

Received: 2014.01.19
Accepted: 2014.02.12
Published: 2014.05.19

Repeated use of albuterol inhaler as a potential cause of Takotsubo cardiomyopathy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 78
Final Diagnosis: Takotsubo cardiomyopathy
Symptoms: Chest discomfort • chest pain • dyspnea • short of breath
Medication: —
Clinical Procedure: —
Specialty: Cardiology

Objective: Unusual or unexpected effect of treatment





Background: Takotsubo cardiomyopathy is an increasingly recognized cardiac condition that usually results from an acute stressor. Some medications are becoming recognized as possible stressors. Albuterol is widely used in general medicine. We report an unusual link between Takotsubo cardiomyopathy and albuterol.

Case Report: A 78-year-old woman presented to our emergency department for chest pain of 2-day duration. The patient had been taking albuterol inhaler therapy for worsening shortness of breath followed by chest pain. Her albuterol use was excessive. There were no other acute stressors. The electrocardiogram showed ST-elevations in the anterior and inferior leads. Emergent coronary angiography showed noncritical coronary artery disease and left ventriculography showed apical ballooning.

Conclusions: When patients taking albuterol present with acute chest pain in the absence of other etiologies, beta-agonist-induced Takotsubo cardiomyopathy should be considered.

MeSH Keywords: Adrenergic beta-Agonists – adverse effects • Beta-agonist • Takotsubo Cardiomyopathy • Albuterol – adverse effects

Full-text PDF: <http://www.amjcaserep.com/download/index/idArt/890388>

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Background

Takotsubo cardiomyopathy (TCM), also known as stress-induced cardiomyopathy, apical ballooning syndrome, and broken heart syndrome, is an uncommon, recently recognized cardiac syndrome. It is characterized by an abrupt onset of chest pain mimicking acute MI in both clinical and electrocardiographic findings. First described in Japan, TCM is becoming more recognized in the USA and Europe. Takotsubo is a Japanese word for a narrow-necked octopus trap, which is resembled by the LV apical ballooning [1].

The pathophysiology is related to transient systolic dysfunction of the LV apex and/or mid-segment without any significant obstructive coronary artery disease, usually followed by complete functional recovery in a few weeks. Its prevalence is about 1.7–2.2% [2]. The pathophysiology of TCM has not been clearly established. A number of studies have suggested that a severe transient mid-ventricular cavity dynamic gradient and catecholamine-induced reduction in subendocardial blood flow lead to significant obstruction and secondary ischemia of the LV apex and anterior wall [3]. An abnormal LV outflow tract gradient is not necessary for the diagnosis.

Case Report

A 78-year-old woman with a past medical history of severe chronic obstructive pulmonary disease (COPD) presented to our emergency department with chest discomfort and shortness of breath that began 2 days before. She had repeatedly used albuterol several times and at least 4 time in 12 hours preceding the emergency room visit. At baseline, she used her inhalers up to 2 times a day, only as needed. Her dyspnea finally culminated in severe chest pain, which prompted her to seek medical attention. She denied any acute emotional stressors that may have precipitated her symptoms. The chest pain was midsternal, 10/10 in severity, without radiation, and was not relieved by analgesics.

In the emergency department, an electrocardiogram was done, which revealed ST-segment elevations in leads II, III, aVF, and V1–V4 with poor R-wave progression (Figure 1). The first troponin level was <0.02 ng/mL (normal value: 0–0.10 ng/mL). She was appropriately treated for an acute coronary syndrome and probable STEMI. In short order, the patient was taken for coronary angiography, which revealed noncritical stenoses of the coronaries and apical ballooning on left ventriculography typical of TCM with an ejection fraction of 40% (Figure 2). The left main artery was normal, and the left anterior descending, left circumflex, and right coronary arteries had mild disease (Figures 3 and 4). An echocardiogram was performed, which revealed severe impairment of the middle and apical segments



Figure 1. The electrocardiogram shows ST-segment elevations in leads II, III, aVF, V1 to V4 with poor R-wave progression. The QTc was 531 ms.

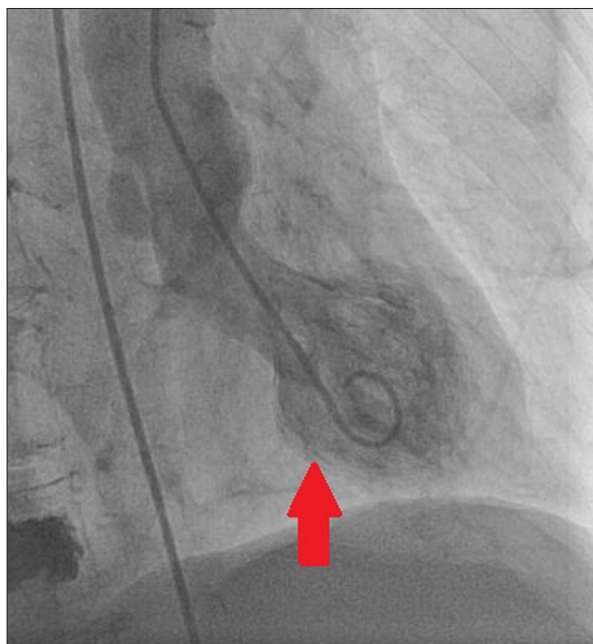


Figure 2. Left ventriculogram shows evidence of apical ballooning typical of Takotsubo cardiomyopathy (red arrow).

of the left ventricle, with an overall ejection fraction of 40–45%, and no evidence of intracavitary LV thrombus (Figures 5 and 6). A mid-cavity gradient was not measured (it is not part of routine echo evaluation, especially with the diagnosis of TCM already made in the catheterization lab) and there was no significant gradient across the LV outflow tract (peak velocity of 1 m/sec; the LVOT gradient of 4 mmHg).

