Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction

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Apical ballooning syndrome (ABS) is a unique reversible cardiomyopathy that is frequently precipitated by a stressful event and has a clinical presentation that is indistinguishable from a myocardial infarction. We review the best evidence regarding the pathophysiology, clinical features, investigation, and management of ABS. The incidence of ABS is estimated to be 1% to 2% of patients presenting with an acute myocardial infarction. The pathophysiology remains unknown, but catecholamine mediated myocardial stunning is the most favored explanation. Chest pain and dyspnea are the typical presenting symptoms. Transient ST elevation may be present on the electrocardiogram, and a small rise in cardiac troponin T is invariable. Typically, there is hypokinesis or akinesis of the mid and apical segments of the left ventricle with sparing of the basal systolic function without obstructive coronary lesions. Supportive treatment leads to spontaneous rapid recovery in nearly all patients. The prognosis is excellent, and a recurrence occurs in <10% of patients. Apical ballooning syndrome should be included in the differential diagnosis of patients with an apparent acute coronary syndrome with left ventricular regional wall motion abnormality and absence of obstructive coronary artery disease, especially in the setting of a stressful trigger. (Am Heart J 2008;155:408-17.)

An association between emotional or physical stressful triggers and adverse cardiovascular events such as death and myocardial infarction has been recognized for many years.1,2 At a population level, earthquakes, wars, and major sporting events have all been linked to a surge in cardiovascular mortality.3,4 Among hospitalized patients, noncardiac surgery is one of the most frequent triggers for cardiovascular events, with the highest risk in those undergoing vascular surgery due to coexisting severe coronary artery disease.5 Myocardial dysfunction may occur in critically ill patients with sepsis due to a pathogen-induced proinflammatory immune response,6 and a reversible cardiomyopathy in critically ill patients has also been reported in the absence of sepsis.7 Similarly, neurologists have recognized an association between subarachnoid hemorrhage and a reversible cardiomyopathy that has been termed neurogenic stunning, characterized by acute brain injury and the absence of coronary artery disease.8,9

Recently, there has been an increasing awareness of a unique cardiac syndrome that has been described as the apical ballooning syndrome (ABS), Tako-Tsubo cardiomyopathy, and stress or ampulla cardiomyopathy.10-11 It has also been referred to as the Broken Heart Syndrome in the popular press. The syndrome overlaps with the aforementioned conditions in that it is a reversible cardiomyopathy that is frequently precipitated by a stressful event and has a clinical presentation that is indistinguishable from a myocardial infarction. This distinct cardiac syndrome was originally described in 1990 in the Japanese population and was called “Tako-Tsubo cardiomyopathy,” named after the octopus trapping pot with a round bottom and narrow neck, which resembles the left ventriculogram during systole in these patients.12 Sporadic case reports followed13 until the last 5 years or so during which several cases series have been reported from around the world, including Europe,14,15,16,17,20 North America,18,21,22 and Australia.23 In 2006, the American Heart Association incorporated ABS into its classification of cardiomyopathies as a primary acquired cardiomyopathy.24

Apical ballooning syndrome is underrecognized and often misdiagnosed. It is an important differential diagnosis of an acute myocardial infarction. We review the best evidence regarding the pathophysiology, clinical features, investigation, and management of ABS.

Incidence

The precise incidence of ABS is unknown due to its novel nature, varied presentation, and evolving
diagnostic criteria. Nevertheless, several studies have estimated that approximately 1% to 2% of all patients presenting with an initial primary diagnosis of either an acute coronary syndrome or myocardial infarction have ABS. According to American Heart Association statistics, there are 732,000 hospital discharges with a primary diagnosis of an acute myocardial infarction in the United States each year. Thus, a conservative estimate of the annual rate of ABS in the United States may be 7,000 to 14,000 cases.

