

CASE OF THE MONTH Timothy Enders DO, Molly Lewandowski MD, Annette Quick MD,
Sindhu Koshy MD, Harshal Patil MD UMKC

Apical Ballooning Syndrome and Multivessel Coronary Vasospasm in a Postmenopausal Woman

Abstract:

Objective: To assess a patient who developed Apical Ballooning Syndrome (ABS)

Aim: To evaluate the potential factors leading to ABS

Background: Apical Ballooning Syndrome is a cause of reversible cardiomyopathy that usually occurs in postmenopausal women. To date, no single cause of ABS has been identified; rather, ABS appears to be a consequence of multiple factors.

Methods: This report evaluates a patient with ABS by comparing her case to the factors believed to contribute to the development of this syndrome.

Results: This case involves a postmenopausal woman who developed multivessel coronary vasospasm and ABS while receiving estrogen replacement therapy (type and strength unknown).

Conclusion: Further studies are indicated to evaluate the possible relationship between estrogen replacement therapy and the development of ABS in postmenopausal women.

Case Report:

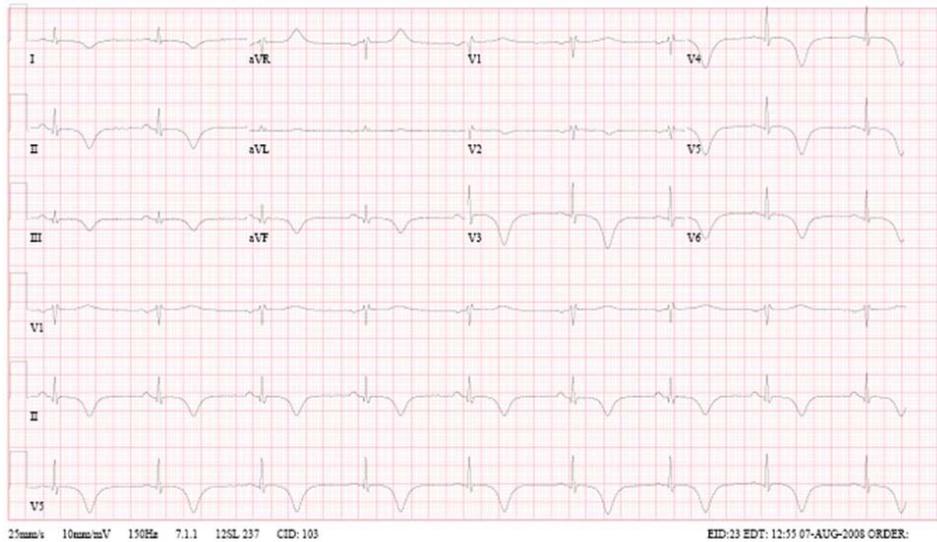
A 59 year old Caucasian female presented to the emergency department with left sided, substernal chest pain which had been increasing in intensity and frequency over the past four months and was not occurring three to four times per day. She described her chest pain as squeezing in nature, lasting 2-3 minutes, and reported that it occurred with exertion and at rest. On the evening prior to presentation, she experienced an episode that lasted 20 minutes which was 10/10 in intensity; she reported that the pain did not radiate and she could not identify any precipitating or alleviating factors. She denied nausea, dizziness or palpitations; however, she did describe diaphoresis and dyspnea with her most recent episode. The patient denied any history of orthopnea or PND. She lives alone and reported increased anxiety due to the loss of her job; she had used much of her savings to pay her bills.

The patient's PMH included hypertension, migraine headaches, fibromyalgia, breast cancer (at age 32) and degenerative disc disease. Past surgical history was limited to a right mastectomy. Home medications included Inderal LA, Fentanyl patch, oxycodone, prn colace and an estrogen supplement of unknown type and dosage. She reported no known drug allergies.

