Indian Heart Journal 70 (2018) 165–174

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Review Article

Takotsubo syndrome

Sanjiv Gupta[a,*], Madan Mohan Gupta[b]

[a] NH Narayana Multispeciality Hospital, Jaipur, India
[b] Heart and Diabetic Clinic, B-19, Rajender Marg, Bapu Nagar, Jaipur, India

ARTICLE INFO

Article history:
Received 17 March 2017
Accepted 11 September 2017
Available online 13 September 2017

Keywords:
Left ventricular failure (LVF)
Regional wall motion abnormalities (RWMA)
Apical ballooning syndrome

ABSTRACT

Takotsubo syndrome is a reversible acute heart failure frequently precipitated by an emotional or physical stress. The clinical presentation resembles acute coronary syndrome. Pathogenesis is complex and may involve brain-heart axis and neuro-hormonal stunning of the myocardium. Coronary angiography reveals normal epicardial arteries with no obstruction or spasm. NT-ProBNP maybe remarkably elevated. Regional wall motion akinesia (RWMA) of left ventricle extends beyond the territory of one coronary artery. Reduced left ventricle ejection fraction (LVEF) and RWMA recover in 6–12 weeks. Prognosis is generally good. Recent meta-analysis shows in-hospital mortality of 1–4.5% and recurrence rate of 5–10% during five year follow-up.

Contents

Abbreviations: ACS, acute coronary syndrome; ECG, electrocardiography; ECHO, echocardiography; EF, ejection fraction; ECMO, extra-corporeal membrane oxygenator; HPA, hypothalamus pituitary axis; IABP, intra-aortic balloon pump; LVAD, Left ventricle assist device; LMWH, Low molecular weight heparin; LVOT, left ventricle outflow tract; LV, left Ventricle; MR, mitral regurgitation; MRI, magnetic resonance imaging; NIS, Nationwide Inpatient Sample; NSTEMI, Non-ST elevation myocardial infarction; NT-proBNP, N-terminal pro brain natriuretic peptide; RWMA, regional wall motion abnormality; SAM, systolic anterior motion; STEMI, ST elevation myocardial infarction; SAH, subarachnoid haemorrhage; TS, Takotsubo syndrome.

* Correspondence to: Flat No 403, Golden Sobhagya, B-81, Rajender Marg, Bapu Nagar, Jaipur 15, India.
E-mail address: gupta98tanya@gmail.com (S. Gupta).

http://dx.doi.org/10.1016/j.ihj.2017.09.005

1. Introduction

Takotsubo syndrome (TS) is an acute reversible heart failure characterized by transient wall motion abnormality of left ventricle (LV) usually following a stressful event.[1] Clinically it mimics acute coronary syndrome (ACS) and presents with chest pain, dyspnoea and hypotensive shock. Electrocardiography (ECG) reveals ST segment elevation or depression, T wave inversion and prolonged QTc interval. There is elevation of cardiac biomarkers like troponin and pro-brain natriuretic peptide (pro-BNP). Transthoracic two-dimensional echocardiography (2D-ECHO) shows regional wall motion abnormality (RWMA), not restricted to one coronary artery territory. Left ventricle ejection fraction (LVEF) is decreased. Coronary angiography, however, reveals normal epicardial coronaries without significant obstruction due to thrombus or plaque rupture. Left ventriculogram may demonstrate acute ballooning of apical region. LV may assume the shape of Japanese Octopus trap-pot called Takotsubo with narrow apex and round dilated bottom. Takotsubo syndrome thus translates to octopus pot resembling shape of LV during systole on imaging studies. Prognosis is fair in over 90% patients with full recovery of RWMA in 3–6 months. Complications do occur in about 10% cases[2] and in-hospital mortality is estimated as 4.5%.[3] There are no standard guidelines on management of TS.

2. Epidemiology

TS was first described by a Japanese cardiologist in 1990.[4] Many case reports and cases series followed initial description.[5] The disease was initially restricted to Japan but it is now well recognized in Europe, United States, Britain and many other countries. Isolated case reports have been published from France, Belgium, Mexico, Australia, Brazil, Israel, Africa, Turkey and Iceland.[6] Since it is a rare disease, several national and international registries have been established to collect the data on epidemiology, diagnostic criteria and natural course of the disease. A few prominent national registries include Japanese Takotsubo Multicentre Registry from Tokyo CCU Network, German Takotsubo Syndrome Registry, Takotsubo Italian Registry, Nationwide Inpatient Sample (NIS) USA and TS Registry Netherland. The International Takotsubo Registry (Inter TAK Registry) was established at University Hospital, Zurich, Switzerland in 2011 in collaboration of 25 world recognized cardiac centres across seven countries in Europe and US. The incidence of TS remained very low (0.2–0.7%) during the period 2002–2010. With increasing interest on this subject, disease has been recognized more frequently.[7] The incidence is around 1.7–2.2% of all patients initially suspected with ACS and finally diagnosed to have TS. The patients are typically Asian or Caucasian (Asian 57.2%, Caucasian 40% and other races 2.8%). NIS, US recognized 6837 patients of TS in first NIS during 2007–08.[8] The second NIS during 2008–2012 recognized 22005 patients of primary TS and 31942 patients of secondary TS.[9] Inter TAK Registry of Switzerland has indentified 1750 patients of TS during 2012–2014.[10]