Age and sex

Apical ballooning syndrome is a unique cardiomyopathy in that it usually occurs in postmenopausal women. Recent review of the published case series reveals that approximately 90% of all reported cases have been in women. The mean age has ranged from 58 to 75 years, with <3% of the patients being <50 years. The reason for the female predominance is unknown but raises the intriguing question as to whether withdrawal from estrogens contributes to the pathogenesis. It has been suggested that ABS may be not be diagnosed in males because of the higher prevalence of coronary artery disease, but this seems unlikely given the consistent sex disparity among all published studies.

Clinical presentation

The clinical presentation in most patients is indistinguishable from an acute coronary syndrome; 50% to 60% present with chest pain at rest, which has an angina-like quality. Dyspnea may also be the initial presenting symptom, but syncope or out-of-hospital cardiac arrest is rare. Intensive care unit patients are likely to present with pulmonary edema, ischemic changes on the electrocardiogram, or elevated cardiac biomarkers. In general, hemodynamic compromise is unusual, but mild to moderate congestive heart failure is frequent. Hypotension may occur because of the reduction in stroke volume and, occasionally, because of dynamic left ventricular outflow tract obstruction. Cardiogenic shock has been reported as a rare complication.

A unique feature of ABS is the occurrence of a preceding emotional or physical stressful event in approximately two thirds of patients. Importantly, such a trigger can not be identified in all individuals, despite a careful history, and hence, its absence does not exclude the diagnosis. A rise in the incidence of ABS was reported after the Central Niigata Prefecture earthquake in Japan in 2004, an observation that leads us to believe that some of the cardiovascular morbidity and mortality associated with
natural disasters, wars, and sporting events may be related to a stress cardiomyopathy.

**Electrocardiogram and cardiac biomarkers**

The most common abnormality on the electrocardiogram (ECG) is ST-segment elevation, mimicking an ST-elevation myocardial infarction (STEMI). However, there is significant variability in the frequency (46%-100%) of this finding in the published literature. At least 2 reasons may account for the variability in the reported frequency of ST-segment elevation. First, the elevation is transient, and hence, the time from symptom onset to presentation may determine whether it is detected. Second, there is potential for selection bias for patients presenting with ST-segment elevation who are likely to undergo prompt coronary angiography and assessment of left ventricular function. Typically, the elevation is present in the precordial leads, but it may be seen in the inferior or lateral leads. Nonspecific T-wave abnormality, new bundle-branch block, and in some cases, a normal ECG may be the finding at presentation. When anterior ST-elevation is present, the magnitude of ST shift is usually less in ABS than that seen in a STEMI. The 12-lead ECG by itself is insufficient for differentiating ABS from STEMI. Characteristic and common evolutionary changes that may occur over 2 to 3 days include...
resolution of the ST-segment elevation, development of diffuse and often deep T-wave inversion that involves most leads, and prolongation of the corrected QT interval (Figure 1). Transient pathological Q waves may rarely develop. The T-wave inversion and QT interval prolongation typically resolve over 3 to 4 months but may occur as early as 4 to 6 weeks and, in some cases, be present beyond 1 year.49,50

Most if not all patients have a modest rise in cardiac troponin T that peaks within 24 hours.14,16,18 The magnitude of increase in the biomarkers is less than that observed with a STEMI and disproportionately low for the extensive acute regional wall motion abnormalities that characterize ABS (Figure 2). Circulating brain natriuretic peptide, a marker of ventricular dysfunction, is invariably elevated and correlates with the left ventricular end-diastolic pressure.21

Coronary angiogram and cardiac imaging

Most patients with ABS either have angiographically normal coronary arteries or mild atherosclerosis.15,54 Obstructive coronary artery disease may rarely coexist by virtue of its prevalence in the population at risk.