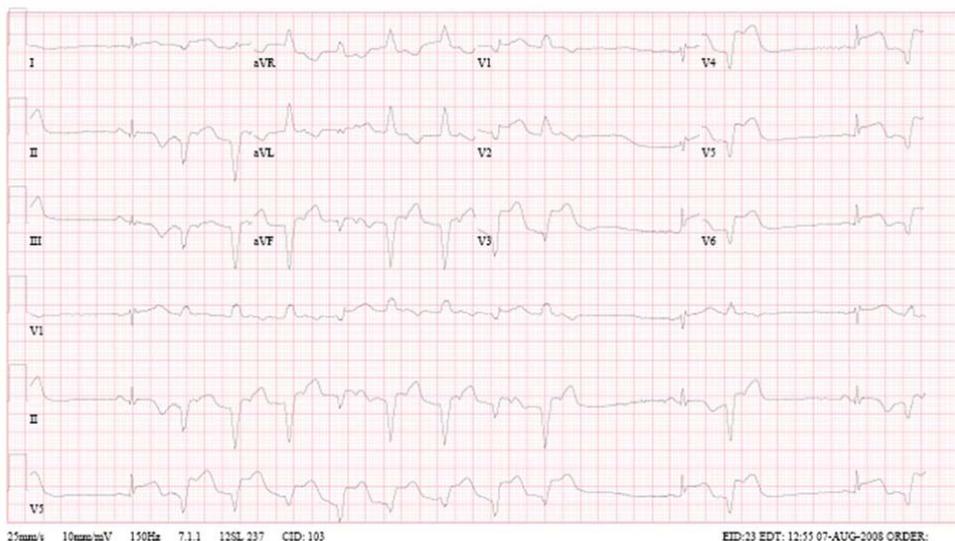
Exam revealed T 97.4F, P 74, BP 139/82, R 16, O₂ sat 98% on RA. No heart or lung abnormalities were found on exam; there were no clinical signs of right or left heart failure (no JVD, rales, peripheral edema).

Her initial lab data revealed a serum troponin-I 0.80 ng/ml, CK-MB mass 6.9 ng/ml, total CK 102 IU/L, serum K 5.5, Ca 9.1, Mg 2.1, Phos 4.3, triglycerides 155, HDL 38, LDL 128, Albumin 2.2; LFTs were otherwise normal. Her WBC was 9900 and hemoglobin was 16.8 g/dl. A urine drug screen was negative. Urinalysis was negative for nitrites and leukocyte esterase.

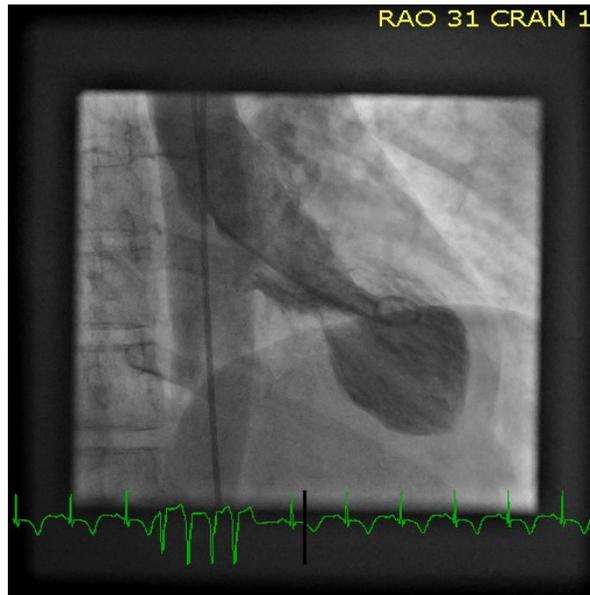
Her initial EKG (below) revealed sinus bradycardia, prolonged QTc and deep, diffuse T wave inversions, suggesting myocardial injury:



