Ibrahim Card Med J 2013; 3(1 & 2): 39-48

Pathophysiologic features of Takotsubo Cardiomyopathy: A review of the literature

Ana Mercedes[1], Tiffany Caza[2], Chowdhury H Ahsan[3]

ABSTRACT

Takotsubo cardiomyopathy is a newly recognized cause of chest pain mimicking a myocardial infarction in post-menopausal women. It is diagnosed based on clinical criteria established at the Mayo Clinic and imaging studies, including echocardiography, cardiac MRI, angiography, and left ventriculography. Several hypotheses have been postulated towards its etiology, with the dominant theory being cathecholamine toxicity to the myocardium in response to a stressful trigger. Pathologic investigations are limited, based mostly on autopsy findings, and represent inflammatory and fibrotic replacement of the myocardium. Here, we will address the current understanding of the disease entity of Takotsubo cardiomyopathy, its clinical mimics, and its pathophysiology.

Key words: Takotsubo cardiomyopathy, apical ballooning syndrome, stress-induced cardiomyopathy, catecholamine cardiotoxicity, endomyocardial biopsy.

INTRODUCTION

Takotsubo cardiomyopathy is a clinical entity that mimics an acute ST-segment elevation myocardial infarction. The condition predominantly affects postmenopausal females. Patients usually present with chest pain following an emotionally or physically stressful event with subsequent onset of a temporary systolic dysfunction without evidence of obstructive coronary artery disease.[1,2,3] This entity is also known as transient apical ballooning syndrome, apical ballooning cardiomyopathy, broken heart syndrome or stress-induced cardiomyopathy.[4]

In 1990, Japanese observers designated the syndrome Takotsubo cardiomyopathy, named after the octopus trapping pot resembled by the pathognomonic left ventricular wall motion abnormalities; which involves bulging out of the apex of the heart with preserved function of the base[5,6] (Figure 1). Multiple variants of the disease have been described including hypokinesis of the base that spares the mid-ventricle and apex; this variant is known as reverse or inverted Takotsubo; global hypokinesis, and left ventricular hypokinesis that is restricted only to the mid-ventricle with sparing of the apex.[7]

The prevalence of Takotsubo cardiomyopathy ranges from 1.7 to 2.2 percent in patients admitted with suspected acute coronary syndrome[2,8] as there are overlapping clinical presentations. The incidence of Takotsubo cases worldwide appears to be on the rise, although this could berelated to clinical advances in the evaluation of patients with chest pain.[4,9] In 2006, the American Heart Association included Takotsubo into its classification of

REVIEW ARTICLE

Authors' Information:

[1]***Ana Mercedes,*** *MD, Department of Cardiology, University Medical Center / University of Nevada School of Medicine, Las Vegas, Nevada*

[2]***Tiffany Caza,*** *MD PhD, Department of Pathology, State University of New York Upstate Medical University, Syracuse, New York*

[3]***Chowdhury H Ahsan,*** *MRCP, MD, PhD, FSCAI, Clinical Professor of Medicine, Director, Cardiac Catheterization & Intervention, University Medical Center/University of Nevada School of Medicine, Las Vegas, Nevada*

Address of Correspondance: ***Chowdhury H Ahsan,*** *Clinical Professor of Medicine, Director, Cardiac Catheterization & Intervention, University Medical Center/University of Nevada School of Medicine, Las Vegas, Nevada,* ***E-mail:*** *chahsan@medicine.nevada.edu*

cardiomyopathies as one of the primary acquired cardiomyopathies.[9]

FIGURE 1 : Japanese octopus trapping pot.

The underlying pathophysiologic mechanisms underlying the development of Takotsubo cardiomyopathy are not well understood, however several hypotheses have been postulated. The purpose of this review, is to examine the pathophysiologic features of Takotsubo cardiomyopathy.

DEMOGRAPHICS

Takotsubo cardiomyopathy is more prevalent in post-menopausal women, which make up 88.8 percent of patients. The mean age at diagnosis is 58 to 75 years, suggesting ahormonal predisposition related to estrogen loss.[2,3,8,9,10] Age may also play a role in the development of Takotsubo cardiomyopathy, due to variations in sympathetic nervous system regulation, as well as endothelial dysfunction and injury over time.[11]

CLINICAL PRESENTATION

The most common clinical manifestations include resting chest pain (present in 50 to 60 percent of patients), dyspnea, pulmonary edema, syncope, tachyarrhythmias, hypotension, and as it is broadly described, a significant amount of the patients present after an emotional or physical stressor.[3,4,12] In patients with Takotsubo cardiomyopathy who have clinical manifestations of shock, the culprit could be a dynamic left ventricular outflow tract (LVOT) obstruction, usually induced by hyperkinesis of the base in the left ventricle.[13]