The characteristic regional wall motion abnormalities involve hypokinesis or akinesis of the mid and apical segments of the left ventricle (Figure 3). There is sparing of the basal systolic function. Importantly, the wall motion abnormality typically extends beyond the distribution of any single coronary artery. Transthoracic echocardiography can detect the regional wall motion abnormality; however, visualization of the true anatomic apex can be difficult, particularly in acutely ill patients. The diagnosis is frequently made in the cardiac catheterization laboratory during left ventriculography because the patients are initially suspected of suffering from an acute coronary syndrome and are referred for urgent or emergency coronary angiography. The right ventricle may reveal similar regional wall motion abnormality in approximately 30% of patients who tend to be sicker and more likely to develop congestive heart failure.41,42 Recently, variants of ABS have been described, occurring in a significant minority of patients with a clinical presentation similar to that of classic ABS.43,44 In these patients, there is preserved function of the apex with wall motion abnormality that involves the mid segments (apical sparing variant) (Figure 4). It is possible that this is simply a manifestation of early recovery of function at the apex in some patients with classical ABS. A rare variant presents with hypokinesis of the base of the heart with preserved apical function (inverted Tako-Tsubo).15 Cardiac magnetic resonance appears to be a useful imaging modality for documenting the extent of the regional wall motion abnormality and differentiating ABS (characterized by the absence of delayed gadolinium hyperenhancement) from myocardial infarction and myocarditis in which delayed hyperenhancement is present.16,25,26,46

Diagnosis

The diagnosis should be considered in the differential diagnosis of any patient with acute myocardial infarction. However, the classic situation is a postmenopausal woman presenting with chest pain or dyspnea that is temporally related to emotional or physical stress, with positive cardiac biomarkers or an abnormal electrocardiogram. Apical ballooning syndrome should also be considered in the differential diagnosis of inpatients, including those in the intensive care unit, who develop an acute reduction in left ventricular systolic function in association with ≥ 1 of the following: hemodynamic compromise, pulmonary edema, troponin elevation, or ECG evidence of ischemia or infarction. There may be a higher prevalence of males in the intensive care unit population.

We have previously proposed the Mayo Clinic criteria for the diagnosis of ABS that can be applied at the time of presentation.13 The criteria have evolved over time as our understanding of the cardiomyopathy improves.49 All 4 criteria must be present. Table II illustrates a modified version of the criteria. In the current version, we no longer exclude patients who develop typical ballooning in the setting of intracranial bleeding, including those with subarachnoid hemorrhage. Neurogenic stunning in this situation has the same features as ABS50,51 and is likely a manifestation of the same spectrum of disease. The diagnosis of ABS is most likely to be made at institutions with cardiac catheterization laboratories where primary percutaneous coronary intervention is
Performing for STEMI and an early invasive strategy is practiced for non STEMI. The absence of obstructive coronary artery disease and characteristic regional wall motion abnormality is likely to lead to the diagnosis. Diagnosing ABS in patients presenting at hospitals without cardiac catheterization laboratories requires a high index of suspicion. Establishing the diagnosis is particularly important if fibrinolytic therapy is being considered for a presumed diagnosis of STEMI. Inappropriate administration of fibrinolytics to a patient with ABS may lead to harm, and it would be reasonable to transfer a patient suspected of the cardiomyopathy for emergency coronary angiography.

Management

Since the presentation mimics an acute coronary syndrome, initial management should be directed towards the treatment of myocardial ischemia with continuous ECG monitoring, administration of aspirin, intravenous heparin, and β-blockers. The optimal management of ABS has not been established, but supportive therapy invariably leads to spontaneous recovery. Once the diagnosis has been made, aspirin can be discontinued unless there is coexisting coronary atherosclerosis. The efficacy of β-blocker therapy has not been formally tested. If tolerated, it is reasonable to initiate β-blockers empirically because excess catecholamines have been implicated in the pathogenesis. The role of combined α-1 and β-receptor blockade with drugs such as labetalol or carvedilol is unknown.