The patient was treated with morphine and nitroglycerin which alleviated her chest pain. She was placed on 2L of oxygen and was given ASA 325 mg, which was continued daily. A heparin drip was initiated and she was started on metoprolol, 25 mg every 12 hours, atorvastatin 80 mg qd, lisinopril 10 mg daily and clopidogrel 600 mg (as a one time dose). Initial CXR was negative for any acute cardiopulmonary process. On the following morning, the patient's chest pain redeveloped and her EKG revealed sinus tachycardia, non-sustained V tach and diffuse ST elevation:



The patient was taken to the cardiac cath lab emergently, where the angiogram revealed 60-70% stenosis in both the proximal LAD and ostial left circumflex arteries, which improved with intracoronary nitroglycerin; the left main and right coronary arteries were angiographically normal. A left ventriculogram revealed hypokinesia and paradoxical movement of the apex (figure, below); contractility at the base was reported to be normal.



The day following the cardiac catheterization, the patient had a 2D echocardiogram which revealed normal LV size and wall thickness. No segmental wall motion abnormalities were seen and the ejection fraction was estimated to be 45%. The patient was also reported to have grade II LV diastolic dysfunction. No significant valvular abnormalities were noted. There was continued hypokinesia of the apex but the findings were much improved.

The patient was started on amlodipine and the metoprolol was discontinued; ASA, lisinopril and prn NTG were continued; her atorvastatin dose was cut to 40 mg per day and she was prescribed a nicotine patch (21 mg per day) to help with cigarette cessation. The patient was discharged to home after 3 days of hospitalization.

Discussion: Apical Ballooning Syndrome (ABS), also known as Takotsubo cardiomyopathy, was first described in Japanese patients by Sato et al., in 1990 [1] and the topic has received increasing attention over the past two decades. One systemic review of 14 studies with 266 patients concluded that nearly 90% of reported patients were women and that the median age range was 58-77 [2]. ABS presents with chest pain and/or dyspnea and can imitate an acute ST-elevation myocardial infarction by clinical and EKG presentation; however, the elevation of serum myocardial markers is usually minimal. The onset of the syndrome is thought to be associated with a physiologic or emotional event and patients may have no angiographic evidence of coronary artery disease. The echocardiogram demonstrates normal basal wall motion with apical akinesis/dyskinesia that cannot be correlated with the distribution of a single coronary vessel. The condition is reversible and has a favorable prognosis, with full recovery often occurring within days to weeks of the acute event [2,3].

An early proposed mechanism for ABS was multivessel epicardial vasospasm; however, this was found in only 3 of 212 patients in the above systemic review [2]; more recent studies have demonstrated that this cause is unlikely though vasospasm may be a component (as in our case). Early, liberal use of nitroglycerin in these patients, who

(cont) are presumed to be having an MI, may mask the actual number of individuals who experience multivessel vasospasm [4].

An abnormality in the coronary microcirculation has also been evaluated as a possible cause for ABS [2,3,4].

Mohri et al. found that 29 of 117 patients (25%) had microvascular spasm; of these 29 individuals, most of whom were women, few had coronary risk factors [5]. One study of 16 women with LV wall motion abnormalities used Thrombolysis In Myocardial Infarction (TIMI) frame counts to evaluate these patients; in all 16 women, the TIMI frame counts were abnormal and usually involved all three major coronary arteries, indicating the possibility of diffuse coronary microcirculatory function impairment [6].

In one systemic review of 542 individuals with ABS, nearly 80% had experienced intense emotional or physical stress, presumably leading to stimulation of the sympathetic nervous system [7,8]. Regional wall motion abnormalities and decreased LV ejection fraction were found in a clinical study where mental stress led to a rise in serum catecholamines [9]; the physical stress of subarachnoid hemorrhage and pheochromocytoma, associated with high catecholamine levels, have been proposed as factors leading to some cases of ABS [10,11]. Apical Ballooning Syndrome has also been associated with high dopamine,, norepinephrine and epinephrine levels [12].

