

Takotsubo cardiomyopathy: a known unknown foe of asthma.

Ourania S. Kotsiou^{1,*}, Alexandros Douras², Demosthenes Makris³, Nikoleta Mpaka²,
Konstantinos I. Gourgoulialis¹

¹Department of Respiratory Medicine, University Hospital of Larissa, Faculty of Medicine,
University of Thessaly, BIOPOLIS, 41500, Larissa, Greece

²Department of Cardiology, General Hospital of Volos, Polimeri 134, 38222, Magnesia, Greece

³Department of Critical Care, University Hospital of Larissa, Faculty of Medicine, University of
Thessaly, BIOPOLIS, 41500, Larissa, Greece

***Corresponding author:** Ourania S. Kotsiou, Department of Respiratory Medicine, University
Hospital of Larissa, Faculty of Medicine, University of Thessaly, BIOPOLIS, 41500, Larissa,
Greece, Tel +30 2413-502812, E-mail: raniakotsiou@gmail.com, Fax +30 2413-501563

Abstract

Introduction:

Patients with uncontrolled asthma are at a greater risk of asthma attacks requiring emergency room visits or hospital admissions. Takotsubo cardiomyopathy is potentially a significant complication in a course of status asthmaticus.

Case study:

We present a 43-year-old female patient who presented with status asthmaticus further complicated with takotsubo cardiomyopathy.

Results:

Recognizing apical ballooning syndrome is challenging in patients with a history of respiratory disease because the symptoms of the last entity may complicate the diagnostic approach. It is difficult to distinguish clinically apical ballooning syndrome from the acute airway exacerbation itself. Both asthma and takotsubo cardiomyopathy share the same clinical presentation with dyspnea and chest tightness. In our patient, the electrocardiographic abnormalities, the rapidly reversible distinctive characteristics of echocardiography and the modest elevation of serum cardiac biomarkers levels, in combination with the presence of a stress trigger (severe asthma attack), strongly supported the diagnosis of broken heart syndrome.

Conclusion:

Clinicians should *re-evaluate asthma management and* be aware of the complications associated with asthma attacks such as stress-induced cardiomyopathy.

Keywords

Apical ballooning syndrome, asthma attack, broken heart syndrome, status asthmaticus, cardiac biomarkers, stress-induced cardiomyopathy

Introduction

Stress-induced cardiomyopathy (also called apical ballooning syndrome, takotsubo cardiomyopathy, broken heart syndrome, or stress-induced cardiomyopathy) is a syndrome characterized by transient regional systolic and diastolic dysfunction of the left ventricle with a variety of wall motion abnormalities. It mimics myocardial infarction regarding the clinical presentation, electrocardiographic findings, and biomarker profile, but in the absence of angiographic evidence of obstructive coronary artery disease or acute plaque rupture [1,2]. The term “takotsubo” is taken from the Japanese name for an octopus trap, which has a shape that is similar to the imaging findings of this entity in the most common and typical form, which are: a systolic apical ballooning appearance of the left ventricle as a consequence of ventricular systolic dysfunction (hypokinesis, akinesis or dyskinesis) and hyperkinesis of the basal walls [3]. It mainly affects postmenopausal women and is often preceded by extreme physical or emotional triggers [4,5]. Men seem to be more prone to physical stress [4-6]. Broken heart syndrome has been associated with “broken lung” disease [6]. Chronic obstructive pulmonary disease, asthma, pulmonary embolism, and malignancies have been described as potential physical triggers for acute stress-induced cardiomyopathy [6]. Asthma exacerbation considered a possible stressor of takotsubo cardiomyopathy, mainly following medical interventions (short-acting β_2 adrenergic receptor agonist, epinephrine providing, intubation) [7,8]. However, the combination of the two entities has been reported sporadically. The pathophysiological pathways in the onset of takotsubo cardiomyopathy in a course of status asthmaticus have not been well elucidated. This paper discusses the case of a middle-aged female patient with uncontrolled asthma, who

displayed acute severe dyspnea as a dominant clinical manifestation of status asthmaticus complicated by apical ballooning syndrome.