Congestive heart failure is the most common complication occurring in approximately 20% of patients and is more likely in the presence of right ventricular involvement. Diuretics are effective in most cases. It is important to exclude dynamic left ventricular outflow tract obstruction with echocardiography in patients with severe heart failure or significant hypotension. Asymptomatic intracardiac pressure gradient may be present in as many one fifth of patients but symptomatic obstruction is uncommon. Dynamic outflow-tract obstruction may be associated with systolic anterior motion of the mitral leaflet and mitral regurgitation. In the absence of heart failure, a cautious trial of intravenous fluids and β-blockers may help by reducing the hypercontractility of the base of the left ventricle and increase cardiac filling, thereby reducing the obstruction. Alternatively, an infusion of phenylephrine may be effective by increasing the afterload and left ventricular cavity size in patients in whom β-blocker or intravenous fluids are contraindicated. Inotropes would be contraindicated in the presence of dynamic outflow tract obstruction. In contrast, cardiogenic shock due to pump failure is treated with standard therapies, which include inotropes and intraaortic balloon counterpulsation.

As with acute myocardial infarction, ABS may rarely lead to mechanical and arrhythmic complications. Mechanical complications reported include free wall rupture and severe mitral regurgitation. Atrial and ventricular arrhythmias may occur, but ventricular tachycardia and fibrillation is rare. Anticoagulation should be considered during the initial presentation if severe left ventricular systolic dysfunction is present and continued for a few weeks with warfarin if there is slow functional recovery to prevent thromboembolism. Left ventricular thrombus may rarely be present during the acute phase, and anticoagulation is clearly indicated in this circumstance.

In our practice, in the absence of contraindications, we empirically recommend chronic β-blocker therapy with the aim of reducing the likelihood of a recurrent episode. Initiation of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy before discharge is reasonable. This is particularly important because the diagnosis may not be certain at the time of discharge and these drugs would be indicated for nonreversible left ventricular dysfunction. Inhibitors of the renin angiotensin system can be discontinued once there is complete recovery of systolic function in ABS. Annual clinical follow-up is advisable because the natural history of ABS remains unknown.

Prognosis

The systolic dysfunction and the regional wall motion abnormalities are transient and resolve completely within a matter of days to a few weeks. In our experience and in other large series complete recovery is seen in virtually all patients by 4 to 8 weeks. This is such a uniform finding that an alternative diagnosis should be considered in patients in whom the cardiomyopathy does not resolve. Patients with ABS generally have a good prognosis in the absence of significant underlying comorbid conditions. The ejection fraction should be

### Table II. Proposed Mayo Clinic criteria for ABS

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<td>1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.</td>
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<td>2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.†</td>
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<td>3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.</td>
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<td>4. Absence of:</td>
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<td>Pheochromocytoma</td>
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<td>Myocarditis</td>
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In both of the above circumstances, the diagnosis of ABS should be made with caution, and a clear stressful precipitating trigger must be sought.† There are rare exceptions to these criteria such as those patients in whom the regional wall motion abnormality is limited to a single coronary territory. It is possible that a patient with obstructive coronary atherosclerosis may also develop ABS. However, this is very rare in our experience and in the published literature, perhaps because such cases are misdiagnosed as an acute coronary syndrome.

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measured in approximately 4 to 6 weeks after discharge from the hospital to document recovery of cardiac function. Inhospital mortality from ABS is very low and unlikely to be >1% to 2%. Overall, the long-term survival is similar to that of the general age-matched population. The subgroup of patients in whom there is a physical trigger such as major surgery or illness appear to have a worse prognosis, most likely related to the underlying condition. The recurrence rate of ABS is no >10%.35

Pathophysiology

The pathophysiology of ABS is not well understood. Several mechanisms for the reversible cardiomyopathy have been proposed, including catecholamine-induced myocardial stunning, ischemia-mediated stunning due to multivessel epicardial or microvascular spasm, and myocarditis (Figure 5). Myocarditis is extremely unlikely to be the mechanism since studies reporting endomyocardial biopsy data have consistently shown the absence of myocarditis.17,24,58,59 Furthermore, cardiac magnetic resonance imaging does not show regional delayed gadolinium hyperenhancement, which is a feature of myocarditis.16,23,26