3. Aetiology and pathogenesis

The exact aetiology is not known. Normal myocardium utilizes 90% of its energy from fatty acid metabolism and only 10% from glucose metabolism. In TS, there appears to be a shift towards glucose pathway with impaired fatty acid metabolism.

Pathophysiology of TS is complex and involves 'brain heart axis' which is still poorly understood. A significant emotional stress, physical trigger or neurological/psychiatric illness typically precedes the development of TS (Table 1). Over 90% emotional events are negative e.g. death of near relative, motor vehicle accident with psychological trauma, natural disasters, fear, anger on familial conflicts, retirement etc. Such events, leading to TS (labelled as 'broken heart syndrome') are responsible for 90% emotional conflicts.[10] Lesser than 10% of emotional triggers are joyful events like birthday ceremonies, wedding anniversaries, winning a jackpot lottery, unexpected joyful meetings with a friend or relation. The joyful events resulting in TS constitute 'Happy Heart Syndrome'.[11] Many a times the trigger is physical e.g. recent surgery, stay in ICU, stroke, severe psychotic illness, exacerbation of chronic disease like asthma, newly diagnosed serious illness etc. All these emotional and physical events act as triggers which act on heart via brain and stress-induced catecholamine release.

The brain-heart axis involves cortex and subcortical areas including amygdale, hippocampus, basal ganglia and hypothalamus in the initial processing of emotional triggers and results in neuro-hormonal stunning of the myocardium. Intra-cranial pathology, particularly subarachnoid haemorrhage (SAH) may produce clinical picture of TS by neurogenic stunning of myocardium.

Several mechanisms have been proposed to explain the pathogenesis of Takotsubo cardiomyopathy characterized by apical ballooning of left ventricle.

3.1. Catecholamine theory

Due to severe emotional or physical stress, overstimulation of hypothalamus pituitary adrenal axis occurs and results in excessive release of catecholamine. Elevated plasma levels of epinephrine and norepinephrine have been demonstrated during the acute phase.[12] Acute onset of TS and its association with pheochromocytoma or paraganglioma have also suggested that TS may be catecholamine induced myocardial dysfunction.[13] Hypercatecholamines results in myocardial stunning and apical ballooning syndrome (ABS). Histological findings on endomyocardial biopsy of TS show necrosis of contraction bands and infiltration by mononuclear cells. Similar findings are seen in experimental and clinical catecholamine cardiotoxicity.[14,15] Apical portion of LV has the highest concentration of adreno-receptors which explains why catecholamines have maximal effect on the apical portion of the LV resulting in apical akinesia, dilatation and ballooning. Catecholamine excess leads to subtle metabolic changes at cellular level. B2-adrenoreceptor mediated GS proteins signalling (+ve inotropic)

Table 1
Triggers for Takotsubo (TS) Syndrome.

PRIMARY TS[a]	SECONDARY TS[b]
A) NEGATIVE EMOTIONAL TRIGGERS* responsible for "Broken Heart Syndrome"	1. Endocrine Disorders
1. Intense grief due to death of spouse, parent, near relative or friend	Phaeochromocytoma, multiple endocrine neoplasias (MEN), autoimmune poly-endocrine syndrome, SIADH syndrome, thyroid disorders etc.
2. Loss of property, home, financial loss, car accident etc	2. Neurologic Disorders
3. Anxiety and panic reactions due to acute illness, accidents, floods, robbery, court matters etc	Subarachnoid haemorrhage (SAH), acute head/spinal injuries, acute neuro-muscular crisis.
4. Interpersonal conflicts, depression, suicidal attempts	3. Respiratory Disorders
5. Major psychiatric illness	Acute exacerbation of COPD
6. Severe anger/frustration	Acute ventilatory failure
7. Retirement, debts, defeats or work stress	4. Obstetric emergencies and Caesarean section
B) POSITIVE EMOTIONAL STRESS* responsible for "Happy Heart Syndrome"	5. Psychiatric Disorders
1. Birthday parties (50th or 80th)	Acute panic/suicidal attempts
2. Wedding – son, daughter	Drug abuse/withdrawal of alcohol
3. Unexplained happy meetings with friend/relative	6. Acute sepsis
4. Becoming grandmother	7. Acute GIT disorders
5. Winning a big lottery/unexpected huge financial gains	8. Dobutamine Stress Echocardiography
6. Happy ceremonies and various happy events e.g. 50th wedding anniversary	9. Excessive IV Catecholamine infusion
C) PHYSICAL TRIGGERS	10. Following general anaesthesia

