

Transient Left Ventricular Apical Ballooning: A Review of the Literature

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ABSTRACT

Transient left ventricular apical ballooning is a newly defined syndrome characterized by sudden onset of chest symptoms, electrocardiographic changes characteristic of myocardial ischemia, transient left ventricular dysfunction—particularly in the apical region, low-grade troponin elevation, and no significant coronary stenosis by angiogram. This syndrome is also referred to as Takotsubo cardiomyopathy, “Ampulla” cardiomyopathy, Human Stress cardiomyopathy, and Broken Heart Syndrome. Emergency physicians, family physicians, general internists, and cardiologists may all encounter this syndrome at the point of contact. The similarity to acute coronary syndrome requires all clinicians who may potentially care for these patients to familiarize themselves with this newly recognized disease. We provide a recent case and review the current literature surrounding this syndrome.

CASE

A 78-year-old female with no prior cardiac history presented to the emergency department with left sided chest and arm discomfort after being in a bus accident. She was not injured in the accident, but rather was rushing to another bus when her symptoms developed. Her initial troponin I was 0.6 ng/mL, but this increased over the next 12 hours and eventually peaked at 7.9 ng/mL. Her initial 12 lead electrocardiogram is detailed in Figure 1. This demonstrates sinus rhythm with multiple ventricular premature complexes and upsloping anterior ST elevation. She was managed as an acute coronary syndrome (ACS) with beta blockers, aspirin, heparin, and eptifi-

batide. The following day she was taken to the cardiac catheterization lab where her coronary angiogram demonstrated minor luminal irregularities. A left ventriculogram demonstrated moderate left ventricular (LV) dysfunction with anterior akinesis and an apical ballooning pattern (Figure 2). Left ventricular ejection fraction was estimated at 40%. A transthoracic echocardiogram was performed and confirmed the left ventricular dysfunction with the extensive anterior-apical akinesis (Figure 3). The patient did well and was discharged home after 48 hours. A follow-up echocardiogram done 4 weeks later demonstrated completely normal left ventricular function (Figure 4). To-date, she continues to do well.

BACKGROUND

This syndrome was first described in the 1990s by Japanese authors as a syndrome of multivessel spasm in Japanese women.¹ Later publications have documented the occurrence of this syndrome in white patients both in Europe and in the United States.^{2,3} The term Takotsubo was developed in Japan due to the likeness of the left ventricle to a pot used by Japanese fisherman to capture octopus. The pot has a round bottom and narrow neck, very similar to the appearance of the LV on left ventriculogram. The concept of reversible LV dysfunction related to ischemia has been previously recognized, however transient apical ballooning seems to be unique in that it is discrete from acute plaque rupture.⁴ The idea that a noncardiac illness could result in significant reversible LV dysfunction was illustrated by Sharkey in 1998.⁵ He reports a series of patients with varying noncardiac diagnoses who developed significant LV dysfunction who subsequently recovered. At that time, it was hypothesized that a catecholamine surge in the context of severe illness was the impetus for the LV dysfunction. Today, transient apical ballooning has become an intensely studied syndrome and has received significant attention of late both in the medical literature and the lay press.^{2,6-8}

EPIDEMIOLOGY

The exact prevalence of the syndrome is unknown. Very

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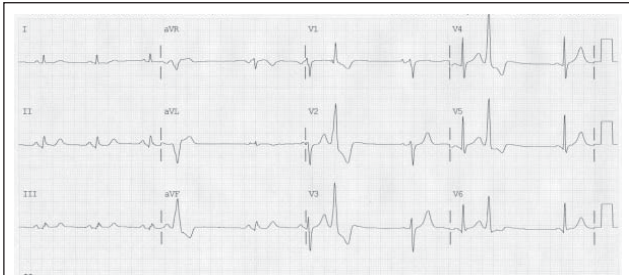


Figure 1. 12 lead electrocardiogram of patient.