Case study

A 43-year-old Caucasian woman, nonsmoker with a medical history of asthma was admitted to the emergency department because of acute appearance of severe dyspnea, chest tightness and dry cough. She was diagnosed with asthma at the age of 32 years. Since then, she has been under continuous medication with an inhaled combination of budesonide with formoterol (160/4.5 micrograms twice daily) and 10 mg montelukast daily. She described flare-ups occasionally. She reported that the last severe attack of asthma driving her to an emergency room, requiring hospitalization was six years ago. However, over the last four weeks her asthma was totally uncontrolled according to the Asthma Control Test (ACT) Questionnaire with a sum score equal to eleven. In detail, she was using rescue nebulizer medication with salbutamol > 3 times per day during this period. The recurrent shortness of breath, which was her dominant symptom, drove to limitation of her activities and she had night awakenings because of cough and chest tightness twice per week. She denied fever, chills, sweats, sputum production or hemoptysis during this period. She only mentioned that she experienced a highly stressful family situation the previous day, which finally drove to a severe exacerbation of dyspnea. She self-treated aggressively with high doses of salbutamol (200 mcg of salbutamol aerosol inhaler repeated every three hours) in addition with regular using of combination drug (320/9 mcg every 8 hours) with no clinical improvement.

On admission, her condition was moderately severe; she was tachypneic with paradoxical thoracoabdominal movement. She was also hemodynamically unstable with an arterial blood pressure of 100/70 mmHg. Arterial blood gas analysis in room air showed respiratory acidosis with pH values of 7.08, oxygen partial pressure of 62 mmHg, oxygen saturation of 93%, and carbon dioxide partial pressure of 88 mmHg. Wheezes could be heard over the lungs in the *expiratory* phase of respiration. The baseline electrocardiography (ECG) showed sinus rhythm of about 100/min and slight no specific ST abnormalities (**Figure 1a**). She had a normal complete blood count, C-reaction protein value, serum creatinine and electrolyte levels. The results of *laboratory* tests on *admission* are presented in **Table 1**. The chest X-ray was normal (**Figure 2**). On her admission, she had a Glasgow Scale of 15/15 but rapidly became unconscious (GSC 7/15). Due to loss of consciousness, *hemodynamic instability and* acute respiratory acidosis despite optimal treatment (nebulized bronchodilators, intravenous injection of 125mg methylprednisolone *and subcutaneous* injection of 0.4mg adrenaline), she was intubated. Arterial blood gas analysis after intubation showed respiratory acidosis with pH values of 7.22, oxygen partial pressure of 85 mmHg and carbon dioxide partial pressure of 70 mmHg with FiO₂ of 0.6. She entered into the Intensive Care Unit (ICU) under volume controlled ventilation and continuous sedation. Blood pressure was 90/50 mmHg, pulse was 92 min and body temperature of 36.6° C. In ICU, controlled hypoventilation allowing for “permissive hypercapnia” was the ventilator strategy that was used. The initial ventilator settings were: FiO₂ = 0.6; with a tidal volume of 450 mL (V_t = 6 ml/kg), respiratory rate (RR) of 12/min, combined with an inspiratory flow rate of 80 L/min. These settings were used with a goal of obtaining a pH, in general, above 7.2 and an end-inspiratory plateau pressure (P_{plat}) under 30 cmH₂O, to minimize intrinsic

positive end-expiratory pressure (ie, auto-PEEP), waiting for airflow obstruction to improve. Because of hypotension, she was treated with intravenous noradrenaline and initial fluid completion in order to maintain blood volume, which gradually improved her hemodynamic condition. Intravenous noradrenaline had definitively withdrawn after a period of four hours. In parallel, she was under aggressive emergency *treatment of status asthmaticus with* repeated doses of inhaled salbutamol and budesonide, intravenous methylprednisolone and magnesium sulphate.

Twenty hours after admission, the patient was complicated with more pronounced electrocardiographic abnormalities without further deterioration of arterial pressure, which was approximately 110/80 mmHg without receiving vasopressors. The electrocardiogram showed a sinus rhythm of about 100/min with inverted T waves in the II, III, and avF leads as well as in precordial leads V4–V6 characteristically pointing to more than one vascular territories (**Figure 1b**). A small rise in cardiac biomarkers *was also observed*. In detail, laboratory tests revealed an elevated troponin (cTnI) concentration of 2.2 ng/mL, slightly elevated levels of B-type natriuretic peptide (BNP = 345 pg/mL) and an elevated *creatine phosphokinase (CPK) value* of 788 U/L. The ratio of serum creatine kinase MB (CK-MB) to total CPK was also elevated (>0.1) as the value of CK-MB was 80 U/L. *The echocardiography* showed an *elevated left cardiac chamber size*, hypokinesia of the *apical-septal* segments of LV walls with apical ballooning walls involvement. The LV ejection fraction was 45% (**Figure 3a & 3b**). Based on these echocardiographic findings, the consulting cardiologists diagnosed Takotsubo cardiomyopathy. Thenceforward, the patient was further comedicated with intravenous esmolol. Its use produced no increase in peak pressures or in airway resistance. She always remained hemodynamically