[a] Adapted from Ghadri et al.[11], EHJ 37: 2823–2829.
[b] Adapted from Lyon et al.[1], EHJ 18:8–27.

is converted to G1 protein signalling (-ve inotropic) leading to reduced myocardial contractility and LV dysfunction.[16]

3.2. Myocardial bridging and myocardial oedema

Myocardial bridging occurs when a coronary artery tunnels through the myocardium rather than overlying and resting on it. This occurs maximally in left anterior descending artery (LAD). Myocardial bridging is normally regarded as a congenital anomaly with no adverse hemodynamic effects. Myocardial bridging may be complete or partial when a segment of coronary artery passes in the tunnel under cover of underlying myocardium. Migliore et al.[17] recently studied 42 consecutive patients of apical ballooning syndrome (ABS) by echocardiography (ECHO), coronary angiography (CAG) with intravascular ultrasound (IVUS), computer tomography angiography (CTA) and cardiac magnetic resonance (Cardiac MR). Myocardial bridging was seen both by CAG and mostly by CTA in 32 ABS patients (76%); 23 with partial and 9 with complete encasement. It was compared with 401 control patients without ABS where CTA demonstrated myocardial bridging in 31% patients ($p < 0.001$). The authors proposed the role of myocardial bridging as potential factor in the pathogenesis of ABS.

Myocardial oedema is characteristic feature in patients with TS/ABS and can be demonstrated by cardiac magnetic resonance. Myocardial oedema, predispose TS patients to develop T wave inversion, QT prolongation and often life −threatening arrhythmias (LTA).[18,19]

3.3. Microvascular dysfunction

Active TS may be due to microvascular spasm/constriction/microemboli. Microvascular dysfunction could be secondary to excessive release of epinephrine.[20,21] Myocardial contrast echocardiography and myocardial single photon emission computed tomography have shown myocardial perfusion defect at microvascular level.

3.4. Left ventricle outflow tract obstruction (LVOTO)

Development of transient mid-cavity obstruction can divide the LV into two cavities with increased wall pressure/stress in the distal apical portion.[22] However LVOTO is a consequence rather than the cause of TS.

3.5. Hormonal and genetic factors

A recent update on Takotsubo syndrome confirmed female preponderance (88.7%) which suggest a role of various reproductive hormones in the pathogenesis of TS.[23] There is also close association between pheochromocytoma and Takotsubo cardiomyopathy. Rare occurrence of TS in siblings and close family relations may indicate a role of genetic factors in pathogenesis of TS.[24–27]

3.6. Role of hypovolemia, hyponatremia and syndrome of inappropriate hyper-secretion ADH (SIADH) in takotsubo syndrome

Falola et al.[28] analyzed 1724 patients of Takotsubo syndrome for precipitating factors. TS was associated more often with various precipitating factors including anxiety, depression, panic mood disorders, heart failure, hyponatremia, hypovolemia, acidosis, alcohol withdrawal, epilepsy, neurologic disorders and cancer while traditional risk facts like obesity, hypertension, diabetes, smoking were less common. The authors proposed a new hypothesis/mechanism involving hypovolemia, hyponatremia and inappropriate hypersecretion of antidiuretic hormone (ADH) in the genesis of TS.

Leva et al.[29] have described a case who developed hyperacute phase of Takotsubo syndrome following peripheral angioplasty on the femoral artery. The procedure was complicated by major bleeding and hypovolemic shock. Though the left arm blood pressure was not recordable, the central arterial pressure was increased. Simultaneous thoracic echocardiography and cardiac catheterization showed basal hyperkinesis of left ventricle, LV apical akinesia, systolic anterior motion (SAM) of mitral leaflet and severe intraventricular gradient. The authors hypothesized that severe hypovolemia was the basic factor which resulted in increased peripheral resistance and release of catecholamines. The patho-physiologic cascade as described above resulted in stretching effect on LV apex leading to apical ballooning and heart failure.

3.7. Cancer and takotsubo syndrome

Prevalence of cancer (primary or metastasis) was studied amongst 114 consecutive patients with TS; 16 patients (14%) had malignancy at the time of clinical presentation of TS while another 11 patients (9.6%) developed cancer on follow up.[13] At molecular level, catecholamines may target tumour cells for growth.