ELECTROCARDIOGRAM (ECG) CHANGES

The most common electrocardiographic manifestations in Takotsubo cardiomyopathy is ST-segment elevation. This typically occurs in the precordial leads, but can also be seen in the inferior and lateral leads. Other changes include non-specific T-wave abnormality, deep T wave inversions associated with QT prolongation, or a new right or left bundle branch block. In some cases, ECG may be normal at presentation. After resolution of ST-segment elevation, diffuse and often deep T-wave inversion that involves most leads occurs. Complete resolution with return to the patient's baseline occurs within 4 to 6 weeks.[4,14,15]

CARDIAC BIOMARKERS

Cardiac biomarkers, especially high-sensitivity troponin assays, are usually mildly elevated, which is unusual in the setting of hemodynamic instability. The levels of troponin T range from 0.01 to 5.2 ng/mL.[2,3,4]

ECHOCARDIOGRAPHIC FINDINGS/LEFT VENTRICULOGRAPHY

Characteristic echocardiographic evaluation, usually demonstrate apical ballooning associated with akinesis or dyskinesis of the apex. The systolic function is diminished, with left ventricular ejection fractions ranging from 20 to 49 percent.[2,3,12,14,16] It has been proposed that the presence of right ventricular apical akinesia during echocardiographic examination, associated with the classic clinical findings could potentially make the diagnosis of Takotsubo cardiomyopathy more likely[16] (Figure 2 and 3).

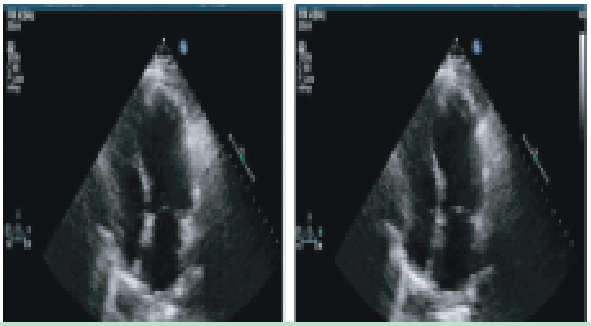

FIGURE 2 : Transthoracic echocardiogram demonstrates apical ballooning involving the left ventricular walls in systole and diastole, not limited to any single coronary territory.

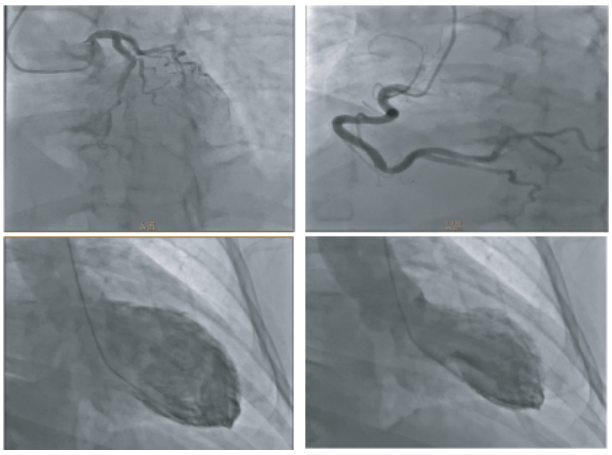

FIGURE 3 : Ventriculogram demonstrating apical ballooning involving the left ventricular walls. basal hyperkinesis, apical and mid segment hypokinesis was noted. Angiogram shows normal coronaries.

CARDIOVASCULAR MAGNETIC RESONANCE IMAGING (CMRI)

CMRI typically demonstrates mid and apical LV segmental wall motion abnormalities. These are often present in multiple coronary territories and are without delayed hyperenhancement of involved regions.[3,9,17] Late gadolinium enhancement (LGE) on CMRI is usually absent in stress cardiomyopathy, contrasting with its presence in myocardial infarction, in which intense subendocardial or transmural LGE is seen. LGE has shown to be useful in differentiating stress cardiomyopathy from myocarditis, where patchy late gadolinium enhancement is commonly seen. CMR could also aid in the diagnosis of thrombus in the left or right ventricle, which may not be detected by echocardiography.[9] An overview of commonly utilized tests in the evaluation of Takotsubo cardiomyopathy are reviewed in Table 1.

TABLE I. An overview of clinical tests used in the evaluation of Takotsubo cardiomyopathy and their associated findings

Clinical test	Results in Takotsubo cardiomyopathy
Electrocardiogram	ST segment elevation (precordial leads > inferior or lateral) Non-specific T wave abnormalities Deep T wave inversions Prolongation of the QT interval New onset of bundle branch block
Echocardiogram	Apical dyskinesis or akinesis with ballooning Reduced systolic function Decreased left ventricular ejection fraction
Cardiac MRI	Absent late gadolinium enhancement of damaged myocardium Can detect presence of thrombus in ventricles
Left ventriculography	Segmental wall motion abnormality (mid/apex of left ventricle)
Clinical chemistry	Increase in troponin I or T Increase in creatinine kinase/CK-MB fraction Increase in serum catecholamines Increase in brain naturetic peptide levels Decrease in plasminogen activator-inhibitor-1 levels

