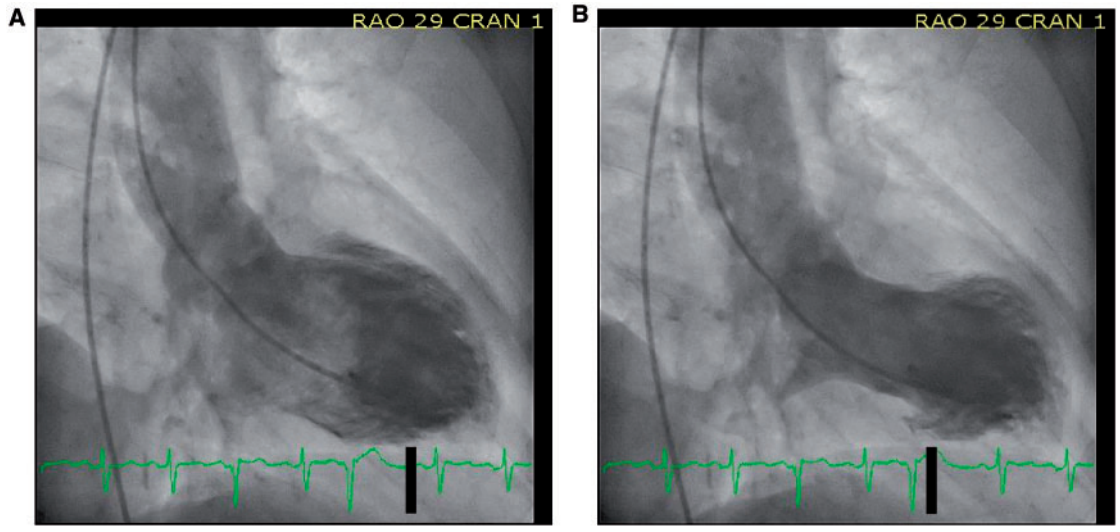

Figure 2 Left ventriculography stills in the [right anterior oblique 29°, cranial 1°] plane. (*A*) It depicts normal left ventricular dimensions at the end of ventricular diastole. (*B*) It demonstrates the typical apical ballooning of the takotsubo syndrome at the end of ventricular systole.

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]

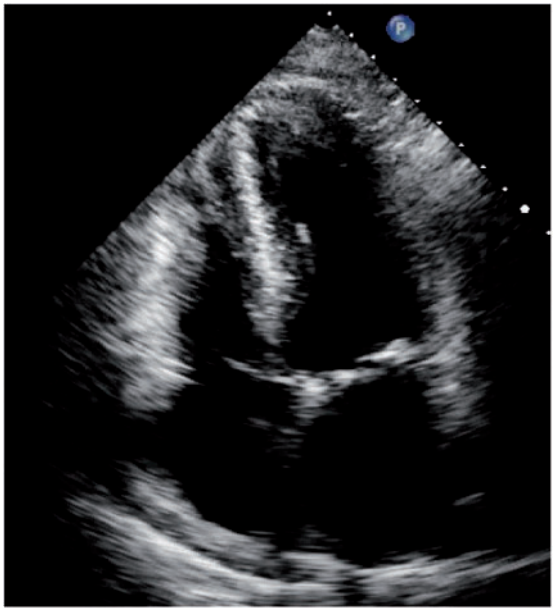

Figure 3 Transthoracic echocardiogram. Four chamber view still demonstrating normal left ventricular size and systolic function.

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

Table 1 Takotsubo cardiomyopathy following exogenous adrenaline administration

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.*[5]	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.*[6]	35, F	Excision of leiomyomas	0.3 mg	Intramyometrial	Mid	Complete recovery
Belliveau and De[7]	30, F	Infiltration into perineum with local anaesthetic following vaginal delivery	1 mg	SC	Mid, basal	Complete recovery
Nazir *et al.*[8]	37, F	Anaphylaxis to food (tomatoes)	0.3 mg	IM	Apical	Complete recovery
Keshtar *et al.*[9]	66, F	Acute airway obstruction (neck tumour)	1 µg/5 mL	Nebulised	Apical	Complete recovery
Ghanim *et al.*[10]	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.*[11]	48, M	Elective shoulder repair	1 mg	IA	Apical	Cardiogenic shock, fatal