3.8. Carbohydrate antigen 125 (CA 125) in TS

Carbohydrate-antigen 125 (CA 125) is a tumour marker normally used in the follow up of patients especially with ovarian cancer to monitor the efficacy of tumour therapy. Possible role of CA 125 in TS was studied by Santoro et al.[30] Serum levels of CA 125 in 63 consecutive patients of TS were measured at admission in acute phase and on follow up for a median duration of 139 days. CA 125 levels at admission were inversely related to LVEF (r-0.30, $p < 0.05$) and directly related hospital stay (r 0.29, $p < 0.05$). CA 125 levels at admission were higher in subjects with adverse events on follow up (88.9 ± 200 vs 20.9 ± 30 U/ml, $p < 0.05$). CA 125 could thus be a useful marker for early risk stratification in patients with TS.

3.9. Mechanic hypothesis

Anatomical variations in sympathetic innervations and adrenergic receptor density with differential dynamic response to emotional/physical stress has been suggested as another hypothesis for Takotsubo syndrome.[31,32] High local concentration of norepinephrine might results in apical hypokinesia and increasing mechanical stress at the apex. The end result would be an increasing LV end diastolic pressure and ballooning of the apex.

3.10. Serum interleukins 6 and 10 (IL-6 & IL-10) levels in TS

Systemic inflammation has been hypothesized as a possible mechanism of TS. Concept of inflammation is supported by the presence of myocardial oedema at CMR and immune cell infiltration with band necrosis on myocardial biopsy in TS. Serum IL-6 and IL-10 are markers of inflammation.[33] The serum levels of IL-6 and IL-10 in 56 TS patients were measured at admission and on follow-up (mean period of 178 days).[34] Serum IL-6 and IL-10 levels were higher in subjects with adverse events at follow up (IL-6:120 ± 294 vs 22 ± 40 pg/ml; $p < 0.05$; IL-10:13 ± 35 vs 2 ± 3 pg/ml, $p < 0.05$). The elevated levels of IL-6 and IL-10 were associated with higher adverse events as well as higher mortality rates, even after correction for age, LVEF and NT-proBNP levels in multivariate Cox-analysis. Inflammation could thus be a mechanism in the pathogenesis of TS. Inflammatory cascade could be proportionately heightened by myocardial catecholamine damage. Serum IL levels might act as additional prognostic marker in TS. Rate of adverse events is higher when both IL- 6 and IL-10 are elevated compared with elevation of either IL-6 or IL-10 alone.

4. CLASSIFICATION[1]

1 PRIMARY TS with/without stress trigger: Primary TS is more common in postmenopausal elderly women. The patients presents primarily with cardiac symptoms of ACS. Physical and emotional stresses are responsible for TS in over 70% patients. However more than one quarter have no clear triggers. Patients with TS have a higher rate of co-existing neurological and psychiatric disorders.[10]
2 SECONDARY TS: Patient with clinical evidence of serious medical/surgical/obstetric and psychotic disorders develop TS during the course of primary illness.

Table 1 summarizes various triggers involved in primary and secondary TS.

5. Clinical profile of TS

Primary TS predominantly occurs in postmenopausal female which forms 90% of the total cases. The chief complaints are chest pain (75%), dyspnoea (26–46%), palpitation and syncope following a severe emotional (28–40%) or physical event (36%) which triggers the cardiac events.[1,10] No trigger is found in about 30% cases. The gender, menopausal status and presence of trigger are, however, not mandatory. About 10% of cases in the largest series (NIS-USA) were men and young women; 35% were without any trigger[8,9]. Co-existing neurological and psychiatric disorders may be present in 46% patients.[10] Physical examination may reveal tachycardia, hypotension and pulmonary oedema. Table 2 summarizes the clinical profile of TS in two recent studies.

6. Electrocardiogram (ECG)

ECG reveals abnormal findings in over 95% patients in the form of ST elevation (43%) or ST depression (8%), T wave inversion (50%) and prolonged QTc interval ($\geq$400 ms). If QTc prolongation is pronounced ($>$500 ms), there is danger of life threatening ventricular tachycardia, torsade de pointes and ventricular fibrillation.[18,19] ECG cannot reliably differentiate between transient apical ballooning syndrome of TS from acute coronary syndrome or myocardial infarction.[35,36]

7. Cardiac biomarkers

During acute phase, serum natriuretic peptides (BNP and NT-proBNP) are always increased along with troponin. BNP and NT-proBNP may be increased 3–5 times (much more than troponin) and are considered more useful diagnostic biomarkers for the diagnosis of TS. In a recent study of cardiac biomarkers in TS and STEMI patients, the concentration of NT-proBNP was greater in TS versus STEMI (4702 pg/ml vs 2138 pg/ml respectively) while troponin and CKMB mass were lesser in TS vs STEMI (Troponin 2.1 ng/ml and CKMB Mass 9.5 ng/ml in TS v/s Troponin 19 ng/ml and CKMB mass 73.3. ng/ml in STEMI[22] (Table 3). The authors concluded that simple biomarkers can distinguish TS from STEMI and the most important accurate marker was ratio of NT-proBNP and Troponins.[37]

Other biomarkers like serum catecholamine, neuropeptide and serotonin are elevated in TS but are usually not measured in routine investigations.

