Cardiac Thrombi in Stress (Tako-Tsubo) Cardiomyopathy: More Than an Apical Issue?

To the Editor: A 61-year-old postmenopausal woman has presented 3 times within 4 years with acute tako-tsubo cardiomyopathy (TTC). Each admission was precipitated by a heated argument and characterized by severe central chest pain, anterior ST-segment elevation, and elevated serum troponin levels; however, angiography revealed normal coronary arteries. Inotropic and noninvasive ventilatory support was required on all 3 occasions and intubation on 1 occasion. Left ventricular (LV) apical thrombus complicated the first episode but resolved with anticoagulation. Rapid normalization of LV systolic function on echocardiography, as well as resolution of the ST-segment elevation on electrocardiography, was observed after each presentation. During the patient's latest admission, coronary angiography (on day 10) revealed a large and mobile LV apical thrombus (Figure 1, top). This thrombus had not been observed on transthoracic echocardiography performed 6 days before angiography, and it had developed despite administration of aspirin and subcutaneous heparin and in the absence of atrial fibrillation on continuous monitoring.

Cardiac magnetic resonance imaging was performed to exclude alternative myocardial pathology. A scan obtained on day 12 showed normalization of LV systolic function with no late gadolinium enhancement. However, in addition to the apical thrombus in the LV, the scan revealed a large thrombus in the left atrial appendage (LAA) (Figure 1, bottom, supplemental video). Echocardiographic assessment of left atrial (LA) function at presentation was suggestive of transient LA enlargement and dysfunction (Table). Screening for thrombophilia was negative.

Left ventricular apical thrombus formation is a known complication of TTC and has been reported in up to 8% of case series,[1] with potential for embolic sequelae. To our knowledge, this is the first published report of LAA thrombus complicating TTC independent of atrial fibrillation. We hypothesize that the following mechanisms are important contributors to thrombus formation in the setting of acute TTC:

1. Catecholamine excess–induced platelet activation and aggregation. Plasma catecholamine levels have been found to be higher at presentation in patients with TTC than in those with ST-segment elevation myocardial infarction.[2] Both norepinephrine and epinephrine have been shown to induce platelet activation.[3]

2. Catecholamine-mediated endothelial and cardiomyocyte injury. Surges of catecholamines may induce cardiac myocyte injury via cyclic adenosine monophosphate–mediated calcium overload[4] or indirectly due to catecholamine-induced endothelial dysfunction and associated damage to underlying myocytes.[5] Myocytes in the LV apex are thought to be particularly sensitive to excessive levels of catecholamines, partly as a result of the higher endothelial to myocardial ratio.[6] Our finding of an LAA thrombus suggests that myocytes in the left atrium may also be sensitive to the pathological milieu of TTC. Atrial dysfunction may be compounded by increased atrial filling pressures secondary to increases in LV end-diastolic pressure. Consistent with this and the current case, patients with TTC have been shown to have worse LA function compared with those with ST-segment elevation myocardial infarction.[7]

Although the occurrence of the LV apical thrombus in the episode of TTC we describe was most likely caused by acute ventricular wall akinesis, we suggest that increased platelet activation and aggregability due to catecholamine release