Since post menopausal women make up the vast majority of patients with ABS, the possible role of estrogen is beginning to receive greater attention. Clinical studies have demonstrated that long term estrogen replacement therapy attenuates vasoconstrictive response to catecholamines in postmenopausal women [4,13] and to mental stress in perimenopausal women [4,14]. In premenopausal women who experience Prinzmetal's variant angina, incidence of anginal attacks and endothelial dysfunction had an inverse correlation with the serum estradiol level [15,16]. Experimental studies have demonstrated that exogenous estrogen protects from the adverse cardiac effects of mental stress in oophorectomized rats [4,17,18].

Conclusion: The cause for Apical Ballooning Syndrome remains uncertain. Multivessel coronary vasospasm, as found in our patient, was once thought to be the cause but has since been found in a minority of cases. It is likely that ABS is a multifactorial condition that includes intense emotional or physical stress leading to a catecholamine surge which, in turn, stuns the myocardium via diffuse microvascular vasospasm; a lack of estrogen protection in postmenopausal women may increase their risk for ABS. Further studies are indicated to evaluate the potential association between ABS and estrogen replacement therapy.

References:

1. Sato, H et al., Takotsubo-type cardiomyopathy due to multivessel spasm. From Clinical Aspects of Myocardial Injury: From Ischemia to Heart Failure, Kodama et al., editors, Tokyo, Japan: Kagakuhyouronsha; 1990: 56-64
2. Gianni, M et al., Apical Ballooning Syndrome or Takotsubo Cardiomyopathy: a systemic review, Eur Heart J 2006; 27(13):1524-1525
3. Bybee, KA et al., Systemic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction, Ann Internal Med 2004; 141:858-865
4. Prasad, A et al., Apical ballooning syndrome (Takotsubo or Stress Cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 2008; 155(3): 413-414
5. Mohri, M et al., Angina pectoris caused by coronary microvascular spasm, Lancet 1998; 351: 1165-1169
6. Bybee, KA 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: 343-346 (continued)

7. Dorfman, TA et al., An unusual manifestation of Takotsubo Cardiomyopathy, *Clin Cardiol* 2008; 31:194-200
8. Dorfman, TA et al., Takotsubo Cardiomyopathy: a review of the literature, *Curr Cardiol Rev* 2007; 3: 137-142
9. Becker, LC et al., Left ventricular, peripheral vascular and neurohormonal responses to mental stress in normal middle-aged men and women. Reference group for the Psychophysiological Investigations of Myocardial Ischemia, *Circulation* 1996; 94: 2768-2777
10. Naredi, S. et al., Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage, *Stroke* 2000; 31: 901-906
11. Otsuka, M. and I. Kahno, Periodic fluctuation of blood pressure and transient left ventricular apical ballooning in pheochromocytoma, *Heart* 2006; 92: 1837
12. Wittstein, IS, et al., Neurohumeral features of myocardial stunning due to sudden emotional stress, *NEJM* 2005; 352: 539-548
13. Sung, BH et al., Estrogen improves abnormal norepinephrine-induced vasoconstriction in postmenopausal women, *J Hypertension* 1999; 17:523-528
14. Komesaroff, PA and SK Esler, Estrogen supplementation attenuates glucocorticoid and catecholamine responses to mental stress in perimenopausal women, *J Clin Endocrinol Metab* 1999; 84: 606-610
15. Kawano, H et al., Menstrual cyclic variation of myocardial ischemia in premenopausal women with variant angina, *Ann Internal Med* 2001; 135: 977-980
16. Keller, KB and L Lemberg, Prinzmetal's Angina, *Am J Crit Care* 2004; 13: 350-354
17. Ueyama, T et al., Estrogen attenuates the emotional stress-induced cardiac responses in the animal model of Takotsubo (Ampulla) Cardiomyopathy, *J Cardiovasc Pharmacol* 2003; 42 (suppl 1): S1, 17-19
18. Sharkey, SW et al., Stress Cardiomyopathy, *J Am Coll Cardiol* 2007; 49: 921