8. Echocardiography (ECHO)

Transthoracic echocardiography with colour Doppler is always the first imaging procedure in the diagnosis of TS.[38] The key ECHO findings in TS consist of a large area of regional wall motion akinesia of LV extending beyond the territory of single coronary artery.[39] The dyskinetic/akinetic myocardial area usually involves apical portion of LV resulting in acute apical ballooning along with dilatation of mid ventricular area. Left ventricle ejection fraction (LVEF) is always compromised and reduced (20–45%). There is a high prevalence of mitral regurgitation (MR) in TS with or without systolic anterior motion (SAM) of anterior mitral leaflet. Left ventricle outflow tract (LVOT) obstruction can be demonstrated in patients with severe acute cardiac failure.[22] Special modern tools of ECHO include real time three dimensional and contrast echocardiography.

Table 2
Clinical Profile of Takotsubo Syndrome.

Parameter	Templin et al.[10]	Ghadri et al.[11]	
		Broken Heart	Happy Heart
Total number of patients	1750	460	20
Women%	89.8	74.5	75
Mean Age (yrs)	66.8	65	71.4
Chest Pain (%)	75.9	72.2	89.5
Dyspnoea (%)	46.9	46.6	26.3
Cardiac Shock (%)	9.9	3.7	NONE
ECG ST elevation (%)	43.7	44.5	50
Mean EF (%)	40.7	42.6	40.2
Co-existing neurologic/psychiatric illness (%)	46.8	Not described	Not described
Triggers (%)		87.3	100
Emotional	28.7		
Physical	36		
Coronary angiography	Normal 85% Co-Existing CAD 15%	Normal	Normal
LV wall motion akinesia pattern (%)			
Apical	81.7	79.8	65
Mid-Ventricular	14.6	16.3	35
Basal	2.2	1.9	–
Focal	1.5	1.9	–
Mortality (%)	4.1	1.1	None

(ECG: electrocardiogram, EF–ejection fraction, LV–left ventricle).

9. Angiography

Coronary angiography is urgently indicated to rule out obstructive ACS (STEMI/NSTEMI). In TS, no obstructive pathology is found; thrombus or plaque rupture is absent. Coexisting mild atherosclerosis without obstruction has been described in <10% cases of TS but fails to explain the severe LV wall abnormality seen in TS.[1] Computed tomography angiography (CTA) is performed using 64 slice computed tomography scanner and is regarded as the best method to diagnose myocardial bridging.[17]

10. Cardiac magnetic resonance (CMR)

CMR provides 3-dimensional view of the anatomy of LV as well as RV. Four major anatomic patterns of regional wall motion abnormality (RWMA) have been recognized—apical ballooning (81.7%), midventricular (14.6%), basal or inverted (2.2%) and focal (1.5%). Table 4 and Fig. 1 summarizes the anatomical variation in the patterns of RWMA. TS involves RV in about 25–30% patients and can be recognized by CMR.[1] CMR is indicated in TS, first within 7 days and then at 2–6 months to judge the recovery of RWMA.[40,41] Late gadolinium enhancement (LGE) can be demonstrated in acute myocardial infarction (and acute myocarditis) but is typically absent in TS.

Table 3
Biomarkers in TS and STEMI.

Serial No	Parameter	TS (n = 66)	STEMI (n = 66)	P value
1	NT-proBNP	4702 pg/ml	2138 pg/ml	
2.	Troponin	2.1 ng/ml	19 ng/ml	
3.	CKMB Mass	9.5 ng/ml	73.3. ng/ml	
4.	Ratios			
a)	NT-proBNP/Troponin	223.2	678.2	<0.001
b)	NT-proBNP/CKMB Mass	81.6	27.5	<0.001
c)	NT-proBNP/EF	110.4	39.4	

Ref. Budnik et al.[37]
(TS–Takotsubo syndrome, STEMI–ST elevation myocardial infarction, NT-proBNP–N-terminal pro-brain natriuretic peptide, CK–creatinine kinase, EF–ejection fraction).