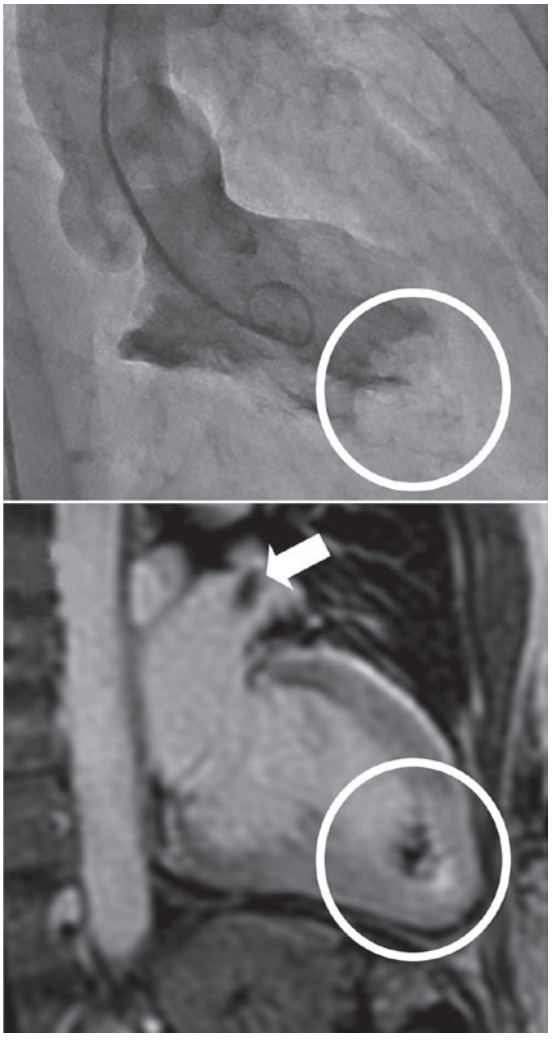

FIGURE 1. Top, Left ventricular apical thrombus (circle) as seen by ventriculography (day 10 of most recent admission). Bottom, Left ventricular apical thrombus (circle) and left atrial appendage thrombus (arrow) as seen on cardiac magnetic resonance imaging (day 12) with use of a gradient echo inversion recovery sequence 2 minutes after gadolinium-diethylenetriaminepentaacetic acid injection (0.2 mmol/kg; inversion recovery time, 350 ms).

TABLE. **Echocardiographic Left Atrial Parameters During the Acute and Recovery Phase of Tako-Tsubo Cardiomyopathy**

	Day 1	Day 7
Left atrial area (cm^2)	20.0	13.5
Mitral E-wave (cm/s)	66	48
Mitral A-wave (cm/s)	56	74
E/A ratio	1.2	0.64

E/A = peak early (E) to peak late [atrial] [A] diastolic filling.

in conjunction with LA stretch and subsequent endothelial injury may also act as contributory factors that favor thrombus development. The global nature of these factors may explain thrombosis in other cardiac chambers, such as the LAA as described in our case. Given the prothrombotic state that characterizes TTC episodes, a review of anticoagulation protocols for this condition may be warranted.

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1. Haghi D, Papavassiliu T, Heggemann F, Kaden JJ, Borggrefe M, Suselbeck T. Incidence and clinical significance of left ventricular thrombus in tako-tsubo cardiomyopathy assessed with echocardiography. *Q J Med*. 2008; 101(5):381-386.

2. Wittstein IS, Thiemann DR, Lima JAC, et al. Neurohumoral Features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005; 352(6):539-548.

3. Ardlie NG, Glew G, Schwartz CJ. Influence of catecholamines on nucleotide-induced platelet aggregation. *Nature*. 1966;212(5060):415-417.

4. Mann DL, Kent RL, Parsons B, Cooper G IV. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation*. 1992;85: 790-804.

5. Brutsaert DL, Meulemans AL, Sipido KR, Sys SU. Effects of damaging the endocardial surface on the mechanical performance of isolated cardiac muscle. *Circ Res*. 1988;62:358-366.

6. Brutsaert DL. Tako-tsubo cardiomyopathy [letter]. *Eur J Heart Fail*. 2007; 9(8):854.

7. Browning JA, Newell MC, Sharkey S, et al. Stress cardiomyopathy depresses left atrial function compared to acute anterior myocardial infarction: left atrial size and function by cardiac MRI [poster]. *J Cardiovasc Magn Reson*. 2010;12(suppl 1):196.

Supporting Online Material
www.mayoclinicproceedings.com/content/85/9/863/suppl/DC1
Supplemental video

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A Big Man With a Broken Heart: Stress-Induced Cardiomyopathy in a Morbidly Obese Man

To the Editor: A 61-year-old morbidly obese man (body mass index, 46 [calculated as the weight in kilograms divided by height in meters squared]) with a history of arterial hypertension, chronic obstructive pulmonary disease, and obstructive sleep apnea was admitted for radical resection of a squamous cell carcinoma of the skin overlying the right zygoma and temporal area extending into the auricle. The patient's postoperative course was uncomplicated until development of substernal chest pain associated with dyspnea and anterolateral ST-segment elevation on electrocardiography (performed while he was in bed) after he had engaged in an argument on postoperative day 14. Cardiac catheterization revealed no obstructive coronary artery disease (Figure 1). Serial electrocardiograms showed persistent ST-segment elevation, but serum troponin levels were negative. A transthoracic echocardiogram demonstrated moderately decreased left ventricular function with an ejection fraction of 35% and apical akinesis (Figure 2), suggesting stress-induced cardiomyopathy (SCM). Given the hypothesis that sex hormones play a modulating role in SCM,[1] sex hormone levels were measured. His serum estrone value was elevated at 7.5 ng/dL, serum estradiol was normal at 27 pg/mL, and free testosterone was depressed at 5.7 ng/dL. He was treated with oral lisinopril, 2.5 mg/d, and oral carvedilol, 12.5 mg twice daily. Echocardiography performed 3 weeks after the patient was discharged from the hospital revealed a normal left ventricular ejection fraction of 65% to 70%, without wall motion abnormalities.