Catecholamines may play a role in triggering the syndrome because many patients have emotional or physical triggers. There is an increasing awareness of the close interaction between cortical brain activity and the heart.60 In clinical studies, mental stress has been demonstrated to reduce left ventricular ejection fraction and, rarely, induce regional wall motion abnormalities in conjunction with a rise in catecholamines.61 Moreover, wall motion abnormalities and depressed ejection fraction have been observed in diseases associated with high catecholamines such as a pheochromocytoma62,63 and subarachnoid hemorrhage.64 Wittstein et al25 have reported very high levels of catecholamines in ABS at the time of presentation, which remained elevated for 7 to 9 days. Endomyocardial biopsies in a subset of their patients demonstrated contraction band necrosis, a feature of catecholamine toxicity. However, neither the elevation in circulating catecholamines21,47 nor the contraction band necrosis17,25,58,59 has proven to be consistent finding. Interestingly, in a rat immobilization stress model of ABS, investigators have been able to induce ST-segment elevation and apical ballooning that can be prevented by the administration of combined alpha and β adrenoreceptor antagonists.65

Early Japanese literature suggested that ABS may result from ischemia due to multivessel epicardial spasm.66 This has not been confirmed in the recent larger series or in our experience, and we believe that epicardial spasm is unlikely to be the underlying cause of ABS in most cases. It is possible that the routine administration of nitrates for ischemic chest pain may obscure the presence of spasm. Tsuchihashi et al13 have reported that coronary spasm may be induced with acetylcholine provocation in 21% of patients in their series. However, the clinical relevance of this finding is questionable because endothelial dysfunction is highly prevalent in postmenopausal women. Microvascular dysfunction measured using angiographic techniques such as myocardial blush grade can
be detected in at least two thirds of the patients at the
time of presentation, and its severity correlates with the
magnitude of troponin elevation and ECG abnormal-
ities.57 Similarly, the TIMI frame count is prolonged in all
3 major epicardial coronary vessels in the acute setting,
indicating the presence of impaired microvascular
flow.14,19 single photon emission computed tomography
using thallium and sestamibi tracers and positron
emission tomography using 13 N-ammonia have consis-
tently demonstrated impaired perfusion in the regions of
the wall motion abnormality.68,69 However, the meta-
abolic defect measured as fatty acid or glucose metabo-
lism in these studies has generally been larger than the
perfusion defect. This may be either because the
primary abnormality in ABS is metabolic dysfunction and
not impaired perfusion or because the microcirculation
recovers more rapidly than the myocardial metabolism.
At this time, it is unknown whether the impairment in
microvascular function is the primary mechanism for the
injury or an epiphenomenon.
It has been suggested that development of a severe
intracardiac gradient due to the basal hypercontractility
may be a primary mechanism for the disease. A geometric
disposition in elderly females with a sigmoid inter-
ventricular septum or hypovolemia in the postoperative
patients may lead to outflow tract or midventricular
obstruction in the presence of excessive catecholamines.
The resulting elevation in wall stress, oxygen require-
ment, and ischemia in the apical segments could cause
apical ballooning.70 However, if this was the case, one
would expect to document an intracardiac gradient more
often than it has been reported in the literature or seen in
our experience.13,16