MAYO CRITERIA

There are four proposed criteria for the diagnosis of Takotsubo cardiomyopathy. These include (1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement. These regional wall motion abnormalities cannot extend beyond a single epicardial vascular distribution. A stressful trigger is often, but not always present; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture (3) new electrocardiographic abnormalities, which include either ST-segment elevation and/or T-wave inversion, or modest elevation in cardiac troponin; and (4) absence of a pheochromocytoma or presence of myocarditis.[4,12]

MANAGEMENT

Takotsubo cardiomyopathy has a transient disease course and usually responds well to supportive therapy. Recovery of the LV systolic function occurs within weeks or months after resolution of the emotional or physical stressor. Due to its similarities, the patients should be presumed to be suffering from an acute coronary syndrome and immediate management should be instituted. There is no controlled data to define the optimal medical regimen or the appropriate duration of therapy for treatment of Takotsubo cardiomyopathy.

The goal of medical therapy is to reverse left ventricular (LV) systolic dysfunction, through treatment with angiotensin converting enzyme inhibitors, beta blockers, and diuretics. Aspirin is also suggested in the presence of co-existing coronary atherosclerosis. A beta blocker should be continued indefinitely in the absence of contraindications or intolerance, due to the likelihood of a late recurrence, which occurs in approximately ten percent of patients. The use of inotropic agents is controversial due to a resulting increase in circulating catecholamines.[3]

COMPLICATIONS

Takotsubo cardiomyopathy causes a risk of thromboembolism, as it induces a transient hypercoagulable state. Loss of LV apex motion increases the risk of intraventricular thrombus formation and subsequent systemic embolization. Therefore, patients can benefit from anticoagulant therapy in the absence of an absolute contraindication. If an intraventricular thrombus is found, the duration of anticoagulation may be modified based on the rate of recovery of cardiac function and resolution of the thrombus.

PATHOLOGY

Although the potential complications and patterns of injury in Takotsubo cardiomyopathy have been well characterized on electrocardiography, echocardiography, cardiac MRI, and clinical chemistry studies, data regarding the histopathologic changes that occur within myocardium in Takotsubo cardiomyopathy are limited. This is because biopsy is not required for diagnosis, and the diagnosis is one of exclusion after ruling out other causes of cardiomyopathy. Endomyocardial tissue examined in a small number of patients and post-mortem samples reveal histologic changes that occur in Takotsubo hearts.[18] Some of these changes are unique when compared to other causes of injury, although most features are non-specific with the presence of inflammation and fibrosis that occur in a number of disease processes. The extent of injury can be focal or diffuse. The areas of the heart that are most affected include the trabeculae carnae of the anterior wall, interventricular septum, and the ventricular myocardium near the apex.[18] Myocardial damage in these areas results in left ventricular wall motion abnormalities with apical ballooning in diastole that can be seen clinically on echocardiography. The pathology and symptoms subside within days to weeks of the triggering event.[18]

Pathology of Takotsubo cardiomyopathy is related to catecholamine-induced damage to the myocardium. Catecholamines released during acute stress responses can cause injury to myocardium in three ways. First, catecholamines can cause direct toxicity to myocytes that manifests as tissue degeneration, myocardial cell damage or lysis, or myocyte loss in a patchy or diffuse distribution. Second, adverse effects on the cardiac microcirculation can result from catecholamine excess. Third, catecholamine excess can induce myocardial stunning.[19] Emotional stress is often the trigger for the initial catecholamine release responsible for this damage. Interstitial edema occurs within hours of catecholamine-induced injury. This is characterized by toxic vacuolization and fatty infiltration of the myocardium. Neutrophils and lymphocytes then infiltrate the injured tissue promoting inflammation, known as myocarditis. Consistent with this, endomyocardial biopsies

taken within a few hours of the onset of a Takotsubo triggering event show infiltration of inflammatory cells including neutrophils and takeover of the myocardium by immature connective tissue. Characteristic features of myocardial damage include epicardial adipose tissue hemorrhage, amyloid deposition, degeneration of myofibrils, and myocyte loss. Myocyte loss is higher in the apex than at the base in Takotsubo hearts and primarily affects the epicardium, anterior wall trabeculae and/or the subendocardium. An increase in eosinophilic staining of myocytes is present in response to the injury and represents myocyte necrosis.[18] The presence of contract bands indicates that the necrotic cell death was recent.