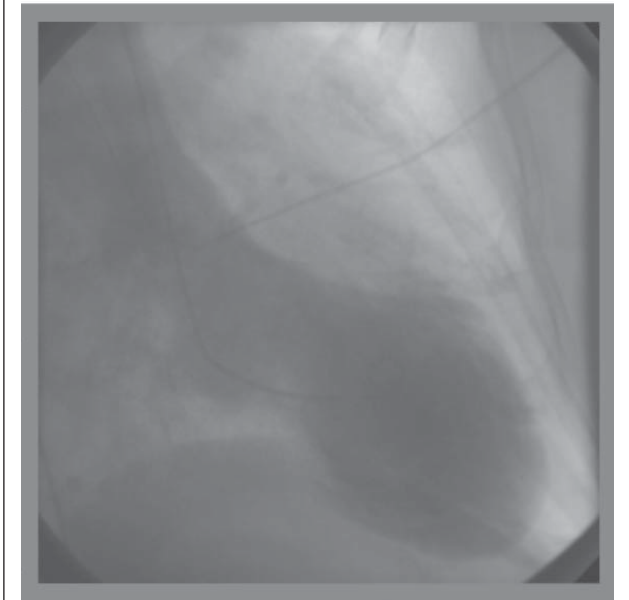


Figure 2. Left ventriculogram of patient with diastole above and systole below demonstrating the apical ballooning pattern with basal hyperkinesis and apical akinesis.

few reports provide an exact estimate of the prevalence. Two series report numbers with the prevalence varying between 1.5% and 2.2% among those presenting with ACS or ST elevation myocardial infarction (STEMI) respectively.^{9,10} Very little data exists with regard to the occurrence of apical ballooning in non-Japanese or non-white populations, and thus the prevalence in other demographic populations is unknown. There is clear evidence of a female preponderance, particularly in postmenopausal females with percentages ranging from 86%-100%.² Given the age of the typical patient with apical ballooning, most of the patients also have risk factor(s) for atherosclerotic vascular disease. This can make obtaining a diagnosis more difficult, particularly at the initial presentation.

CLINICAL PRESENTATION

Patients with apical ballooning typically describe a stressful event prior to the onset of symptoms. This stressful event may be emotional, physical, or psychological in nature. The exact percentage of those with a stressful event is unknown. Bybee’s series reports 14%-38% of patients with an emotional stressor and 17%-77% of patients with a physiologic stressor.² Various stressor events have been described including death of a loved one, severe noncardiac illness, medical procedure, or exercise; however a stressor by history is not required for the diagnosis.^{3,11}

The physical presentation at the time patients seek medical care is varied. Patients usually have symptoms suggestive of myocardial ischemia and left ventricular dysfunction. Typical symptoms include dyspnea and chest discomfort. Case reports of syncope at presentation are also documented in the literature.^{9,11} Patients who are asymptomatic from a cardiovascular perspective have been reported to have apical ballooning in previous reports.¹² These patients have symptoms related to another illness, which presumably triggers the apical ballooning. The exact prevalence of those without cardiovascular symptoms is unknown, however it would appear to be rare based on current literature.

DIAGNOSTIC STUDIES

The laboratory workup is usually characterized by some degree of myocardial biomarker elevation. Desmet’s series of 13 white patients’ reports peak values for troponin I and CK-MB fraction. The peak values for troponin I range from 2.0 to 97.6 µg/mL with the majority being <20 µg/mL, and the peak values for CK-MB range from 5.2 to 115.7 µg/mL.³ The largest series by Tsuchihashi reports elevated CK levels in 52%

of their patients and elevated troponin T levels (>0.25 ng/mL) in 72% of 88 Japanese patients.¹³ The amount of LV dysfunction found on both echocardiography and ventriculography does not seem to correlate well with the biomarker level. This finding has led many authors to conclude that coronary disease is not related to the pathogenesis of apical ballooning. Brain type natriuretic peptide (BNP) levels have also been assayed in some patients with apical ballooning. Akashi found elevated BNP levels (mean 522.5 pg/mL) in 7 of the 10 patients with apical ballooning.¹⁴

Electrocardiography is a critical tool in the work-up of a patient with suspected ACS and/or LV dysfunction. The EKG findings in patients with apical ballooning tend to be very similar to those patients with acute coronary syndrome as evidenced by our patient. Patients can have ST elevations, ST depression and nonspecific T wave changes with the majority having anterior ST elevation. The ST segment changes seem to occur primarily in the precordial leads. The early evolution of the EKG changes can be similar to those with anterior infarct patterns with the subsequent development of Q waves and secondary T wave changes. One author has reported that the ST changes occur more in the anterolateral precordial leads as compared to acute anterior myocardial infarction.¹⁵ The QT interval has also been prolonged in some patients with apical ballooning with a corrected QT in 1 series of $578 + 96$ ms, although this is not a consistent finding.¹¹

