

Apical Ballooning Syndrome or Tako-tsubo Cardiomyopathy: What We Know About It

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Abstract

Apical ballooning syndrome (ABS) is a reversible cardiomyopathy with presentation mimicking an acute coronary syndrome. So in clinical practice, it is essential to consider it in the differential diagnosis of patients presenting with chest pain, especially in postmenopausal women. Coronary angiography is usually indicated to achieve a proper diagnosis. Typically, patients do not have significant coronary artery lesions. Left ventriculography and echocardiography reveal a regional systolic dysfunction with akinesis of the midventricle, apex and compensatory hyperkinesis of the basal ventricular segments. Occurrence of an emotionally or physically stressful event is a feature of ABS but its absence does not exclude this diagnosis. Several pathophysiologic mechanisms had been proposed. The prognosis of ABS is good. In this review, we highlight the clinical manifestations, pathophysiology and management of this syndrome.

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Introduction

Apical ballooning syndrome (ABS) is a recognized form of heart disease that has been categorized as an acquired primary cardiomyopathy.¹

It was described for the first time in the Japanese population in 1991 and called Tako-tsubo cardiomyopathy [Tako-tsubo is a pot with a round bottom and narrow neck used for trapping octopus in Japan] and characterized as resting ischemic chest pain, ST elevation on ECG and absence of obstructive coronary artery disease. Other names used to describe this syndrome include broken heart syndrome, stress cardiomyopathy, amphora cardiomyopathy or ampulla cardiomyopathy.²

It is often misdiagnosed as an acute coronary syndrome (ACS) related to occluded epicardial coronary arteries. Its

incidence is 1 to 2% of patients who present with ACS. This syndrome has been reported in European, American and Asian populations.²

Diagnosis

Proposed criteria for the clinical diagnosis of ABS include:

1. Transient akinesis or dyskinesis of the left ventricular apical and midventricular segments with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution,
2. Absence of obstructive coronary disease or angiographic

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evidence of acute plaque rupture,

3. New electrocardiographic abnormalities

4. Absence of Recent significant head trauma, Intracranial bleeding, Pheochromocytoma, Obstructive epicardial coronary artery disease, Myocarditis, Hypertrophic cardiomyopathy.² Patients typically do not have obstructive coronary disease but cases of ABS with severe coronary artery disease have been reported.

Occurrence of an emotionally or physically stressful event is a feature of ABS but its absence does not exclude the diagnosis. Events such as exhausting work, death of relatives, catastrophic medical diagnosis, devastating financial loss, asthma attack, gastric endoscopy, prolonged electrophysiology study and ablation,³ permanent pacemaker implantation,⁴ surgical operations,^{5,6} meningitis,⁷ pneumothorax,⁸ hyponatremic seizure,⁹ anaphylactic reaction,¹⁰ cocaine use¹¹, central nervous system accidents,¹²⁻¹⁵ induction of general anaesthesia,¹⁶ frequent epinephrine medication in management of refractory asthmatic attack,¹⁷ opioid withdrawal,¹⁸ alcohol withdrawal,¹⁹ lightning strike,²⁰ hypoglycemic attack,²¹ neuroleptic malignant syndrome,²² plasmapheresis for treatment of myasthenic crisis,²³ acute pancreatitis,²⁴ earthquake,²⁵ treadmill exercise tolerance test,²⁶ scorpion bites,²⁷ adrenalectomy for Pheochromocytoma,²⁸ high dose dobutamine infusion during pharmacological stress myocardial perfusion imaging and thyrotoxicosis²⁹ have been reported. ABS can occur in critically ill patients admitted at intensive care units.³⁰⁻³²

Clinical features

Most patients present with chest pain at rest. Some patients present with dyspnea and rarely present with syncope or sudden cardiac death (SCD). ABS often occurs in postmenopausal women but it may occur in young women and men.² The majority of ABS cases manifest at night and in the cold seasons. These women usually have a short stature (less than 158 cm) and a small body surface area (less than 1.62 m²).³³ The majority of ABS patients also have other cardiovascular risk factors (overweight, hypertension, insulin resistance, dyslipidemia, tobacco). The mean age of presentation ranges from 58 to 75 years old.³⁴

In physical examination, left ventricular apical bulge is palpable in 80% of patients. A MR murmur can be heard in 5% of patients. Tachycardia is always present, and 70% of patients have an arrhythmic pulse.³³

Cardiac biomarkers

Most of patients have a small increase in cardiac biomarkers. In a study, troponin was positive in 86.2% and CK-MB was positive in 73.9% of cases.³⁵ In a study, the consecutively performed measurements after admission showed a continuous decline in a short time period indicating immediate recovery of myocardial function. Serum levels of

creatinine kinase (CK), CK-MB and troponin T were initially increased but returned to normal values within two days.³⁶ Most patients have findings of mild to moderate congestive heart failure so many of them have elevated level of BNP.