11. Miscellaneous procedures

These research tools include myocardial perfusion imaging (SPECT), positron emission tomography (PET) and endomyocardial biopsy.

12. Diagnostic criteria

Many National TS Registries have laid down their own criteria for the diagnosis of TS. Mayo clinic criteria were modified and are widely accepted.[36] All the four criteria of Mayo clinic must be fulfilled. European Heart Failure Association (EHFA) have further amended and established seven criteria.[1] Table 5 compares the Mayo clinic and EHFA criteria for TS. Two main conditions which warrant differentiation from TS on urgent basis are acute coronary syndromes and acute myocarditis. Various differentiating criteria are summarized in Table 6.

13. Prognosis

Primary TS was originally regarded as a benign condition with good prognosis with complete recovery of EF in 95.7% patients.[42] However TS is now considered a more serious condition and life threatening acute cardiac complications may develop in the clinical course of Takotsubo syndrome.[43] These include pulmonary oedema due to acute LV failure, LV out flow tract obstruction (LVOT)[22], severe mitral regurgitation (MR),[44,45,46] cardiogenic shock, life threatening arrhythmias,[18] thrombus formation in the akinetic portion of LV and LV wall rupture.[47,48] Each complication requires specialized medical or surgical management.

14. Mortality

In a large meta-analysis of 2120 patients out of 37 studies from 11 different countries the in-hospital mortality of TS was 4.5% (95% CI, 3.1–6.2, 12 = 60.8%).[3] In a recent study on trends in hospitalization of TS in USA, the in-hospital mortality was 1.1% in primary TS and 3.2% in secondary TS which was associated with a higher incidence of cardiogenic shock, respiratory failure and cardiac arrest. Mortality was higher in men compared to women in TS.[9]

Table 4
ANATOMICAL PATTERNS OF LV WALL MOTION ABNORMALITY ON LV ANGIO.

No	Anatomical pattern	Lyon et al.[1]	Templin et al.[10]
1.	Apical ballooning	75–80%	81.6%
2.	Mid LV dilatation	10–15%	14.6%
3.	Basal (inverted)	5%	2.2%
4.	Rare variants: focal, global, RV, biventricular	–	1.5%

(LV–left ventricle, RV–right ventricle).

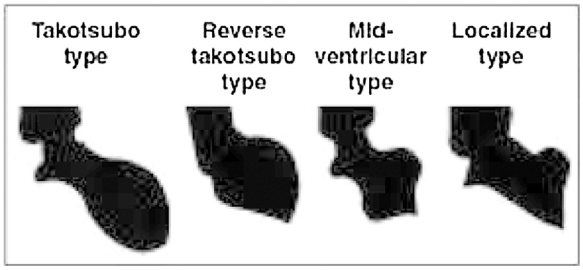


Fig. 1. Anatomic Variants of Takotsubo Syndrome.

15. Indicators of high risk

1 Age <75 years
2 Presence of serious complications e.g. pulmonary oedema, hypotension, serious arrhythmias
3 LVEF <35%
4 Presence of MR/LV wall rupture, apical thrombus
5 Bi-ventricular involvement
6 ECG: QTc > 500 ms
7 BNP ≥ 600 pg/ml, NT-proBNP ≥ 200 pg/ml

16. Management of primary takotsubo cardiomyopathy

No randomized clinical trials (RCTs) exist to support any specific therapy for TS. Fortunately TS has a favourable prognosis and majority cases recover in 3–6 months. Hence major aim of therapy is to sustain life and give supportive treatment to tide over the complications.[49,50,51] Table 7 shows a summary of drugs usually prescribed during acute phase and follow up treatment of Takotsubo syndrome (Brunetti et al.).[49] The patients should be managed in ICU/CCU. Urgent coronary angiography, echocardiography and biochemical assessment should be performed to make a correct diagnosis and assessment of risk stratification. Over 90% patients without serious risk factors recover in 3–6 months. Patients with LVEF >45% need supportive therapy with cardioselective beta blockers (carvedilol or metoprolol), aspirin, ACE inhibitors and statins. If LVEF is 35–45% beta blockers with/without ACEI inhibitors or ARBs may be indicated.[10,11] Airway obstruction, if severe, is a contraindication for beta blockers. Patients with complications and LVEF <35% need specialist care and management for cardiogenic shock, pulmonary oedema and arrhythmias. Prevention and treatment for apical thrombus may be necessary using heparin (Flowchart 1).

(A) Cardiogenic Shock

Sympathomimetic drugs like nor epinephrine, dopamine, dobutamine are avoided or contraindicated. Mechanical support in form of intra-aortic balloon counterpulsation (IABP) may be required after careful assessment for LVOT obstruction. Others may need LV Assist Devices (LVADs) and extra-corporeal membrane oxygenation (ECMO).[1] Prevention of thromboembolism is achieved by use of low molecular weight heparin (LWMH). Intravenous levosimendan and milrinone have been employed with good results.