Concurrent ischemia due to impaired microcirculation in Takotsubo cardiomyopathy[20] results in fibrinoid degeneration in arterial system, primarily affecting arterioles, which will ultimately result in left ventricular dysfunction.[21] Patients with pre-existing arteriosclerosis, particularly the elderly, may be at increased risk due to further ischemic injury. During ischemic injury, there is concurrent enlargement of perivascular macrophages, forming Antischkow cells. Due to focal ischemia, myofibril necrosis can occur. This occurs due to catecholamine excess-induced hyperviscosity that impairs perfusion within small blood vessels.[22] Excess endothelial cell apoptosis further contributes to microcirculatory injury.[23]

Damaged myocytes are taken up by macrophages in a multinuclear giant cell reaction. Damaged myocytes are removed and replaced with expanded interstitium, which forms a segmentation pattern can be present within the myocardium. Aggregation of damaged myocytes and replacement fibrosis occurs as the acute inflammatory response subsides, which occurs in three days and up to a few weeks following the initial injury. Acute pericarditis can also be present in the recovery phase.[24]

Since the injury to the myocardium is a result of either direct myocyte damage or ischemia, tissue damage can occur at areas typically not subject to ischemia, since either mechanism of injury can occur. Epicardial involvement is common in Takotsubo, which can differentiate from other causes of coronary ischemia, which typically spares epicardium. This is because epicardium is normally well supplied by the coronary vasculature and is not a site subject to ischemia. The degree of myocyte loss in Takotsubo cardiomyopathy is much less than in patients who have a recent or remote history of myocardial infarction. Stenosis or occlusion of coronary vasculature does not occur in Takotsubo cardiomyopathy, further differentiating from damage due to a myocardial infarction. However both disease processes present with elevations in cardiac enzymes that are released from damaged myocytes. This injury is circumferential and can extend from the mid-portion of the heart to the apex of the ventricle, which is the site of the most damage.

Long-standing Takotsubo cardiomyopathy is associated with chronic myocarditis with fatty infiltration of the heart, lymphocytic infiltration in the endomyocardium, fibrosis within the interstitium, contraction band necrosis, and loss of myocytes. Chronicity is rare, however, affecting less than ten percent of patients. Myocyte injury due to Takotsubo cardiomyopathy is reversible if the stress trigger or source of catecholamine excess is no longer present. Case reports of serial endomyocardial biopsies have shown that myocyte loss and immature connective tissue infiltration that occur following a trigger event are reversible, returning to mature connective tissue a month following initial injury and biopsy.

Anatomic diagnosis of Takotsubo cardiomyopathy by a biopsy is very rare. Most patients will have resolution after the inciting event and it is usually diagnosed clinically based on Mayo criteria after other causes of chest pain including acute coronary syndromes, coronary artery stenosis, and coronary artery spasm have been ruled out.[9] Electrocardiographic changes and cardiac enzymes (including troponins) are elevated during Takotsubo cardiomyopathy and acute coronary

syndromes, making differentiation at initial clinical presentation difficult.[25] However, some clinical chemistry tests can help in identification of patients with Takotsubo cardiomyopathy. Patients with Takotsubo cardiomyopathy have an increased plasmin activator inhibitor-1 (PAI-1) level and increased erythrocyte deformability index, findings which correlate with stress-induced hyperviscosity, which occurs early in the disease course. Increased PAI-1 and erythrocyte deformability index also occurs in patients with pheochromocytoma, however.[26]

Clinical presentation as well as pathology of Takotsubo cardiomyopathy overlaps with that of pheochromocytoma. Patients with pheochromocytoma rarely present with an "inverted" Takotsubo pattern due to the toxic effects of catecholamines on the myocardium.[27] This has also been reported in the high stress state of thyrotoxicosis.[28] Catecholamine release during Takotsubo cardiomyopathy is also an adverse effect evoked during chemotherapy identified with a subset of drugs,[29] and is thought to be caused by mitochondrial toxicity.[30] Therefore, a pheochromocytoma must be ruled out for a diagnosis of Takotsubo cardiomyopathy based on the Mayo criteria.

HISTOLOGIC MARKERS

Takotsubo cardiomyopathy generally has a good prognosis and a less than ten percent recurrence risk, however, some fatalities have occurred.[31] Autopsies from Takotsubo cardiomyopathy deaths have revealed that Takotsubo patients have cardiomegaly and evidence of subendocardial damage with coagulative necrosis.[18] This has also been seen in animal models of Takotsubo cardiomyopathy. All Takotsubo hearts contained interstitial fibrosis and approximately half had the presence of myocyte hypertrophy. Early changes of inflammatory infiltration and necrosis resolve quickly and are rarely seen at autopsy. The cardiac conduction system and coronary vasculature are often normal in Takotsubo patients.