Electrocardiography

ECG can be normal but ST elevation is the most frequent finding on ECG, often in left precordial leads. Other abnormalities can be nonspecific T wave abnormality or ST elevation in limb leads. 20% of ABS cases have an ST depression in three or more leads.³³ Occasionally, pathologic Q wave may be seen. Prolongation of corrected QT interval is a frequent finding.² A prolonged PR interval or new bundle branch block are less common than above mentioned changes.³⁷ In one study, ST elevation was present in 76 to 86% of patients. T wave abnormalities were seen in 58 to 70% and Q wave in 26 to 38% of patients.³⁵ There was a prolonged PR interval in 24% of cases, mostly with a first-degree AV-block, supraventricular beats in 45% of cases and a left or right bundle branch in less than 5% of cases; 37% of cases had pathological Q waves in three or more leads (mostly V1-3); 33% of cases had ventricular premature beats and 23% of cases had a ventricular tachycardia.³³ Evolutionary changes include resolution of the ST elevation and diffuse and deep T wave inversion. Giant negative T waves are seen in 86% of cases, especially on the 3rd day and, rather characteristic for ABS, again after 2-3 weeks. In 20% of cases, the T changes may be seen years later.³³ The ECG is not a useful tool to distinguish a definite diagnosis. However, the T wave inversion is deeper and the QT interval is more prolonged in stress-induced cardiomyopathy at 3 days or later.³⁷ The direction of the ST segment deviation on the surface ECG usually does not accurately localize an involved region. Indeed, the ECG indicates many lesions, and the ST elevations are typically in non-contiguous leads. The T-wave changes are not parallel to the ST deviation.³³

In a study, the absence of reciprocal changes, absence of abnormal Q waves, and the ratio of ST-segment elevation in leads V (4-6) to V (1-3) all showed a high sensitivity and specificity for diagnosing ABS.³⁸ The combination of ventricular arrhythmias and prolonged QT intervals may favor the occurrence of torsades de pointes and this arrhythmia may be lethal. Most Q waves disappear within 6-12 months, but in 3% of cases they are permanent (expressing a myocardial scar). Most ST changes disappear within 1 year.³³

Echocardiography

A pattern of regional wall motion abnormality extending the distribution of a single epicardial coronary artery is common in ABS. Regional left ventricular ejection fraction (LVEF) is markedly reduced (up to 35%) in the mid-portion and severely reduced (up to 20%) in the apical region.³³ The right ventricle is involved in 1/3 of patients. Patients with



ABS had significantly greater RV free wall and LV lateral wall dysfunction as compared with patients with ACS.³⁹

Mean ejection fraction ranges from 20 to 49% which improves to normal at varying ranges from a few days to a few weeks. A significant change in LV wall thickness and reversible valve insufficiencies are other characteristics of ABS.

As mentioned, during acute phase, all patients have moderate to severe mid-ventricular dysfunction and apical akinesia or dyskinesia with preserved or hypercontractility of basal portion, but the regional wall motion abnormalities are transient. So assessment of LVEF should be performed at ^{4 to 6} weeks after discharge from hospital.²

Angiography

Patients with ABS typically do not have obstructive coronary artery disease.

In most patients with ABS, the coronary arteries are smaller and shorter than usual and in 40% of cases there is an anomaly, with hypoplastic branching in the apical region.³³

Spontaneous multivessel epicardial spasm is uncommon and after ergonovine or acetylcholine infusion, it was observed only in 30% of patients.

The left ventriculography shows characteristic wall motion abnormality of mid and apical segments. There is hypercontractility of basal segment.

