



BRIEF COMMUNICATIONS

Tako-tsubo-like cardiomyopathy after EpiPen administrationC. M. Zubrinich,¹ H. M. Omar Farouque,² S. E. Rochford,¹ and M. F. Sutherland¹Departments of ¹Respiratory and Sleep Medicine, and ²Cardiology, Austin Health, Heidelberg, Victoria, Australia**Key words**

tako-tsubo-like cardiomyopathy, adrenaline, anaphylaxis, angioedema, EpiPen.

Correspondence

Michael F. Sutherland, Department of Respiratory and Sleep Medicine, Austin Health, Studley Road, Heidelberg, Vic. 3084, Australia. Email: msutherl@bigpond.net.au

Received 25 June 2007; accepted 11 August 2007.

doi:10.1111/j.1445-5994.2008.01748.x

Abstract

Tako-tsubo-like cardiomyopathy is characterized by acute chest pain, electrocardiographic changes and increased cardiac enzymes in the absence of obstructive coronary vessel disease. We describe the development of tako-tsubo-like cardiomyopathy in an elderly woman after the use of an EpiPen for generalized urticaria and angioedema. As adrenaline may participate in the pathogenesis of this condition, the need for careful patient selection and education in the use of adrenaline self-injectors remains imperative.

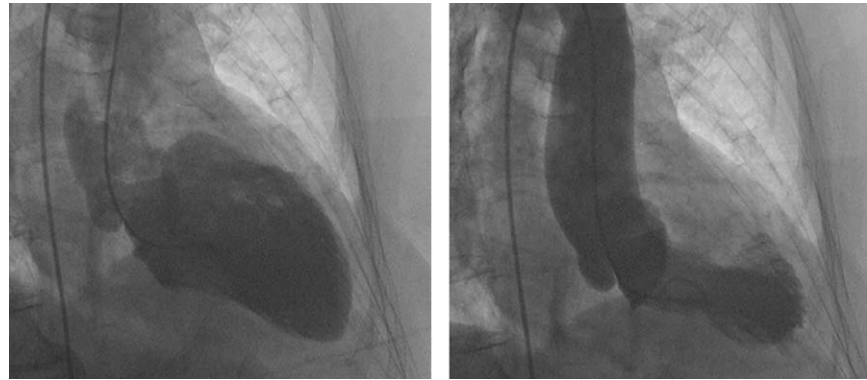
A 76-year-old woman had experienced several episodes of rapid-onset generalized urticaria and oral angioedema over 2 years. On one occasion, she had attended the emergency department (ED) but had not previously been treated with adrenaline. She was referred to our specialist allergy clinic where initial assessment suggested that the episodes may have been idiopathic with probable exacerbation by indomethacin. The patient was advised to cease indomethacin and avoid all non-steroidal anti-inflammatory medications. Because of the severity of the urticaria and oral angioedema, the aetiological uncertainty and concern regarding the potential for glottic angioedema, she was prescribed injectable adrenaline (EpiPen) as part of an anaphylaxis plan and educated in its use. Her medical history included hypertension, osteoporosis and gastro-oesophageal reflux but no known coronary artery disease (CAD). Her medications before admission included oxprenolol 20 mg daily, raloxifene 60 mg daily and ranitidine 150 mg twice daily.

One month later, she developed lip angioedema with generalized urticaria and used her EpiPen. She was treated in the ED with promethazine and hydrocortisone alone and her symptoms resolved. There was no hypotension or tachycardia, and she was given no additional adrenaline. Two hours after her initial reaction and EpiPen use, she developed acute central chest pain without electrocardiogram (ECG) abnormalities. The cardiac troponin I level taken an hour later was increased at 1.69 µg/mL (normal

<0.06 µg/mL). The pain initially resolved with sublingual nitrate, but there was further chest pain associated with lateral T wave inversion and a further rise of the troponin I to a peak of 2.39 µg/mL. A provisional diagnosis of an acute coronary syndrome was made and a coronary angiogram carried out. There was no evidence of significant obstructive coronary disease. However, there was segmental left ventricular (LV) dysfunction with apical akinesis (Fig. 1) consistent with tako-tsubo-like cardiomyopathy. This regional wall motion change could not be explained on the basis of ischaemia in a single coronary arterial territory. The corrected thrombolysis in myocardial infarction (TIMI) frame count, as an indicator of coronary blood flow, was normal for the left anterior descending artery at 20 (range 19–24) but slightly prolonged at 34 for the right coronary artery (range 16–26) and 34 for the left circumflex artery (16–31). The patient was managed expectantly, and an echocardiogram 6 weeks later showed normal LV systolic function. Circulating catecholamines were not measured acutely or subsequently. Her urticaria and angioedema subsequently settled with discontinuation of the raloxifene and she currently remains well.