Coronary angiography is performed in virtually all patients diagnosed with apical ballooning. Angiograms do not show any evidence of occlusive coronary disease (stenosis $>50\%$) in any vessel segments. Right heart catheterizations performed at the time of presentation reflect the patient's clinical heart failure with varying degrees of elevation in filling pressures. Left ventriculograms are often performed to assess LV function in patients with symptoms suggestive of ventricular dysfunction. Ventriculography demonstrates severe antero-apical dyskinesia with hypercontractility of the basal segments. The apex has a ballooning appearance as can be seen in Figure 2. Calculated ejection fractions at presentation typically range from 20%-50%. Echocardiography typically confirms the presence of antero-apical akinesis or dyskinesia, but also can detect other potential complications related to apical ballooning. These include mitral regurgitation primarily related to systolic anterior motion of the anterior leaflet, dynamic left ventricular outflow obstruction, and thrombus formation. Nuclear single-photon computed tomographic myocardial imaging has been performed on

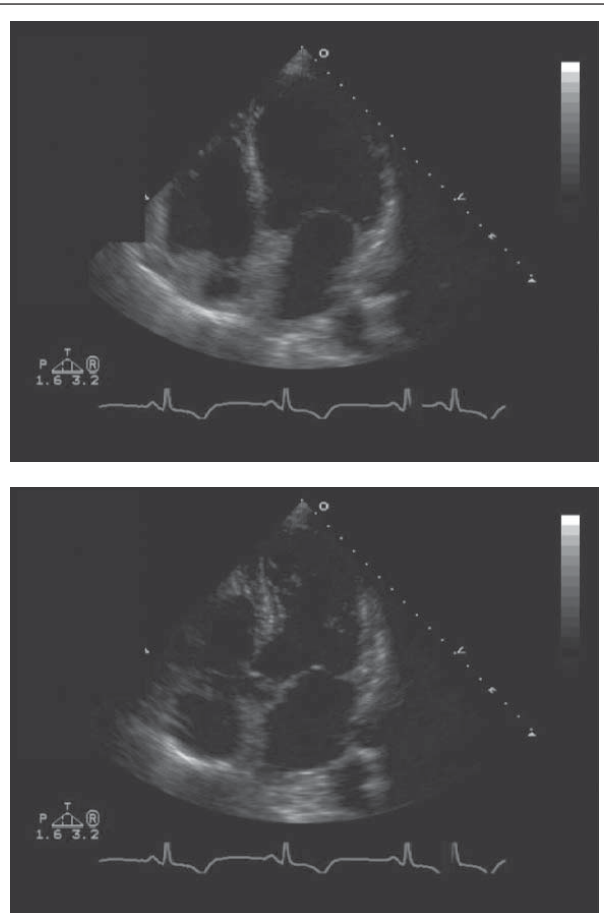


Figure 3. Transthoracic echocardiogram with apical 4-chamber views of the patient during her acute illness demonstrating basal hyperkinesis and apical dyskinesia. Diastole is above and systole is below.

patients with apical ballooning. Findings demonstrate decreased uptake in the anteroapical regions in the acute phase, however this abnormality returns to normal with repeat scanning several weeks after recovery.¹⁶ A recent series provided cardiac MRI data on 21 of 22 patients.⁶ The MRIs confirm the echocardiographic findings of dyskinesia in the mid and apical LV segments but also document a lack of delayed gadolinium hyperenhancement consistent with viable myocardium. This finding fits nicely with the clinical picture of complete recovery of left ventricular function.

CLINICAL COURSE AND POTENTIAL COMPLICATIONS

The clinical course of apical ballooning is characterized by congestive heart failure of varying degrees with the potential for significant hemodynamic compromise. The literature reflects this variability with some patients requiring hemodynamic support with pressor agents