In recent years, several studies have suggested that SCM is associated with increased catecholamine and sympathetic activity.[1] The sex and age predominance of SCM, which seems to occur mainly in postmenopausal women, suggests that estrogens may adversely modulate sympathetic activity and therefore increase susceptibility to SCM. Conversely, the lower incidence of SCM in healthy men suggests that androgens may play a protective regulatory role in the pathophysiology of SCM. The protective role of androgens may be lost in obese men because of altered sex hormone balance with decreased testosterone levels.

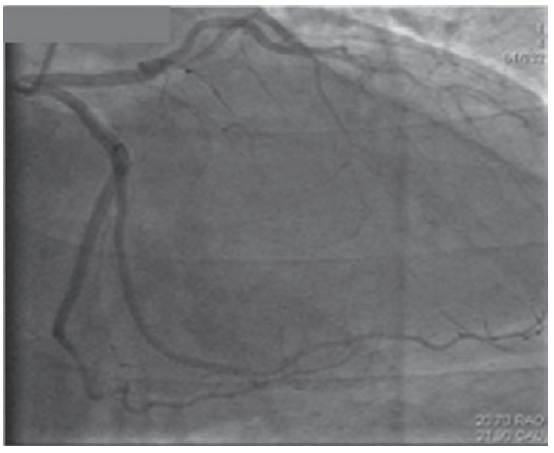

FIGURE 1. Angiogram revealing clean coronary arteries.

These clinical considerations are supported by several experimental and clinical studies. Male rat arteries showed greater vasoconstriction in response to adrenergic nerve stimulation compared with female rat arteries. Estradiol reduces the response to vasoconstrictors in both male and female arteries.[2] In postmenopausal women, attenuation of sympathetic nerve discharge may be induced by administration of transdermal estrogen.[3] Estrogen also down-regulates β1-adrenergic receptor expression.[4]

Testosterone has been reported to cause a direct and rapid vasodilatory effect in coronary arteries.[5] Intracoronary administration of testosterone, at physiological concentrations, dilates coronary arteries and increases coronary blood flow in men with established coronary artery disease.[6] Testosterone is thought to induce vasodilatation by blocking a membrane-associated calcium channel.[7] Efflux of potassium through channels in vascular smooth muscle is another possible mechanism of the vasodilatory effects of testosterone.[8]

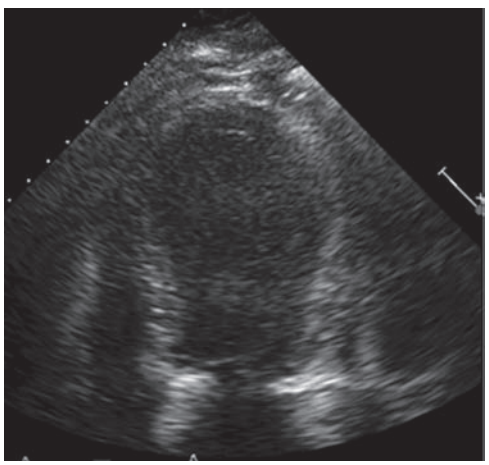

FIGURE 2. Transthoracic echocardiogram revealing apical ballooning shortly after chest pain episode.

TABLE. **Sex Hormone Levels by Sex and Age Cohort**

	Current patient	Adult male	Premenopausal female	Postmenopausal female
Estrone (ng/dL)	7.5	1.5-6.5	1.5-25.0	1.5-5.5
Estradiol (pg/mL)	27	10-50	20-750	<20
Free testosterone (ng/dL)	5.7	5.0-21.0	1.0-8.5	0.6-6.7

Data from reference 9.

In postmenopausal women, estradiol and estrone levels are closer to those of healthy adult men than those of premenopausal women (Table). The lower levels of estrogen in the absence of testosterone may explain the greater vulnerability of postmenopausal women.

Our patient's free testosterone level was at the lower limit of normal, and his estrone level was above the limits of normal for an adult male. This sex hormone profile in a morbidly obese man likely results from aromatization of androgens to estrogens. Also, several studies have linked obesity to endothelial dysfunction. Therefore, it is plausible that this patient was particularly vulnerable to catecholamine-induced vasospasm in the absence of the protective effects of high estrogen or normal testosterone levels.

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1. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352(6):539-548.

2. Garcia-Villalon AL, Buchholz JN, Krause DN, et al. Sex differences in the effects of 17 beta-estradiol on vascular adrenergic responses. *Eur J Pharmacol*. 1996;314(3):339-345.