Controversies
There is debate over the most suitable nomenclature
for ABS.71,72 Tako-Tsubo cardiomyopathy12 and ABS13
were the original names proposed by the Japanese.
Most non-Japanese-speaking physicians are not familiar
with the meaning of Tako-Tsubo. Apical ballooning
syndrome has become popular because it is descriptive
of the appearance of the left ventricle. However, ABS
does not account for the less common variants. Some
have favored using stress cardiomyopathy or neuro-
genic stunned.71 These descriptions also are not all
encompassing because a stressor is absent in one third
of patients, and the role of the nervous system in the
pathophysiology remains to be established.
There is also divergence of opinion as to the reason for
the apparent increase in incidence of ABS. We believe
that it is not a new disease entity but that its recognition
has increased because of the greater use of cardiac
imaging, coronary angiography, and sensitive cardiac
biomarkers such as troponin. In addition, such cases may
have been diagnosed as aborted myocardial infarctions or
myocarditis in the past. Others believe that ABS may
indeed be a “novel” cardiomyopathy with a true rise in
incidence. It is speculated that the decreasing use of
hormone replacement therapy among postmenopausal
women may have contributed to its emergence. A
protective role of estrogens is possible because the
cardiomyopathy predominantly occurs in postmenopau-
sal women. Experimental data indicate that estrogen
supplementation may abolish the deleterious effect of
mental stress on cardiac function in ovariectomized
rats.71,73 Similarly, clinical investigations have found that
chronic estrogen supplementation attenuates the hemo-
dynamic and catecholamine responses to mental stress,74
and catecholamine mediated vasoconstriction.75
An intriguing hypothesis that merits further investiga-
tion is that ABS is not a unique cardiomyopathy, but
myocardial stunning resulting from a spontaneously
aborted myocardial infarction in the territory of a large
left anterior descending (LAD) artery.74 To support their
hypothesis, Ibanez et al have published data on five
patients demonstrating the presence of plaque rupture by
intravascular ultrasound that was not detected by
angiography.77 However, there are several reasons why
this mechanism is unlikely to account for the pathophy-
siology of most cases of ABS. First, the regional wall
motion abnormality in typical cases is far greater than
what can be accounted for by even a large wrap-around
LAD. Second, plaque rupture has not been reported in
any large case series. Third, extensive regional wall
motion abnormality of the right ventricle in one third of
patients cannot be explained on the basis of LAD territory
ischemia. Fourth, the female predominance would be
unusual for a manifestation of coronary atherosclerosis.

Conclusions
Apical ballooning syndrome is a distinctive reversible
cardiomyopathy that mimics an acute coronary syn-
drome. It should be included in the differential diagnosis
of patients with an apparent acute coronary syndrome
with regional wall motion abnormality and absence of
obstructive coronary artery disease.
One of the hallmarks of ABS is that it is almost
exclusively seen in postmenopausal women. This is
unique to the medical field and warrants further
investigation regarding the potential mechanisms. The
central hypothesis that a catecholamine surge is respon-
sible for the cardiomyopathy is challenged by the sex
disparity. If this was the predominant mechanism, one
would expect similar incidence in men and women. In
fact, males have a greater adrenergic response to mental
stress.57 Thus, additional hypotheses should be enter-
tained to explain the phenomenon. It is possible that,
in women, estrogen plays a protective role on the vascular
bed from the adverse effects of catecholamine surges.
Thus, a relative deficiency of estrogen after menopause
may predispose them to developing ABS. An alternative potential mechanism for the female predisposition is that women are more likely to have microvascular disease than men. Thus, the preexisting microvascular dysfunction in women may certainly lead to myocardial ischemia in response to mental or physical stress. This hypothesis is underscored by the observation that women have a higher incidence of acute coronary syndrome with normal epicardial coronary arteries.

Future research also needs to explore why (1) a very small proportion of the population appears to be at risk for ABS suggesting a role for genetic predisposition; (2) in the classic variant, there is sparing of the basal segments of the heart with characteristic dysfunction of the apical and mid segments; and (3) the recurrence rate is low despite the repeated exposure to stressful events over a lifetime. Finally, there is a need to establish a registry for ABS to investigate its natural history and conducting randomized trials of pharmacotherapy aimed at strategies to promote myocardial recovery and prevent recurrence.

References


72. Parodi G. Transient left ventricular apical ballooning— the need for a common terminology. Int J Cardiol 2007;116:405.