Our patient was diagnosed with Takotsubo cardiomyopathy, supported by an acute presentation and ECG consistent with acute myocardial infarction, as well as the findings of apical ballooning on left ventriculography and non-critical CAD on angiography. She was treated in the cardiovascular intensive



Figure 3. Left coronary angiography with noncritical disease of the left anterior descending and left circumflex arteries.



Figure 4. Right coronary artery angiography with noncritical disease.

care unit for a few days with a medical regimen including aspirin, carvedilol, lisinopril, high-dose atorvastatin. Her hospital course was unremarkable and she was discharged in stable condition. An echocardiogram performed 6 weeks later revealed complete normalization of her LV function.

Discussion

The most common precipitating feature for TCM is physical or emotional stress [4]. Previous reports showed an increased incidence after earthquakes in Japan, and in patients undergoing

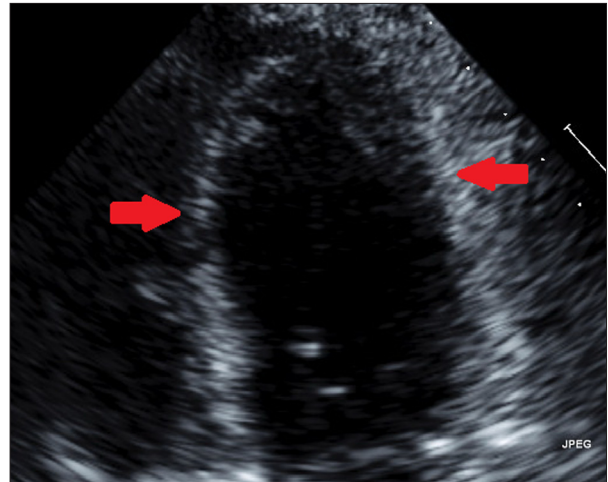


Figure 5. Echocardiography shows the left ventricle in diastolic phase (red arrows).

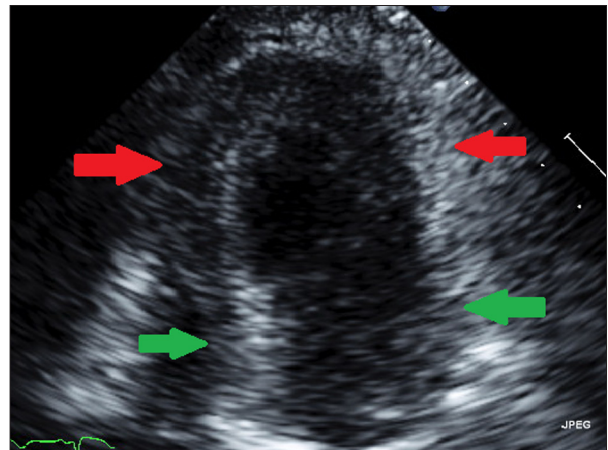


Figure 6. Echocardiography shows the left ventricle in systolic phase revealing severe dysfunction of the apex (red arrows) and hyperdynamic contraction of basal segments (green arrows).

noncardiac surgery or presenting with noncardiac medical emergencies. When measured early after the inciting event, plasma catecholamine levels are found to be substantially elevated—up to 34 times higher than the normal resting levels [5].

Beta-2 agonists are selective medications; however, it is well known that they lose their selectivity at higher doses [6]. In fact, multiple authors described increased cardiac events with these “selective” beta-2 agonists, including a 3-fold increased risk of idiopathic cardiomyopathy and a 7-fold increased risk of myocardial infarctions in newly prescribed inhaled beta-2 agonists [7–9]. In a study on rats, chronic beta-adrenoreceptor activation using isoproterenol was associated with myocardial apoptosis, potentiating myocardial infarction/reperfusion injury, and reductions in LV systolic chamber function [10,11]. Abraham et al. reported 9 patients who developed TCM after

Table 1. The Naranjo Adverse Drug Reaction (ADR) Probability Scale for our patient.

Questions	Yes	No	Do not know	Our patient
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	+1
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Our patient's cumulative Score				+6

Score of: 0 = doubtful ADR, 1-4 = possible ADR, 5-8 = probable ADR, greater than 9 – definitive.

either dobutamine or epinephrine injections. Some of these patients had supra-therapeutic doses. In that paper, classical features of TCM were observed, including cardiac isoenzyme elevation, QTc interval prolongation, rapidly reversible cardiac dysfunction, and left ventricular ballooning variants [12]. Rarely, abrupt withdrawal of long-acting beta blockers may lead to TCM [13].