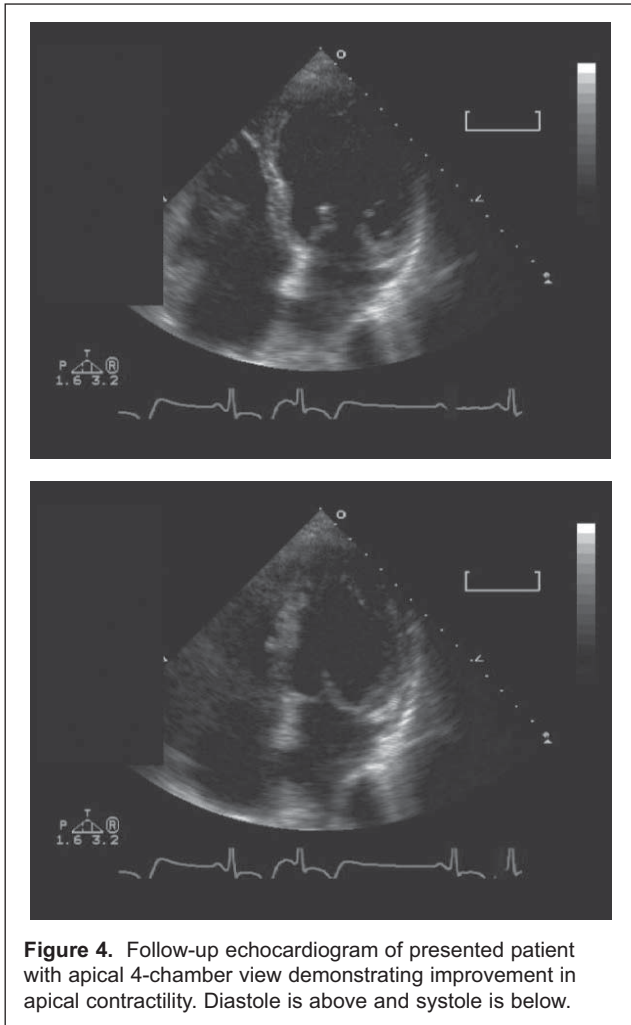


Figure 4. Follow-up echocardiogram of presented patient with apical 4-chamber view demonstrating improvement in apical contractility. Diastole is above and systole is below.

or a balloon pump while others remain asymptomatic following their initial presentation. The frequency with which patients require intra-aortic balloon pump placement ranges from 0% to 46% depending on the particular series.² The requirement for pressor agents is not well reported in the literature to date. Both supraventricular and ventricular arrhythmias have been reported including paroxysmal atrial fibrillation, sinus bradycardia, atrioventricular block, non-sustained ventricular tachycardia, sustained ventricular tachycardia, and ventricular fibrillation. Reported serious ventricular arrhythmias are quite rare. The basal hyperkinesia, apical dyskinesia, and potential systolic anterior motion of the mitral valve allow for the development of a dynamic intraventricular gradient or LV outflow tract gradient. This is invariably transient and resolves with improvement in apical contractility or removal of a pressor agent. The exact frequency of this gradient is unknown; however the largest series by Tsuchihashi reports an occurrence of 18% with a gradient greater than

30mm Hg.¹³ Mitral regurgitation with systolic anterior motion of the anterior leaflet has also been reported, which fits well with the intraventricular pressure gradient. Other potential complications have been reported in case reports including LV thrombus and ventricular free wall rupture.^{17,18}

Patients with apical ballooning have excellent short-term mortality. Desmet's series of 13 patients reports 1 hospital death with a mortality of 8%, however all other significant series report in hospital mortality of 0%-1%.³ Patients recover LV function over a course of days to weeks. Long-term mortality has not been well studied as of yet, although it appears to be good based on the limited data acquired thus far. The potential for recurrence has not been well studied in a prospective series; however, retrospective series have reported recurrence rates ranging from 0% to 8%.²

MANAGEMENT

No clear algorithm has been proposed with regard to managing patients with apical ballooning. Most patients are managed according to ACS guidelines initially as their presentation is very similar and often ACS leads the initial differential diagnosis. Supportive care with hemodynamic support and tailored therapy based on potential complications is the standard based on current literature. A series of 3 cases managed with beta blockers reported improvement with therapy in the 2 patients with significant intraventricular pressure gradients.¹⁹ Thus, therapy must be dictated by clinical course and patient-specific complications. An echocardiogram early in the clinical course can assess for a potential LV outflow tract gradient and may accelerate accurate classification of the patient's condition. Those patients with LV outflow tract gradients should be managed with therapy to minimize the gradient (beta blockers, calcium channel blockers, or increased afterload) and avoidance of therapies that exacerbate the gradient (i.e. diuretics, pressors, IABP). Other complications, including atrial or ventricular arrhythmias, pulmonary edema, and pump failure, should be managed in a patient-specific fashion.

POSSIBLE ETIOLOGIES

The idea that excess catecholamines could potentially trigger myocardial dysfunction has received significant attention in the past. It has been well documented that disorders characterized by significantly elevated levels of catecholamines such as subarachnoid hemorrhage and pheochromocytoma can trigger reversible LV dysfunction.²⁰⁻²² This relationship has triggered others to search

for a potential link between catecholamine excess and transient apical ballooning.