There are no specific histochemical or immunohistochemical markers to assist in diagnosis of Takotsubo cardiomyopathy on biopsy or post-mortem sections. The histochemical stain, 2,3,5-Triphenyl tetrazolium chloride (TTC) applied to heart sections of Takotsubo patients reveals lack of red subendocardial staining, which is maintained in normal hearts that have not undergone an ischemic injury.[32] TTC reacts with dehydrogenases to form a red formazan compound during oxidative phosphorylation, with loss of staining indicative of cell death.[32]

Immunohistochemical staining of C4d can highlight necrotic myocytes in Takotsubo patients, which are largely clustered within the subendocardium.[32] C4d staining represents recent activation of the classical complement pathway, as it is the product of C3 convertase. C4d deposition occurs by complement activation by macrophages of the innate immune response. However, C4d staining is non-specific to Takotsubo cardiomyopathy, with positivity in areas of ischemic necrosis following a MI, in other ischemia-reperfusion injuries, in post-transplant rejection of a donor heart, and in dilated cardiomyopathy.[32] Within the intima of the myocardium, there is an increase in capillary density, which may be compensatory due to surrounding focal ischemia. These can be highlighted with immunohistochemistry of endothelial markers, such as CD31 or CD34. Due to these non-specific pathologic findings, correlation with clinical presentation, ECG changes, and imaging studies is necessary. Further research can be done to identify specific biomarkers, preferentially present in the serum or plasma rather than the myocardium itself, to assist in diagnosis of the disease.

PATHOPHYSIOLOGY

Several mechanisms of injury have been proposed in Takotsubo cardiomyopathy pathogenesis, as the etiology of the disease is currently uncertain. These include, but are not limited to, transient coronary vasospasm, microvascular damage, development of myocarditis,

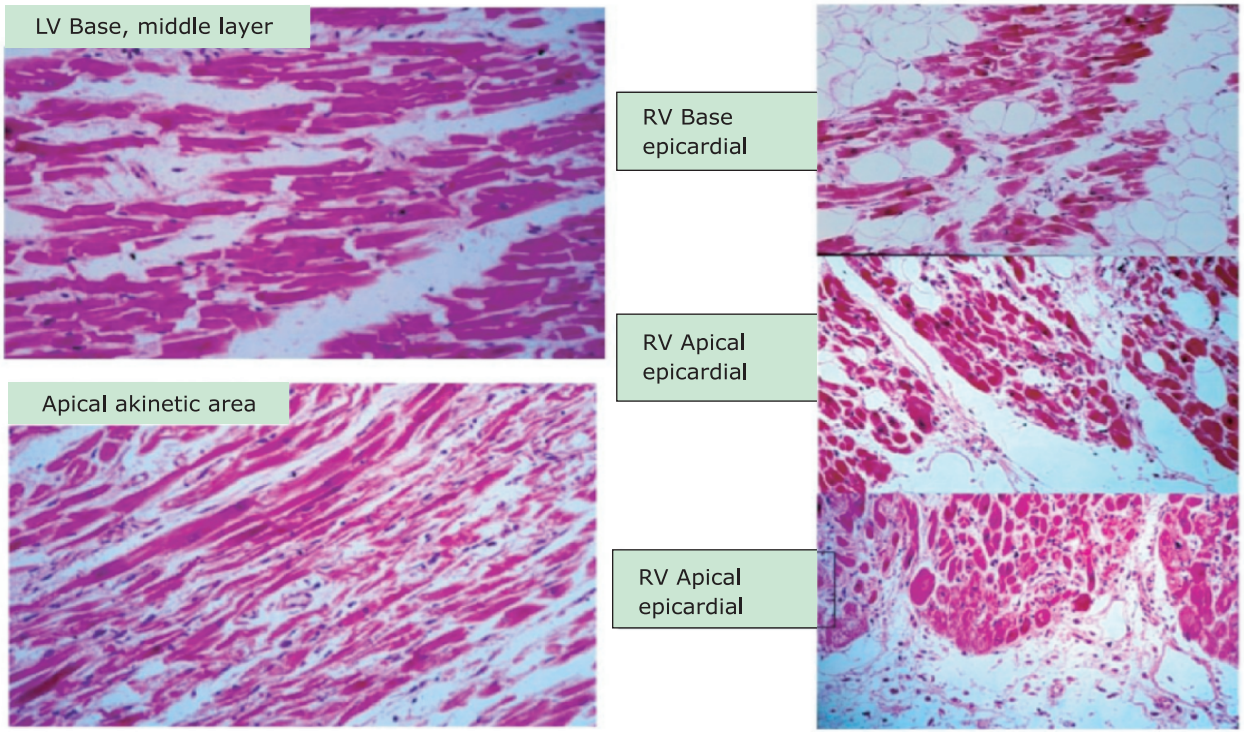

FIGURE 4 : *Marked segmentation of myocytes was observed in the middle layer of the hyperkinetic basal left ventricle (lower left). Damaged cells had undergone atrophy and lysis in the akinetic apical segment (lower left). There were similar lesions in the right ventricle. Segmentation was seen even in myocytes which were sparse in the adipose tissue in the basal outer layer (upper right). In the right ventricle in the apical aspect (middle right), there were marked myocyte injuries and lysis and interstitial cell infiltration in addition to segmentation. Similarly, when the apical left ventricle in the epicardial aspect (lower right) was examined, there was myocyte damage near the epicardial aspect and cell infiltration into the epicardium. Myocardial tissue: H&E stain, x200. Sachio Kawai (2012). Pathology of Takotsubo (Ampulla) Cardiomyopathy, Cardiomyopathies - From Basic Research to Clinical Management, Prof. Josef Veselka (Ed.), ISBN: 978-953-307-834-2.*