3. Vongpatanasin W, Tuncel M, Mansour Y, et al. Transdermal estrogen replacement therapy decreases sympathetic activity in postmenopausal women. *Circulation*. 2001;103(24):2903-2908.

4. Thawornkaiwong A, Preawnim S, Wattanapermpool J. Upregulation of beta 1-adrenergic receptors in ovariectomized rat hearts. *Life Sci*. 2003;72(16):1813-1824.

5. Yue P, Chatterjee K, Beale C, et al. Testosterone relaxes rabbit coronary arteries and aorta. *Circulation*. 1995;91(4):1154-1160.

6. Webb CM, McNeill JG, Hayward CS, et al. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation*. 1999;100(16):1690-1696.

7. Jones RD, English KM, Pugh PJ, et al. Pulmonary vasodilatory action of testosterone: evidence of a calcium antagonistic action. *J Cardiovasc Pharmacol*. 2002;39(6):814-823.

8. Ding AQ, Stallone JN. Testosterone-induced relaxation of rat aorta is androgen structure specific and involves K+ channel activation. *J Appl Physiol*. 2001;91(6):2742-2750.

9. Gardner DG, Shoback D, eds. *Greenspan's Basic & Clinical Endocrinology*. 8th ed. New York, NY: McGraw Hill; 2007.

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Tailoring Diagnosis and Management of Pericardial Disease to the Epidemiological Setting

To the Editor: We read the comprehensive review "Pericardial Disease: Diagnosis and Management" by Khandaker et al[1] with interest. We would like to highlight certain aspects of tuberculous pericarditis that were not mentioned in the review but that we consider to be relevant to most patients with pericarditis who live in developing countries where tuberculosis (TB) is endemic. Developing countries harbor 80% of the population of the world. In countries that have a high burden of infection with human immunodeficiency virus (HIV), such as South Africa, tuberculous pericarditis accounts for 50% and greater than 90% of large pericardial effusions in HIV-negative and HIV-positive patients, respectively.[2] It is an important cause of cardiac morbidity and mortality and presents specific diagnostic and therapeutic challenges.[3,4]

The tuberculin skin test is not a reliable test in this epidemiological setting because of the background prevalence of TB, mass Bacille Calmette-Guérin immunization, and the likelihood of cross-sensitization from environmental mycobacteria.[5] In a contemporary series in South Africa, a positive tuberculin skin test result of 10 mm or greater had a sensitivity, specificity, positive predictive value, and negative predictive value of 89%, 56%, 82%, and 69%, respectively.[6] This is relevant despite the high prevalence of TB as a cause of large pericardial effusions because, when the diagnosis is wrong in those treated on a presumptive basis, there is a 5-fold increased risk of death.[4] A diagnosis can sometimes be established by demonstrating TB elsewhere, such as in the sputum, but these are insensitive methods. Even invasive methods to examine the pericardium or pericardial fluid directly are insensitive with respect to microscopic examination, culture, and polymerase chain reaction, resulting in the development of diagnostic algorithms that use tests of pericardial fluid such as assays for adenosine deaminase, interferon γ, or lysozyme, which have high sensitivities and specificities as indirect tests of TB.[3,6] At the University of Cape Town, routine tests of pericardial fluid include assays for adenosine deaminase, lactate dehydrogenase, and protein to differentiate between an exudative and transudative process, in addition to those listed by Khandaker et al.

Despite these efforts, the diagnosis sometimes remains a presumptive one. In areas with a high prevalence of TB, a pericardial effusion is often considered to be tuberculous in origin unless an alternative diagnosis is apparent. Furthermore, treatment often needs to be commenced before a bacteriological diagnosis is established. This approach does not apply in regions where the prevalence of TB is low. Therefore, the diagnostic and therapeutic approach to large pericardial effusion is dependent largely on the background prevalence of TB in the community of the patient.[7]

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1. Khandaker MH, Espinosa RE, Nishimura RA, et al. Pericardial disease: diagnosis and management. *Mayo Clin Proc*. 2010;85(6):572-593.
2. Reuter H, Burgess LJ, Doubell AF. Epidemiology of pericardial effusions at a large academic hospital in South Africa. *Epidemiol Infect*. 2005;133(3):393-399.
3. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. *Circulation*. 2005;112(23):3608-3616.
4. Mayosi BM, Wiysonge CS, Ntsekhe M, et al. Mortality in patients treated for tuberculous pericarditis in sub-Saharan Africa. *S Afr Med J*. 2008;98(1):36-40.
5. Ng TT, Strang JI, Wilkins EG. Serodiagnosis of pericardial tuberculosis. *QJM*. 1995;88(5):317-320.
6. Reuter H, Burgess L, van Vuuren W, Doubell A. Diagnosing tuberculous pericarditis. *QJM*. 2006;99(12):827-839.
7. Syed FF, Mayosi BM. A modern approach to tuberculous pericarditis. *Prog Cardiovasc Dis*. 2007;50(3):218-236.