stable. The 3rd day, the ECG showed unchanged diffusely inverted T waves (**Figure 4**). Thereafter, levels of all the *cardiac biomarkers* measured showed a *gradual decline*. She was extubated the 4th day of hospitalization. Respiratory symptoms were improved and she had excellent *arterial blood gas* values breathing room air. The 9th day the ECG remained abnormal with slighter diffuse T abnormalities (**Figure 5**). Repeat echocardiographic assessment on day 10 monitored full recovery of the left ventricular wall motion abnormalities. At that time she was submitted to coronary angiography that showed: absolutely normal coronary arteries with no luminal irregularities, normal ventriculography, with no wall motion abnormalities and an ejection fraction over 60% (**Figure 6**). After hospital discharge, she was medicated with carvedilol (6.25 twice a day) and ramipril (2.5 once a day) for 3 months. Her ECG returned to normal 60 days after the index event (**Figure 7**). In addition, she was given a *referral* to the Respiratory Department for further evaluation of asthma. She was in medication with *inhaled budesonide/formoterol combination* and leukotriene receptor antagonist. Dose adjustments were made depending on patient's asthma symptoms. She experienced a good outcome despite the major cardiopulmonary event suffered early on in her presentation. During the follow-up period, she was found to have complete recovery and full resolution of respiratory symptoms.

Results

The rapidly reversible distinctive characteristics of echocardiography (ypokinetic globally dilated apical segments, normally contracting basal segments); the new electrocardiographic abnormalities (T-wave inversion); the modest elevation of levels of cardiac biomarkers in serum, in combination with the presence of a stress trigger (severe asthma attack); and the absence of pheochromocytoma or myocarditis strongly supported the diagnosis of takotsubo

cardiomyopathy according to the last proposed criteria for the diagnosis of stress-induced cardiomyopathy [1].

Discussion

Recognizing takotsubo cardiomyopathy is challenging, especially in patients with a history of respiratory disease because the symptoms of the last entity may complicate the diagnostic approach. It is difficult to distinguish apical ballooning syndrome from the acute airway exacerbation itself. Both asthma and takotsubo cardiomyopathy share the same clinical presentation with dyspnea and chest tightness. We should have in mind stress-induced cardiomyopathy as a complication of a severe asthma attack [8]. The etiology of transient left ventricular apical ballooning in the course of an asthmatic attack has not yet been fully understood. Multifactorial pathophysiologic mechanisms were likely to be involved. The most accepted pathogenic hypothesis considers a rapid elevation of circulating catecholamine triggered by emotional and/or other physical stress such as asthma attack itself [8,9]. It has been reported that the concentrations of plasma norepinephrine and epinephrine increase more in patients with takotsubo cardiomyopathy than in patients with acute coronary syndrome [9]. Sympathetic stimulation of adrenoceptors in the ventricular myocardium is achieved through local release of norepinephrine by sympathetic nerve endings directly innervating the myocardium (through hypothalamus trigger) and diffusion of circulating catecholamines (epinephrine and norepinephrine) into the myocardium from the coronary circulation [10]. Catecholamines are the primary triggers of emotional stress-induced cardiac changes and exert their action via activation of alpha- or beta-adrenoceptors [10,11]. *Catecholamines* excess has a global effect on the myocardium through two ways. First, they lead to diffuse microvascular

spasm or dysfunction resulting in acute myocardial stunning [9-16]. It is predicted that norepinephrine may trigger coronary vasospasm by stimulating the α_1 -receptor in coronary blood vessels. Secondly, direct exposure of myocardium to catecholamine is considered to be extremely toxic [12,17,18]. Direct effects of catecholamines upon the myocardium are cellular damage, contraction band necrosis, defects in perfusion, altered cellular metabolism, and negative inotropic effects of epinephrine *via* stimulation of the cardioprotective β_2 -adrenergic receptor G_i signaling pathway, a process called stimulus trafficking [12]. Heart biopsies have revealed that hearts from patients with conditions which increased the sympathetic tone showed an association of myocardial disarray and contraction band necrosis, hallmarks of myocardial catecholamine toxicity [18].