and catecholamine-induced damage.[33] As pathology of Takotsubo cardiomyopathy is similar to myocardial damage due to high catecholamine states, such as in patients with pheochromocytoma, this is the predominant theory. The catecholamines implicated in Takotsubo cardiomyopathy primarily include norepinephrine and epinephrine. These catecholamines have different foci of myocardial injury, dependent on differential effects of epinephrine and norepinephrine on cardiac afterload.[34] Although the source of catecholamine production is typically endogenous from the adrenal glands, exogenous administration of epinephrine and cocaine abuse has also been linked to disease development.[35,36] Catecholamine-induced injury can occur due to the stress hormones themselves, or by excessive activation of catecholamine receptors in the myocardium.

Stressors (physical or emotional) trigger hypothalamic and limbic system activation, which excites the autonomic centers within the medulla. Excitation of post-synaptic sympathetic neurons result in release of norepinephrine, while signals to the adrenal medulla trigger epinephrine release. Catecholamine action by norepinephrine and epinephrine result in activation of alpha and beta receptors of the sympathetic nervous system. Alpha receptor activation increases blood pressure, triggers arterial contraction, and transiently reduces flow through the coronary circulation. Beta receptor activation triggers myocardial contraction with

obstruction of the left ventricular outflow tract. Mechanical wall stress results and there is an increase in oxygen demand of the myocardium. Increased oxygen demand creates oxidative stress, which also reduces contraction of the left ventricle.[9] Further oxidative and mechanical wall stress occur during aging and in estrogen depletion in post-menopausal women, the population most susceptible to development of Takotsubo cardiomyopathy.[37,38] Increased oxidative and mechanical wall stress in the setting of a high catecholamine state is the "perfect storm" for development of Takotsubo cardiomyopathy (Fig. 1). An improved understanding of the mechanisms behind disease development can lead to improved treatment and recurrence prevention.

CONCLUSION

In the past two decades, an increased understanding and awareness of the clinical entity of Takotsubo cardiomyopathy has led to recognition based on clinical symptoms, electrocardiography, and imaging studies. However, the disease overlaps with other causes of chest pain and increased sympathetic outflow, and differentiation of these conditions can be difficult. An improved understanding of the pathophysiology behind Takotsubo development will lead to improved therapeutic choices and could potentially reduce recurrence risk, particularly in susceptible individuals. Pathologic insights have come mainly from post-