A tako-tsubo is a narrow-necked Japanese pot used to catch octopus. The name was applied to this condition because of the similarity in appearance of the left ventriculogram during systole to a tako-tsubo.¹ It is also known as 'transient left ventricular apical ballooning' or 'stress cardiomyopathy' and is classically seen in postmenopausal

Figure 1 Left ventricle in diastole (left panel) and systole (right panel) showing apical akinesis and vigorous contraction of the basal segments.



women.² In this condition, features that mimic myocardial ischaemia, such as chest pain, ECG changes and increased cardiac enzymes, are associated with segmental myocardial systolic dysfunction, typically involving the apex, in the absence of obstructive coronary disease. LV impairment resolves over several weeks, although complications such as cardiogenic shock and LV rupture have been described.³ There is a wide range of precipitants, including acute psychological stress, surgery and a variety of acute medical illnesses.⁴ Although the pathophysiology is incompletely understood, transient impairment of the coronary microcirculation is postulated. Circulating catecholamines are generally increased and are thought to be involved in the pathogenesis.⁵

Adrenaline administration has been reported to precipitate acute myocardial infarction in those with existing CAD,⁶ and other acute coronary events after administration have been attributed to coronary vasospasm in the absence of obstructive coronary disease.⁷ Ferry *et al.* reported apparent development of an acute myocardial infarction after in-hospital treatment of a generalized allergic response with adrenaline. Coronary angiogram carried out 4 weeks later was normal.⁸ Anaphylaxis itself has cardiovascular effects beyond hypotension including reports of ECG changes, arrhythmias and acute systolic dysfunction.^{9,10} In our patient, the cardiac troponin was already increased an hour after the onset of chest pain, suggesting that cardiac ischaemia may have commenced around the time of the adrenaline administration 3 h earlier rather than at the time of first chest pain.

The role and relevance of beta-blockers are worthy of consideration in this case. Patients receiving beta-blockers may experience more severe anaphylactic reactions with relative refractoriness to adrenaline administration.¹¹ Beta-blockade may blunt the response to treatment with adrenaline and also allow unopposed alpha-adrenergic effects to predominate. Our patient was already on a low daily dose of oxprenolol, a non-selective β -adrenoceptor antagonist. Although her resting heart rate of 74

beats per minute (b.p.m.) at a prior attendance when well may suggest a minimal degree of beta-blockade, the initial (and highest) recorded heart rate on ambulance attendance after EpiPen administration on the day of the event was 92 b.p.m. This failure to mount a tachycardia in response to adrenaline administration may well be explained by beta-blocker effect. However, beta-blockers have been empirically used by some to treat features of tako-tsubo-like cardiomyopathy, particularly left ventricular outflow tract obstruction, although this recommendation is based on limited data and extrapolation from other cardiac conditions.¹² Kyuma *et al.* gave propranolol intravenously in three cases of tako-tsubo-like cardiomyopathy and observed the acute effects.¹³ The two patients who had evidence of left ventricular outflow tract obstruction did show an improvement in their ECG and left ventricular wall motion abnormalities. However, unlike propranolol, oxprenolol displays intrinsic sympathomimetic activity. Thus, through its partial agonist effect, it may have paradoxically perpetuated the catecholamine effects postulated to be contributory in tako-tsubo-like cardiomyopathy.

Raloxifene is a selective oestrogen receptor modulator, which has both oestrogen agonist and antagonist properties at different sites. It is known to favourably modify the lipid profile but does not significantly alter the risk of coronary vascular events in postmenopausal women.¹⁴ In an animal model specifically assessing its cardiac effects, administration of oestrogen or raloxifene restored protection against the effect of epinephrine in the ovariectomized rat.¹⁵ It is interesting to consider the possibility that this effect of oestrogen may be one of the mechanisms underlying the observation that the majority of cases of tako-tsubo-like cardiomyopathy are seen in postmenopausal women. If true, however, then raloxifene may be expected to give some protection against this condition. Although in our patient, the TIMI frame count was within the normal range in the territory of the left anterior descending artery, it was prolonged in the other vascular

fields. In a published series of 16 women with tako-tsubo-like cardiomyopathy, all were found to have abnormal TIMI frame counts, typically in multiple vascular territories.¹⁶ These data further support the understanding that the process is a diffuse abnormality of the coronary microvasculature.