Levosimendan is a new catecholamine sparing positive inotropic drug. It is a calcium sensitizer and K-ATP channel opener and used in the management of heart failure. It increases myocardial contractility and has anti-stunning anti-ischemic effects. Levosimendan is given as a 10 min loading dose (4–6 ug/kg) followed by infusion for 24 h (0.1–0.2 ug/kg/min). IV infusion of Levosimendan is associated with decrease in plasma endothelin level. Levosimendan is useful in acute heart failure and cardiogenic shock of Takotsubo syndrome.[52,53]

(B) PULMONARY ODEMA

due to acute left ventricular failure (LVF) is treated with standard decongestive medical therapy.

(C) ARRHYTHMIAS

Arrhythmias require careful monitoring during hospitalization.

(i) Atrial fibrillation (AF) is responsible for about 20% of all arrhythmias in TS. Treatment includes beta-blockers and anticoagulation. Correction of hyperkalaemia associated with TS often results in spontaneous cardioversion of atrial fibrillation.[54]

(ii) Ventricular arrhythmias: may be life threatening when QTc exceeds 500 ms. Madias et al.[33] has reported an incidence of 8.6%. Life threatening arrhythmias (LTA) included torsade de pointes (Tdp) and ventricular tachycardia/fibrillation (VT/VF). Migliore et al.[19] assessed the incidence of LTA during acute and subacute phase in 61 consecutive cases of ABS. LTA was diagnosed in 3 patients (4.9%). All three patients of Tdp required external defibrillation and two required implantable cardioverter defibrillator (ICD). Two patients developed AV block and required temporary pacing followed by permanent pacemaker implantation (PPM). ICD/PPM were not needed after 4–6 weeks in all 4 patients. QTc > 500 ms and giant negative T waves were seen in all 3 patients with LTA. Constant monitoring is requires because QTc interval may change day to day during initial 4–6 weeks. QTc > 500 ms tends to develop in patients with bradyarrythmias, hypokalemia and hypomagnesaemia and it may be necessary to correct biochemical deficiency of potassium and magnesium to reverse Tdp. Temporary ventricular pacing is necessary in most cases to control Tdp. Implantable cardioverter defibrillator (ICD) is usually required for 4–6 weeks. ECG abnormalities & RWMA usually disappear on follow up of patients after 4–6 weeks.

16.1. Atrioventricular block (AV block)

AV block requires temporary pacing during hospitalization. Few may require permanent pacemaker (PPM).

(D) Prevention/Treatment for apical thrombus by IV heparin or LWMH.

(E) LVOT Obstruction: IV beta blockers may be beneficial

(F) MITRAL REGURGITATION: needs symptomatic management; role of surgery is debatable.

Table 5
DIAGNOSTIC CRITERIA FOR TAKOTSUBO SYNDROME.

Modified Mayo Clinic Criteria[36]	European Heart Failure Association Diagnostic Criteria[1]
1. Transient hypokinesia or akinesia of LV with regional wall motion abnormality, majority involving apex & mid LV (or other areas) extending beyond the distribution of single epicardial artery; hypokinesia invariably (but not always) follows stressful trigger which could be emotional or physical.	1. Transient regional wall motion abnormalities of LV (or RV) myocardium which are frequently but not always preceded by stressful trigger (emotional or physical).
2. Appearance of new ECG abnormalities like ST elevation, T inversion, Q waves with mild elevation of troponins and pro-BNP markers	2. The regional wall motion abnormality usually (exceptions reported) extends beyond a single epicardial vascular distribution and often results in circumferential dysfunction of the ventricular segment involved.
3. Absence of obstructive lesion (plaque rupture, thrombus or spasm) of epicardial coronary artery (thus excluding STEMI, NSTEMI and prinzmetal angina)	3. New and reversible ECG abnormalities (ST segment elevation, ST depression, LBBB, T wave inversion and/or QTc prolongation in acute phase
4. Absence of phaeochromocytoma and myocarditis	4. Significant elevation of serum natriuretic peptide (BNP or NT-proBNP) during acute phase.
	5. Positive but relatively small elevation of cardiac troponin measured with a conventional assay (troponin −ve cases have been reported).
	6. Absence of culprit atherosclerotic disease including plaque rupture, thrombus formation and coronary dissection or other pathological conditions to explain the pattern of temporary LV Dysfunction e.g. hypertrophic cardiomyopathy, viral myocarditis etc.
	7. Recovery of ventricular function on cardiac imaging on follow up (3–6 months).