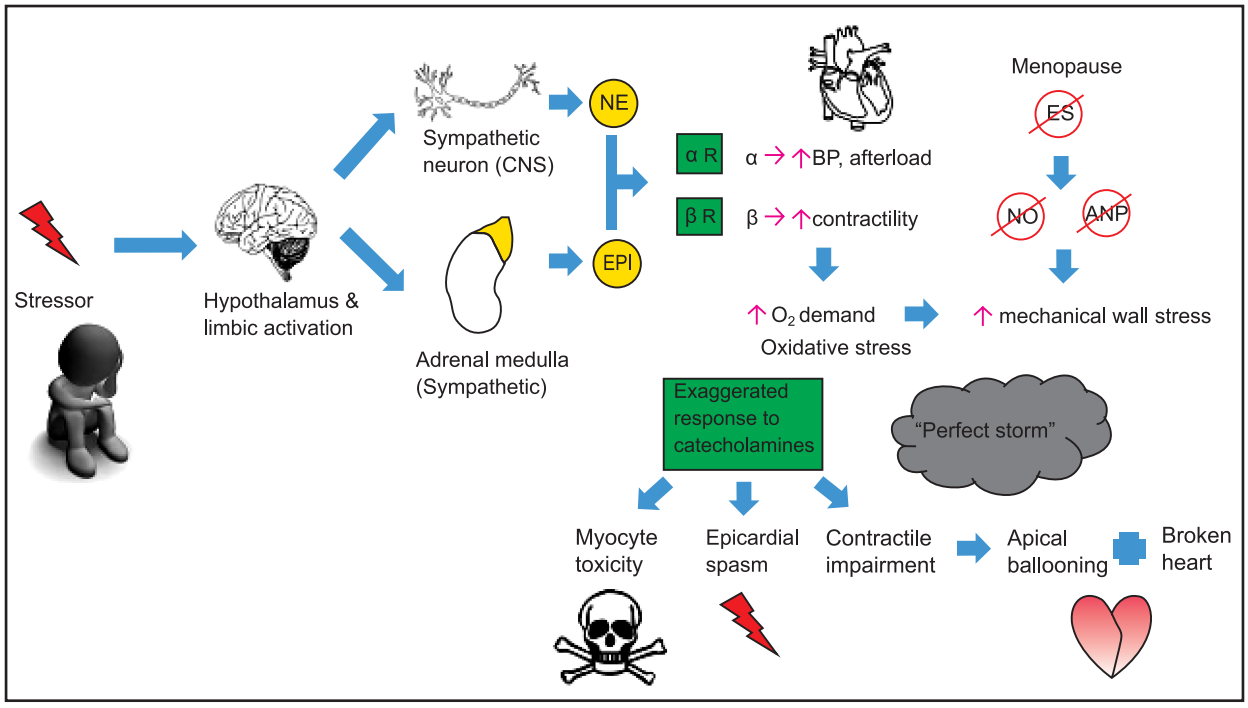

FIGURE 5 : *An overview of the pathophysiology of Takotsubo cardiomyopathy. Physical or emotional stressors trigger activation of the hypothalamus and limbic system within the brain. This leads to post-synaptic activation of sympathetic neurons that release norepinephrine (NE) and induction of the release of epinephrine (EPI) from the adrenal medulla. NE and EPI activate α and β receptors of the autonomic nervous system and trigger increases in blood pressure, heart rate, and contractility. These cause an increase in mechanical wall stress. In post-menopausal women, low estrogen states trigger a reduction in nitric oxide (NO) and atrial natriuretic peptide (ANP), which causes further mechanical and oxidative stress and creates the "perfect storm" for catecholamine toxicity. An exaggerated response to catecholamines results in toxicity to cardiac myocytes, epicardial spasm, and contractile impairment of the left ventricle of the heart. Contractile impairment results in apical ballooning, causing "broken heart" syndrome.*

mortem examination of Takotsubo hearts and may not reflect the pathology seen in a majority of patients, as the disease is rarely fatal. There is an inherent need for a molecular biomarker to distinguish Takotsubo cardiomyopathy from other ischemic conditions and cardiomyopathies.

REFERENCES

1. Abe Y, Kondo M, Matsuoka R, Araki M, Dohyama K, Tanio H. Assessment of clinical features in transient left ventricular apical ballooning. *J Am Coll Cardiol* 2003;41(5):737-42.
2. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* 2006;27(13):1523-29.
3. Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, LongeTF, Maron BJ. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005;111(4):472-79.
4. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008;155(3):408-17.
5. Sato H, Tateishi H, Uchida T, et al. Kodama K, Haze K, Hon M, eds. *Clinical Aspect of Myocardial Injury: From Ischaemia to Heart Failure.* Tokyo: Kagakuhyouronsya; 1990:56-64.
6. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. *J Cardiol* 1991;21(2):203-214.
7. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, Carbone I, Muellerleile K., Aldrovandi A, Friedrich MG. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA* 2011;306(3):277-86.
8. Kurowski V, Kaiser A, von Hof K, Killermann DP, Mayer B, Hartmann F, Radke PW. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest* 2007;132(3):809-16.
9. Akashi YJ, Goldstein DS, Barbara G, Ueyama T. Takotsubo cardiomyopathy a new form of acute, reversible heart failure. *Circulation* 2008;118(25): 2754-62.
10. Tarkin JM, Khetyar M, Kaski, JC. Management of Tako-tsubo syndrome. *Cardiovasc Drugs Ther* 2008;22(1): 71-77.
11. Sader MA, Celermajer DS. Endothelial function, vascular reactivity and gender differences in the cardiovascular system. *Cardiovasc Res* 2002;53(3): 597-604.
12. Bybee KA, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, Rihal CS. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med* 2004;141(11):858-65.
13. Villareal RP, Achari A, Wilansky S, Wilson, JM. Anteroapical stunning and left ventricular outflow tract obstruction. *Mayo Clin Proc* 2001;76(1):79-83.
14. Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M. Angina Pectoris-Myocardial Infarction Investigations in, J. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. *J Am Coll Cardiol* 2001;38(1): 11-18.
15. Dias A, Franco E, Mercedes A, Hebert K, Messina D, Quevedo HC. Clinical features of takotsubo cardiomyopathy–s single-center experience. *Cardiology* 2013;126(2):126-30.
16. Donohue D, Ahsan C, Sanaei-Ardekani M, Movahed MR. Early diagnosis of stress-induced apical ballooning syndrome based on classic echocardiographic findings and correlation with cardiac catheterization. *J Am Soc Echocardiogr* 2005;18(12):1423.
17. Eitel I, Behrendt F, Schindler K, Kivelitz D, Gutberlet M, Schuler G, Thiele H. Differential diagnosis of suspected apical ballooning syndrome using contrast-enhanced magnetic resonance imaging. *Eur Heart J* 2008; 29(21):2651-59.
18. Kawai S. Pathology of Takotsubo (Ampulla) Cardiomyopathy. In: Veselka J. (Ed.). *Cardiomyopathies - From Basic Research to Clinical Management,* 1 ed. InTech. China: Shanghai; 2012;709-25.
19. Lyon AR, Rees PSC, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy - A novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nature Clinical Practice Cardiovascular Medicine* 2008; 5(1):22-29.
20. Layland J, Whitbourn R, MacIsaac A, Somaratne J, Wilson, A. Takotsubo cardiomyopathy: Reversible elevation in microcirculatory resistance. *Cardiovascular Revascularization Medicine* 2012; 13(1):66-68.