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In reply: Syed and colleagues make very interesting and important points on tuberculous pericarditis that were not mentioned in our review article. In developed countries, the incidence of tuberculous pericarditis has declined substantially during the past half century; meanwhile, in developing countries, tuberculous pericarditis is still endemic, as outlined by Syed and colleagues. Because of the paucity of cases of tuberculous pericarditis at our institution, our clinical experience in this area is limited and our review was aimed at addressing major diagnostic and management dilemmas in pericardial disease seen in our practice. Syed and colleagues point out that routine tests of pericardial fluid at the University of Cape Town include assays for adenosine deaminase, lactate dehydrogenase, and protein to differentiate between an exudative and transudative process. In areas where the prevalence of TB is high, pericardial effusions are likely to be tuberculous in origin and treatment is started before a bacterial diagnosis is made. We are in agreement that diagnostic testing and management of the various pericardial syndromes need to be tailored to the epidemiological profiles of a particular geographic region. We thank Syed and colleagues for their important contribution on diagnostic and management dilemmas of tuberculous pericarditis in developing countries that were not addressed by our review.

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CORRECTION

Incorrect data in text and table: In the article by Arora et al entitled "Topical Corticosteroid Treatment of Dysphagia Due to Eosinophilic Esophagitis in Adults," published in the July 2003 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2003;78(7):830-835), incorrect data were published in the abstract and in the Results section of the article and in 1 table. On page 830, incorrect data on sex and age were given in the first sentence (lines 1-2) of the Results section of the abstract. The sentence should read as follows: The **15** men and **6** women ranged in age from **27** to **66** years at diagnosis (mean, **36** years). On page 831, incorrect data on sex were published in the second sentence (lines 2-3) of the Results section. The sentence should read as follows: The **15** men and **6** women had a lengthy history (>6 years) of solid-food dysphagia. On page 832, lines 3 through 6, right-hand column, an incorrect number was published. The sentence should read as follows: Despite the paucity of GERD [gastroesophageal reflux disease]-like symptoms, **17** of the 21 patients had been treated with daily doses of a proton pump inhibitor for at least 9 months before their evaluation at the Mayo Clinic. On page 832, lines 8 through 10, right-hand column, an incorrect number was published. The sentence should read as follows: Only **10** patients described a prior history of atopy (hay fever, asthma, or eczema) or had a documented drug allergy. On page 831, incorrect data were published in Table 1. Table 1 is shown here with corrected data in boldface.

TABLE 1. **Demographic and Clinical Features of Adults With Eosinophilic Esophagitis**[a]

Patient No./ sex	At onset of dysphagia	At diagnosis	Heartburn symptoms (>2/wk)	History of atopy[b]	History of drug allergies	Estimated weight loss in previous year (kg)	Treated with PPIs (>1 y)
1/M	15	**36**	No	No	No	2	Yes
2/M	29	32	No	No	No	3	Yes
3/M	22	**30**	Yes	No	No	1	Yes
4/M	20	**27**	No	Yes	No	0	Yes
5/M	15	**32**	No	No	Yes	0	Yes
6/M	29	**50**	No	Yes	No	0	Yes
7/**F**	29	**31**	No	No	No	1	Yes
8/M	30	**53**	No	No	Yes	0	Yes
9/F	**41**	**41**	Yes	No	No	1	Yes
10/M	**12**	**24**	No	No	No	**ND**	**ND**
11/M	29	**35**	No	**Yes**	No	**1**	Yes
12/M	**41**	**60**	Yes	No	No	**0**	Yes
13/M	**13**	**19**	**Yes**	**ND**	No	0	Yes
14/M	**33**	**43**	**Yes**	**Yes**	Yes	**ND**	Yes
15/**F**	**10**	**66**	No	**Yes**	**Yes**	**1**	**No**
16/M	**30**	**33**	**Yes**	No	No	**ND**	Yes
17/M	**15**	**17**	No	No	Yes	**2**	**No**
18/F	**14**	**26**	Yes	**Yes**	No	**0**	Yes
19/F	**ND**	**21**	**Yes**	**Yes**	No	0	**Yes**
20/M	12	**36**	No	No	No	ND	Yes
21/F	38	**41**	No	No	No	0	No

[a] ND = not documented; PPI = proton-pump inhibitor.
[b] Hay-fever, milk intolerance, asthma.

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