The different occurrence of wall motion abnormalities could be explained by inter-individual anatomical differences in the distribution of β -adrenergic receptors [9,12,17,18]. It is speculated that the greater effect at the apical myocardium may be due to a higher density of beta-2-adrenoreceptors at this location [11,14]. It has been recently shown that the apical ventricular region has a greater $\beta_2:\beta_1$ adrenoceptor ratio, with a higher responsiveness and vulnerability to sympathetic stimulation [11,15,16]. On the other hand, norepinephrine mediated beta1-receptor stimulation may trigger hyperdynamic basal contraction because there are more beta1 sympathetic nerve endings and norepinephrine in the basal myocardium.

Moreover, patients with severe respiratory diseases are highly exposed to the risk of developing transient left ventricular apical ballooning due to the high dosages of β_2 -agonists used. In asthma, pharmacological treatments may potentiate such an effect, although the asthmatic attack itself was reported as the predominant trigger in 35% of published cases [19,20]. An epinephrine

injection overdose or the inhalation of an excessive amount of short-acting beta-2-adrenoceptor agonist (SABA) may be responsible agents. B-mimetics could have acted as a preconditioning factor for cardiomyopathy or aggravated the sympathetic nervous system stress [19]. Furthermore, exogenously *administered* (intravenous) epinephrine may increase the risk of takotsubo cardiomyopathy [20]. In addition, hypoxemia, hypercapnia, and acidosis, which potentially complicate the respiratory disease, can induce sympathetic nerve stimulation and increase catecholamine release and activation.

Takotsubo cardiomyopathy is known to be reversible; however, it often presents with cardiac complications during the acute phase, such as life-threatening ventricular arrhythmias, pump failure, cardiac rupture and systemic embolism. In severe cases, respiratory failure or death can occur [21]. Hospital mortality is reportedly 1.7–6% [22,23].

There is no consensus on pharmacological treatment of takotsubo cardiomyopathy. Based on the suspected pathophysiology of the disease, adrenergic blockade using beta-blocker therapy is employed [24]. The question then arises of what is the role of β 2-agonists and b-blockers in the management of combined respiratory disease exacerbation and apical ballooning syndrome. On the one hand, stress of acute pulmonary conditions, especially via pulmonary medication, contributes to the development of takotsubo cardiomyopathy as we noted before. On the contrary, beta blockers are contraindicated in bronchospasm. Several reports state that the ultra-short-acting beta-1 selective adrenergic antagonists such as esmolol can be safely used in patients with airway hyperreactivity [25-27]. In *our case study*, esmolol had no clinical impact in airway resistance however the patient was also in bronchodilators which should be co-administered in such cases [25-27]. We describe a woman in a premenopausal period that has

several triggers for takotsubo cardiomyopathy, such as uncontrolled asthma that drives to a continuous high dose of nebulized β -adrenergic agonists, a strong emotional stressful situation before the symptomatology onset. Finally, the hypoxemia and acidosis revealed in air blood gases are also implicated in the sympathetic nervous system stimulation and catecholamine cardiotoxicity. Deeper knowledge of the pathophysiological pathways as well as coordination between the involved specialties, are considered of high importance.

Conclusion

The diagnosis of takotsubo cardiomyopathy is not always straightforward. The diagnosis may be even more difficult in a patient who presents with status asthmaticus. It is of great significance to keep in mind the possible acute cardiologic complication of a severe asthmatic attack in a form of takotsubo cardiomyopathy. In order to establish the proper diagnosis, it is essential to analyze electrocardiogram tracings with meticulous attention, determine troponin concentration and perform echocardiography as early as possible. Moreover, this case study emphasizes the vital importance of the control concept in the management of asthma and care coordination between the involved specialties.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1. Patient's laboratory data on admission.

Hematology	Coagulation	Biochemistry	Arterial blood gas analysis
WBC = $10 \times 10^3/\mu\text{L}$	PT = 130%	AST = 50 IU/L	pH = 7.08
Neu = 86%	APTT = 24 sec	ALT = 88 IU/L	pCO ₂ = 88 mmHg
Lym = 10%	D-dimer = 0.7 $\mu\text{g/mL}$	LDH = 386 IU/L	pO ₂ = 62 mmHg
Eosino = 0%		CPK = 170 U/L	HCO ₃ = 24 mmol/L
RBC = $450 \times 10^4/\mu\text{L}$	Serology	UN = 26 mg/dL	Lac = 0.9 mmol/L
Hb = 11.1 g/dL	CRP = <0.5 mg/dL	Cr = 0.4 mg/dL	
Hct = 34.3 %	BNP = 150 pg /mL	Na = 139 mmol/L	
Plt = 211.000/ μL	Troponin-I = 0.1 ng/mL	K = 4.4 mmol/L	
		Ca = 8.6 mg/dL	