21. Kume T, Akasaka T, Kawamoto T, Yoshitani H, Watanabe N, Neishi Y, Yoshida K. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. *Circulation Journal* 2005;69(8):934-939.

22. Cecchi E, Parodi G, Giglioli C, Passantino S, Bandinelli B, Liotta AA, Mannini L. Stress-induced hyperviscosity in the pathophysiology of takotsubo cardiomyopathy. *American Journal of Cardiology* 2013;111(10):1523-1529.

23. Uchida Y, Egami H, Uchida Y, Sakurai T, Kanai M, Shirai S, Oshima T. Possible participation of endothelial cell apoptosis of coronary microvessels in the genesis of takotsubo cardiomyopathy. *Clinical Cardiology* 2010; 33(6):371-77.

24. Maruyama T, Hanaoka T, Nakajima H. Acute pericarditis in the recovery phase of transient left ventricular apical ballooning syndrome (takotsubo cardiomyopathy). *Internal Medicine* 2007;46(22): 1857-60.

25. Twerenbold R, Reichlin T, Mueller C. Clinical application of sensitive cardiac troponin assays: Potential and limitations. *Biomarkers in Medicine* 2010;4(3):395-401.

26. Jiang Q, Gingles NA, Olivier MA, Miles LA, Parmer RJ. The anti-fibrinolytic SERPIN, plasminogen activator inhibitor 1 (PAI-1), is targeted to and released from catecholamine storage vesicles. *Blood* 2011; 117(26):7155-63.

27. Van De Walle SOA, Gevaert SA, Gheeraert PJ, De Pauw M, Gillebert TC. Transient stress-induced cardiomyopathy with an "inverted Takotsubo" contractile pattern. M*ayo Clinic Proceedings* 2006; 81(11):1499-1502.

28. Martin CS, Ionescu LN, Barbu CG, Sirbu AE, Lambrescu IM, Lacau IS, Fica SV. Takotsubo cardiomyopathy and transient thyrotoxicosis during combination therapy with interferon-alpha and ribavirin for chronic hepatitis C. *BMC Endocrine Disorders* 2014:14.

29. Smith SA, Auseon AJ. Chemotherapy-Induced Takotsubo Cardiomyopathy. *Heart Failure Clinics* 2013;9(2):233-42.

30. Finsterer J, Ohnsorge P. Influence of mitochondrion-toxic agents on the cardiovascular system. *Regulatory Toxicology and Pharmacology* 2013; 67(3):434-45.

31. Singh K, Carson K, Usmani Z, Sawhney G, Shah R, Horowitz J. Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy. *International Journal of Cardiology* 2014;174(3):696-701.

32. Hudacko RM, Fyfe BS, Mehra A, Moreyra AE. Takotsubo cardiomyopathy: Pathologic insights from a fatal case. *Internet Journal of Cardiology* 2010:8(1).

33. Nef HM, Möllmann H, Akashi YJ, Hamm CW. Mechanisms of stress (Takotsubo) cardiomyopathy. *Nature Reviews Cardiology* 2010;7(4):187-93.

34. Redfors B, Ali A, Shao Y, Lundgren J, Gan, LM, Omerovic E. Different catecholamines induce different patterns of takotsubo-like cardiac dysfunction in an apparently afterload dependent manner. *International Journal of Cardiology* 2014;174(2):330-36.

35. Khoueiry G, Abi Rafeh N, Azab B, Markman E, Waked A, Abourjaili G, Costantino T. Reverse takotsubo cardiomyopathy in the setting of anaphylaxis treated with high-dose intravenous epinephrine. *Journal of Emergency Medicine* 2013;44(1):96-99.

36. Sundbøll J, Pareek M, Høgsbro M, Madsen EH. Iatrogenic takotsubo cardiomyopathy induced by locally applied epinephrine and cocaine. *BMJ case reports*, 2014.

37. Kuo BT, Choubey R, Novaro GM. Reduced estrogen in menopause may predispose women to takotsubo cardiomyopathy. *Gender Medicine* 2010;7(1):71-77.

38. Ueyama T, Kasamatsu K, Hano T, Tsuruo Y, Ishikura F. Catecholamines and estrogen are involved in the pathogenesis of emotional stress-induced acute heart attack. *Annals of the New York Academy of Sciences* 2008;1148:479-85.