At the basic science level, researchers have documented differences in beta adrenergic receptor density and tissue levels of catecholamines between the apex and base of the left ventricle in animal models.^{23,24} This difference in receptor density could explain the unique regional variation seen in apical ballooning. Recently, a rat model showed inhibition in the development of apical ballooning with metoprolol and prazosin.²⁵ These same authors demonstrated that the genetic activation characterized in their rat model could also be inhibited by metoprolol and prazosin and concluded that catecholamine toxicity with activation of α and β adrenergic receptors was the primary trigger in apical ballooning.²⁶ Some have used nuclear perfusion imaging with different radiolabeled tracers to study a possible relationship between sympathetic excess and apical ballooning. Owa and colleagues demonstrated different recovery courses for metaiodobenzyl-guanidine (MIBG) and I-123 methyl-iodopheny pentadecanoic acid (BIMPP) perfusion imaging in patients with apical ballooning.²⁷ They concluded that a disturbance in sympathetic innervation was related to the apical ballooning syndrome. A recent publication measured serum catecholamine levels in their series and found significantly elevated levels as compared to a control group with Killip class 3 myocardial infarction.⁷ However, another series failed to consistently demonstrate elevated levels of serum catecholamine levels.²⁸ The temporal relationship between a stressful event and the clinical syndrome seems to substantiate a significant link between catecholamines and apical ballooning. Most authors seem to agree that catecholamines play a role in the development of the syndrome; however it remains unclear if these neurohormones represent secondary elevation or a causative agent.

Ischemia resulting in reversible LV dysfunction has also been well documented in the past.⁴ Coronary angiograms have been unsuccessful in documenting significant angiographic disease to date. A recent series of 5 patients included intravascular ultrasound (IVUS) of the left anterior descending artery to assess for atherosclerosis.²⁹ They found that all 5 of their patients had single ruptured plaques in their mid LAD by IVUS, concluding that ACS with subsequent early reperfusion and stunned myocardium was the potential etiology of apical ballooning. It appears unlikely that ischemic heart disease plays a significant role given that the territory of ventricle involved can extend well beyond that of a single epicardial vessel. This has been previously demonstrated by echocardiograms and perfusion imaging.

Several other theories have been hypothesized as to the etiology of transient apical ballooning. These include multivessel spasm, microvascular dysfunction, transient obstruction to left ventricular outflow, and myocarditis. Coronary spasm has been studied in patients with apical ballooning. Authors have attempted to induce vasospasm in patients with apical ballooning with inconsistent results. In the largest series to date, Tsuchihashi and others attempted to induce spasm in 48 patients with only 21% success.¹³ Biopsy specimens obtained during catheterization of patients with apical ballooning have been nondiagnostic. Viral titers have been measured in an attempt to assess for viral myocarditis with no significant elevation obtained.²⁸ Nuclear scans documenting limited uptake in the apex suggest abnormal fatty acid metabolism potentially related to microvascular dysfunction, however this has yet to be causally linked.³⁰

The female preponderance and initial Japanese predilection are both very intriguing and beg the question of a potential genetic or hormonal susceptibility. More recent data have now characterized this syndrome both in white females and a few males. Whether there is biologic susceptibility is unknown at the present time. To date, no clear etiology of apical ballooning has been well accepted, and this will likely remain an intense area of interest and future study.

CONCLUSIONS

Recently, a group from Mayo Clinic proposed a diagnostic system that requires the presence of 4 criteria.² These included (1) transient akinesis or dyskinesis of the left ventricular apical and mid-ventricular segments with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution, (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture, (3) new EKG abnormalities (either ST-segment elevation or T-wave inversion), and (4) absence of recent significant head trauma, intracranial bleeding, pheochromocytoma, obstructive epicardial coronary disease, myocarditis, and hypertrophic cardiomyopathy. These criteria require that a cardiac catheterization be performed, which may limit the number of patients physicians are able to diagnose. It's conceivable that this syndrome is under-diagnosed with smaller hospitals using thrombolytics rather than primary angioplasty for possible new ST elevation myocardial infarction patients. The criteria otherwise seem reasonable; however we would suggest that ST segment depression also be included as we have seen several such patients at our institution.

Our case demonstrates the typical presentation characterizing this syndrome, highlighting its similarity to ACS. Primary care clinicians and cardiovascular specialists must recognize this syndrome as a distinct entity when caring for those with potential ACS. Transient apical ballooning appears to be a syndrome primarily in women who are exposed to a significant stressor and subsequently develop EKG changes with reversible LV dysfunction. The probable relationship with a hyperadrenergic state may define a role for long-term therapy with beta blockers to prevent potential recurrence. Future study will most certainly be needed in order to elucidate and more clearly define potential risk factors for this syndrome, etiology and pathogenesis, appropriate therapies, and long term recurrence risk.

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