Atypical forms

A "typical" apical wall motion abnormality is only seen in 60% of patients.⁴⁰ Hurst et al described a variant of ABS in which only the midventricular is affected with hypercontractility of apical and basal segments.⁴¹

Mazzarotto et al reported a case of ABS with anterior location of wall motion abnormalities.⁴²

Magnetic resonance imaging

Contrast-enhanced cardiovascular magnetic resonance (CMR) is a useful adjunct in the diagnostic work up of patients with ABS. It may be helpful in excluding myocardial infarction, because delayed gadolinium hyperenhancement is not a feature of ABS.²

Delayed hyperenhancement on gadolinium-enhanced CMR, which is indicative of active inflammation (e.g. myocarditis) or myocardial fibrosis (e.g. myocardial infarction), is usually absent in patients with ABS.⁴³

Cardiac scintigraphy

An abnormal subendocardial perfusion is present in 90% of patients. A reverse distribution phenomenon is detected in more than 80% of patients.³³

In a study, technetium-99m tetrofosmin tomographic imaging revealed decreased uptake at the apex of the left ventricle in 85% of patients that later returned to uniform.⁴⁴

123I-MIBG is a radiolabelled analogue of noradrenaline and depicts the distribution of cardiac sympathetic innervation. Pessoa et al observation showed that ABS is associated with a cardiac sympathetic innervation deficit characterized by a reduced global 123I-MIBG uptake and an apical uptake defect. The lack of ⁶⁷Ga uptake in the acute phase of this syndrome indicates that ABS is probably not associated with an inflammatory process.⁴⁵ In another study, initial 123I-MIBG myocardial scintigraphy in patients with ABS, depicted a unique pattern of ventricular asynergy and indicated the existence of cardiac sympathetic hyperactivity, although coronary blood flow was maintained. The mismatch between perfusion and innervation reinforces the hypothesis of a primary neurogenic disorder.⁴⁶

Pathophysiology

The precise etiology and pathophysiology of this syndrome remain unknown. Several mechanisms have been proposed including multivessel epicardial spasm, catecholamine induced myocardial stunning, coronary microvascular dysfunction and myocarditis.

A genetic etiology was postulated in two sisters with ABS.⁴⁷ Also, there is some evidence that viruses can have a role in pathophysiology of ABS.⁴⁸⁻⁴⁹

Dote and associates suggested coronary vasospasm as the pathogenic mechanism; however, induction of coronary vasospasm by acetylcholine or ergonovine has yielded mixed results. In some series, vasospasm in at least one epicardial coronary artery was present in most patients, whereas Akashi and colleagues did not observe any coronary vasospasm in patients who underwent an acetylcholine challenge.⁵⁰

Akashi et al found that the standard deviation of the mean cycle length of normal-normal R-R (NN) intervals over 24 h (SDNN), and the 24-h standard deviation of the mean value of the difference between the NN intervals for each 5-min segment (SDANN) improved significantly during three month follow up. These results support the hypothesis that acute autonomic dysfunction can cause neurogenic stunning of the myocardium.⁵¹

In a study using positron emission tomography with ¹³N-ammonia and ¹⁸F-fluorodeoxy glucose within 72 hours of presentation with ABS, all patients exhibited reduced glucose uptake in the mid-LV and apical myocardial segments, which was out of proportion with perfusion abnormalities in half of the cases.⁴⁰ In another study, Feola et al observed severe degree and transient pattern of the impairment of tissue metabolism in the dysfunctioning left ventricle with nearly preserved myocardial blood flow at rest. This pattern is known as inverse metabolic/perfusion mismatch. The severe

reduction of glucose metabolism in dyskinetic myocardium without electrocardiographic signs of necrosis, as well as only minor cardiac-specific enzymatic release, suggests that apical ballooning represents a transient metabolic disorder on the cellular level, rather than a structural contractile disease of the myocardium.⁵²

It is possible that an impaired or differential sympathetic activation is responsible for the inhomogeneous contractile response to adrenergic stimulation (stress or physical effort) between the basal and periapical regions. This condition, in turn, results in transient left ventricle outflow tract (LVOT) obstruction.

In myocardial segments with abnormal functional innervation, as detected by MIBG myocardial scintigraphy, dobutamine stress echocardiography elicits functional abnormalities comparable to those observed in the acute phase of the disease, linking abnormal regional beta-adrenergic stimulation with abnormal cardiac presynaptic innervation.⁵³

Impaired myocardial perfusion due to abnormal microvascular blood flow is frequently present in patients with ABS and correlates with the extent of myocardial injury. So microvascular dysfunction may play a pivotal role in the pathogenesis of myocardial stunning in ABS.⁵⁴

In a study, TIMI frame counts were abnormal in all patients and often abnormal in all 3 major coronary vessels, suggesting that the diffuse impairment of coronary microcirculatory function may play a role in the pathogenesis of the syndrome.⁵⁵

In these patients, a catecholamine-mediated endothelial injury might be responsible of microvascular coronary dysfunction.⁵⁶

Serial non-invasive measurements of coronary blood flow in a case suggested transient impairment of the coronary microcirculation during the acute phase of the syndrome.