Recently, Saeki *et al.* have described a 62-year-old Japanese man who developed tako-tsubo-like cardiomyopathy, diagnosed on the basis of echocardiography, after inpatient administration of a total of 2.4 mg of subcutaneous adrenaline for an asthma exacerbation.¹⁷ In contrast, the dose in an adrenaline-automated self-injector is 0.3 mg. To our knowledge, tako-tsubo-like cardiomyopathy after self-injection with a single dose of adrenaline has not been previously reported. There were other potential contributors to the development of the condition in our patient such as the acute medical and psychological stress associated with the allergic reaction. However, we believe it is likely that the adrenaline was at least contributory in this case, given the time-course of events and the postulated role of catecholamines in pathogenesis.

Adrenaline is considered a safe and effective treatment for anaphylaxis, but its use is not completely without risk. Those with cardiovascular comorbidities are one group at risk of adverse effects, and this case raises the possibility that postmenopausal women may form another potential risk group. However, more clinical evidence is needed before firm conclusions can be drawn. There has been an increasing debate about prescription and use of adrenaline autoinjectors.¹⁸ They can be life-saving when used in systemic anaphylaxis, but if used inappropriately, the risk-benefit ratio is altered.¹⁹ Patients are educated to use adrenaline only if they get throat swelling or other life-threatening respiratory or cardiovascular symptoms. It is doubtful in retrospect that this patient had true anaphylaxis and arguably did not need to use her EpiPen with lip swelling and generalized urticaria alone. Self-injectable adrenaline will and should remain the first-line therapy of anaphylaxis; however, this case reaffirms the need for careful patient selection and education in its use.

References

- Kurisu S, Sato H, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K *et al.* Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J* 2002; 143: 448–55.
- Dec GW. Recognition of the apical ballooning syndrome in the United States. *Circulation* 2005; 111: 388–90.
- Akashi YJ, Tejima T, Sakurada H, Matsuda H, Suzuki K, Kawasaki K *et al.* Left ventricular rupture associated with Takotsubo cardiomyopathy. *Mayo Clin Proc* 2004; 79: 821–4.
- Ako J, Sudhir K, Farouque HM, Honda Y, Fitzgerald PJ. Transient left ventricular dysfunction under severe stress: brain-heart relationship revisited. *Am J Med* 2006; 119: 10–17.
- Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G *et al.* Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; 352: 539–48.
- Davidson JR, Lambrechtsen J, Egstrup K. [ST elevation myocardial infarction after therapeutic injection of adrenaline]. *Ugeskr Laeg* 2006; 168: 1137–8.
- Saff R, Nahhas A, Fink JN. Myocardial infarction induced by coronary vasospasm after self-administration of adrenaline. *Ann Allergy* 1993; 70: 396–8.
- Ferry DR, Henry RL, Kern MJ. Adrenaline-induced myocardial infarction in a patient with angiographically normal coronary arteries. *Am Heart J* 1986; 111: 1193–5.
- Brown SG. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. *Curr Opin Allergy Clin Immunol* 2005; 5: 359–64.
- Raper RF, Fisher MM. Profound reversible myocardial depression after anaphylaxis. *Lancet* 1988; 1: 386–8.
- The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005; 115 Suppl 2: S483–523.
- Bybee KA, Kara T, Prasad A, Lerman A, Barnes GW, Wright RS *et al.* Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med* 2004; 141: 858–65.
- Kyuma M, Tsuchihashi K, Shinshi Y, Hase M, Nakata T, Ooiwa H *et al.* Effect of intravenous propranolol on left ventricular apical ballooning without coronary artery stenosis (ampulla cardiomyopathy): three cases. *Circ J* 2002; 66: 1181–4.
- Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; 355: 125–37.
- Nemcsik J, Morschl E, Egresits J, Kordás K, László F, László FA *et al.* Raloxifene lowers ischaemia susceptibility by increasing nitric oxide generation in the heart of ovariectomized rats in vivo. *Eur J Pharmacol* 2004; 495: 179–84.
- Bybee KA, Prasad A, Barsness GW, Lerman A, Jaffe AS, Murphy JG *et al.* Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. *Am J Cardiol* 2004; 94: 343–6.

- 17 Saeki S, Matuse H, Nakata H, Fukahori S, Kohno S. Case of bronchial asthma complicated with Takotsubo cardiomyopathy after frequent epinephrine medication. *Nihon Kokyuki Gakkai Zasshi* 2006; **44**: 701–5.
 - 18 Gold MS. EpiPen epidemic or good clinical practice? *J Paediatr Child Health* 2003; **39**: 376–7.
 - 19 Johnstone SL, Unsworth J, Gompels MM. Adrenaline given outside the context of life threatening allergic reactions. *BMJ* 2003; **326**: 589–90.
-