Recent studies have demonstrated that inhaled beta-2 agonists may also contribute to TCM. In a cohort of 100 patients at the Mayo clinic, Elesber et al. reported that no identifiable stressors were found in 44% and 4 patients (4%) had asthma/COPD exacerbation as the sole physical stress. The authors did not report any medications used by the patients prior to the event [14]. Stanojevic et al. reported the first case of TCM associated with status asthmaticus. In their case, they reported an excessive amount of albuterol inhaler use by the patient [15]. Although it is very difficult to ascertain an independent role of beta-2 agonists in the development of TCM, the association is being increasingly recognized [14,15].

In summary, a few anecdotal case reports and research studies have suggested a relationship between sympathicomimetic

agents and TCM. This is especially relevant with albuterol being widely prescribed around the world. Our case highlights a possible “overdose” effect of albuterol. The Naranjo Adverse Drug Reaction Probability (Naranjo scale) is a helpful tool to use in assessing whether an adverse reaction is due to the use of a particular medication. In our case report, the Naranjo scale may not be applicable because an “overdose” of albuterol was suspected [16] and repeat exposure to the same dose 35 of the same ‘offender’ or the use of a ‘placebo’ is unethical. Nevertheless, a calculated score of at least 6 (probable ADR) [17] may be appropriate to our patient (Table 1).

Conclusions

Beta-2 activation/agonists have been increasingly recognized as potential etiological factors in several cardiac pathophysiological processes. Patients with asthma/COPD exacerbations may develop TCM possibly related to overuse of beta-2 agonists.

Conflict of interest

None.

References:

1. Jenab Y, Taher M, Shirzad S: Broken heart syndrome: a case report. *J Tehran Heart Cent*, 2012; 7(3): 136–39
2. Kurowski V, Kaiser A, von Hof K et al: Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest*, 2007; 132(3): 809–16
3. Joe BH, Hwang HJ, Park CB et al: Takotsubo cardiomyopathy recurrence with left ventricular apical ballooning following isolated right ventricular involvement: A case report. *Exp Ther Med*, 2013; 6(1): 260–62
4. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T: Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. *Circulation*, 2008; 118(25): 2754–62
5. Lyon AR, Rees PS, Prasad S et al: Stress (Takotsubo) cardiomyopathy – a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nature clinical practice. Cardiovascular Medicine*, 2008; 5(1): 22–29
6. Cazzola M, Matera MG, Donner CF: Inhaled beta2-adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease. *Drugs*, 2005; 65(12): 1595–610
7. Au DH, Lemaitre RN, Curtis JR et al: The risk of myocardial infarction associated with inhaled beta-adrenoceptor agonists. *Am J Respir Crit Care Med*, 2000; 161(3 Pt 1): 827–30
8. Coughlin SS, Metayer C, McCarthy EP et al: Respiratory illness, beta-agonists, and risk of idiopathic dilated cardiomyopathy. The Washington, DC, Dilated Cardiomyopathy Study. *Am J Epidemiol*, 1995; 142(4): 395–403
9. Martin RM, Dunn NR, Freemantle SN, Mann RD: Risk of non-fatal cardiac failure and ischaemic heart disease with long acting beta 2 agonists. *Thorax*, 1998; 53(7): 558–62
10. Hu A, Jiao X, Gao E et al: Chronic beta-adrenergic receptor stimulation induces cardiac apoptosis and aggravates myocardial ischemia/reperfusion injury by provoking inducible nitric-oxide synthase-mediated oxidative stress. *J Pharmacol Exp Ther*, 2006; 318(2): 469–75
11. Osadchii OE, Norton GR, McKechnie R et al: Cardiac dilatation and pump dysfunction without intrinsic myocardial systolic failure following chronic beta-adrenoreceptor activation. *Am J Physiol Heart Circ Physiol*, 2007; 292(4): H1898–905
12. Abraham J, Mudd JO, Kapur NK et al: Stress cardiomyopathy after intravenous administration of catecholamines and beta-receptor agonists. *J Am Coll Cardiol*, 2009; 53(15): 1320–25
13. Tomcsanyi J, Javor K, Arabadzisz H et al: [Takotsubo cardiomyopathy: a novel beta-adrenergic blocker withdrawal syndrome]. *Orvosi Hetilap*, 2013; 154(7): 267–71
14. Elesber AA, Prasad A, Lennon RJ et al: Four-year recurrence rate and prognosis of the apical ballooning syndrome. *J Am Coll Cardiol*, 2007; 50(5): 448–52
15. Stanojevic DA, Alla VM, Lynch JD, Hunter CB: Case of reverse takotsubo cardiomyopathy in status asthmaticus. *Sout Med J*, 2010; 103(9): 964
16. Seger D, Barker K, McNaughton C: Misuse of the Naranjo Adverse Drug Reaction Probability Scale in toxicology. *Clin Toxicol*, 2013; 51(6): 461–66
17. Naranjo CA, Busto U, Sellers EM et al: A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*, 1981; 30(2): 239–45