The improvement of the microcirculation parallels the regression of the wall motion abnormalities.

There is some evidence suggesting that the apical myocardium may be more responsive to sympathetic stimulation and may be more vulnerable to sudden catecholamine surges.⁵⁷ A longitudinal, base-to-apex decline in LV myocardial perfusion has also been proposed as a possible alternative explanation.⁵¹ Data of a study suggested that myocardial bridging possibly enhanced by catecholamines during stress may contribute, in association with left ventricular hypertrophy, to the preferential apical localization of ABS.⁵⁸

The reason for the much more common occurrence in post-menopausal women is unclear. Several explanations have been proposed. Sex hormones may exert important influences on the sympathetic neurohormonal axis and on coronary vasoreactivity.

Women appear also to be more vulnerable to sympathetically mediated myocardial stunning. Post-menopausal alteration of endothelial function in response to reduced estrogen levels has been advocated as a possible alternative explanation.³⁶

Pathology

Endomyocardial biopsy data from five patients have been published. Four had interstitial infiltrates consisting primarily of mononuclear lymphocytes, macrophages, and contraction bands without myocyte necrosis. The other patient had an extensive lymphocytic infiltrate and multiple foci of contraction-band myocyte necrosis (a sign of catecholamine cardiotoxicity).⁵⁹

Prognosis and complications

The prognosis of patients experiencing this syndrome is generally favorable.

In-hospital mortality is less than 2%. LVEF recovers slowly: after 6 months of follow-up, the apical ventricular ejection is often 40% or less. LVEF is usually normalized within 12 months.

In many patients, reduced stroke volume and dynamic LVOT obstruction can produce hypotension and even cardiogenic shock.

Other complications include cardiogenic shock due to LV dysfunction, ventricular septum perforation,⁶⁰ left free wall rupture,⁶¹ left ventricle apical rupture,⁶² embolic stroke,⁶³ torsade de pointes⁶⁴ and acute pericarditis.⁵⁷

Nef et al reported a case of ABS complicated by a prolonged third-degree atrioventricular block requiring the implantation of a pacemaker.⁶⁵

Chandrasegaram et al reported a case of ABS with acute pulmonary edema, severe mitral regurgitation and systolic anterior motion of the mitral valve with significant left ventricular outflow tract obstruction. The left ventricular outflow tract obstruction and mitral regurgitation were corrected by mechanical mitral valve replacement.⁶⁶

RV involvement is common in ABS and seems to be associated with a more severe impairment in LV systolic function. It may be suspected by the presence of pleural effusion.⁶⁷

The recurrence rate of ABS is no more than 10%. Blessing et al described a case where repeated emotional stress caused recurrent ventricular dysfunction in varying regions of the left ventricle.⁶⁸

Management

The optimal management of ABS has not been established. Beta blockers are useful. Inappropriate administration of fibrinolytic to patients with ABS may be harmful and it would be appropriate to transfer the patients for emergent coronary angiography. Diuretics may be useful for treatment of CHF. Anticoagulants should be considered to prevent thromboembolism until recovery of wall motion abnormality.



If there is considerable dynamic LVOT obstruction in patients who are hemodynamically unstable, a cautious trial of beta blockers may be helpful. In this condition, using inotropes is contraindicated but infusion of phenylephrine can be effective because it increases afterload and ventricular cavity size. Cardiogenic shock should be treated with inotropes and intraaortic balloon pump.

Levosimendan has been suggested as the inotrope of choice in cardiogenic shock secondary to ABS. Once the diagnosis of ABS has been made, ASA can be discontinued unless there is coexisting coronary atherosclerosis. Some recommend chronic beta-blocker therapy. Such course of action may be useful in reducing the likelihood of a recurrent episode.

Ueyama et al suggested that estrogen supplementation partially prevented emotional

stress-induced cardiovascular responses both by indirect action on the nervous system and by direct action on the heart.⁶⁹

Conclusion

ABS is a recognized reversible cardiomyopathy. Clinicians should consider this syndrome in the differential diagnosis of patients presenting with chest pain, especially in post-menopausal women with a recent history of emotional or physical stress.

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