Continued

Table I *Continued*

References	Age, gender	Clinical setting	Epinephrine dose	Administration route	Takotsubo pattern	Outcome
Murthy *et al.*[12]	49, M	Bradycardia, hypotension	0.3 mg	IV	Mid	Complete recovery
Alyonan *et al.*[13]	50, F	Anaphylaxis to insect bite, unspecified	1 mg	IV	Apical	Complete recovery
Esnault *et al.*[14]	49, F	Hypotension during laparoscopic cholecystectomy	1 mg	IV	Mid, basal	Cardiogenic shock requiring extra-corporeal membrane oxygenation. Complete recovery
Khoeuiry *et al.*[15]	44, F	Anaphylaxis to iodine contrast	1 mg	IM	Mid, basal	Complete recovery
Sundbøll *et al.*[16]	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.*[17]	31, F	Exercise-induced anaphylaxis	0.3 mg	IV	Basal	Complete recovery
Patankar *et al.*[18]	44, F	Angioedema (ACE inhibitor)	3.3 mg	SC	Apical	Complete recovery
Harle *et al.*[19]	39, F	Inadvertent injection (in context of adrenal stress testing)	1 mg	IV	Mid, basal	Complete recovery
Magri *et al.*[20]	26, F	Severe allergic reaction to proton-pump inhibitor	0.5 mg	IM	Apical	Complete recovery
Scheiba *et al.*[21]	81, M	Anaphylaxis to Hymenoptera sting	1 mg	IV	Apical	Complete recovery
Winogradow *et al.* (2 patients)[22]	70, F	Anaphylaxis to Hymenoptera sting	0.3 mg	IV	Apical	Complete recovery
	37, F	Anaphylaxis to Hymenoptera sting	1 mg	IV	Apical	Complete recovery
Geppert *et al.*[23]	70, F	Anaphylaxis to Hymenoptera sting	0.3 mg	IV	Apical	Complete recovery
Subramaniam *et al.*[24]	26, F	Inadvertently large dose (in context of inotropic support)	4.5 mg	IV	Mid, basal	Complete recovery
Von Knobelsdorff-Brenkendhoff *et al.* (2 patients)[25]	31, F	Endoscopic nasal surgery	Not reported	IN	Mid	Complete recovery
	59, M	Endoscopic nasal surgery	Not reported	IN	Mid	Complete recovery
Abraham *et al.* (6 patients)[26]	30, F	Attempted suicide	40 mg	IV	Apical in three patients, basal in three patients	Complete recovery in all patients
	24, F	Liposuction	1 mg	IV		
	48, F	Cosmetic facial surgery	1 mg	IV		
	44, F	Keloid scar repair	Not reported	IV		
	20, M	Injection into rectal vein during colonoscopy	5 mg	IV		
	54, F	Syncope	1 mg	IV		
Lainez *et al.*[27]	61, M	Anaphylaxis to anaesthesia	High-dose adrenaline and noradrenaline infusions	IV	Apical	Complete recovery
Litvinov *et al.*[28]	24, F	Anaphylaxis to food	5 mg	IM	Basal	Complete recovery
Manivannan *et al.*[29]	41, M	Anaphylaxis to Hymenoptera (bee) sting	1 mg	IV	Apical	Complete recovery
Osuori *et al.*[30]	46, F	Status asthmaticus	Not reported	IV	Apical	Complete recovery
Volz *et al.*[31]	27, M	Self-administration (IV drug user)	2 mg	IV	Apical	Complete recovery
Zubrinich *et al.*[32]	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.

immediate early genes.[36] Alpha- or beta-agonist stimulation leads to up-regulation of immediate early genes in the perfused rat heart.[36] 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.[37] Findings on endomyocardial biopsy in patients with the takotsubo syndrome include contraction band necrosis, dense eosinophilic transverse

bands and an interstitial mononuclear inflammatory response.[37] 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.[37] Elevated catecholamine levels decrease the viability of myocytes through cyclic adenosine monophosphate (AMP)-mediated calcium overload.[38,39] Catecholamines are also a potential source of oxygen-derived free radicals and, in animal models, cause myocyte injury.[39] 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.[35,40] 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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