(ECG-electrocardiogram, LV-left ventricle, BNP-brain natriuretic peptide, STEMI-ST elevation myocardial infarction, NSTEMI-NonST elevation myocardial infarction, RV-right ventricle, LBBB-left bundle branch block).

Table 6
Differential Diagnosis Between Takotsubo Syndrome, ACS & Myocarditis.

No	Parameter	TS	ACS	Acute myocarditis
1.	Age	>50 yr	Any age	Younger age
2.	Sex	Female 90%	Either	Either
3.	Trigger	Present in 70%	Doubtful	? viral infection
4.	Pericardial rub	Absent	±	±
5.	Biomarkers			
	Troponin	+	+++	+
	NT-Pro BNP	+++	+	+
6.	ECHO	RMWA beyond the territory of single coronary artery LVEF 30–45%	RWMA corresponding to culprit coronary artery LVEF 45–60%	RWMA± LVEF variable
7.	Coronary Angiography	Normal	Obstruction by thrombus/plaque rupture	Normal
8.	Cardiac MRI	LGE Absent	LGE present	LGE present
9.	Endomyocardial biopsy	Necrosis of contraction bands	Coagulation necrosis	Inflammatory cells
10.	Demonstration of viral etiology	Absent	Absent	Present

(TS- Takotsubo syndrome, ACS-acute coronary syndrome, BNP-brain natriuretic peptide, ECHO- echocardiography, RWMA-regional wall motion abnormalities, LVEF-left ventricle ejection fraction, MRI-magnetic resonance imaging, LGE-late gadolinium enhancement).

Table 7
Treatment of Takotsubo Cardiomyopathy.

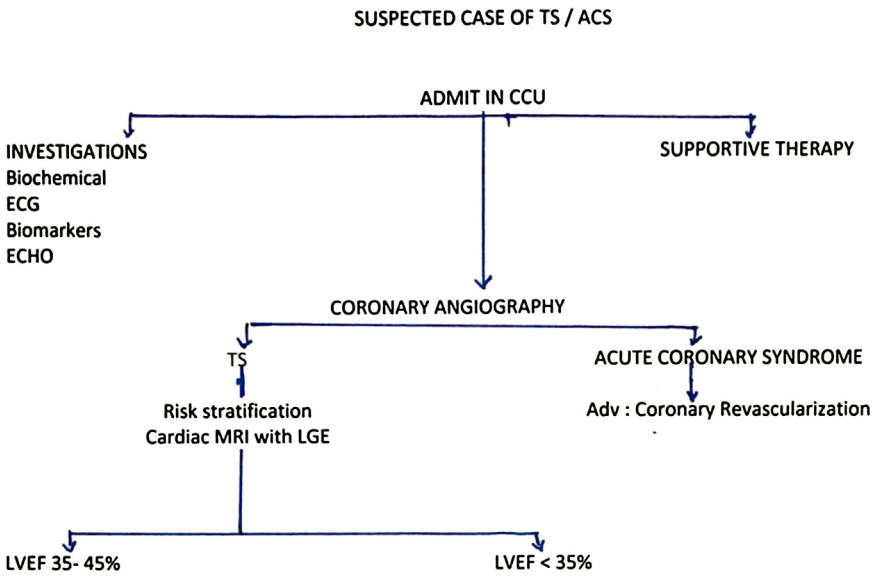
(A) During Acute Phase

Drugs	Potential benefit	Short comings
Antiplatelet	Coronary flow	Lack of evidence
Anticoagulant	Prevention of apical thrombosis	Bleeding tendency
Beta blockers	LVOT	Hypotension
ACE-Inhibitors	LV remodelling	Lack of evidence
Calcium channel blockers	Coronary spasm	Poor evidence
Anti-arrhythmic	Arrhythmias	QT prolongation
Diuretic	Pulmonary oedema	Hypotension
Livosimedan	Cardiogenic shock, high risk patients	Hypotension, arrhythmias
Mechanical Support	Severe hypotension, cardiogenic shock	Not always available

(B) Treatment on Follow-up

Drugs	Potential benefit	Short comings
Beta blocker	Block catecholamine surge	Lack of evidence
ACE Inhibitors	? prolong survival	Lack of evidence
Antiplatelet	Coronary flow	Lack of evidence

Reference: Brunetti et al.[49], Future Cardiology 2016, Sep 12, Vol 12 (5), 563-72. http/www.carsteintschoepe.de/ursfiles/23. Takotsubo Kardiomyothie, 2017.



Cardiogenic Shock	IABP, LVAD, ECMO
Acute LVF	IV diuretics, Levosimedan, mechanical ventilation
Arrhythmias	IV Beta Blockers IV Amiodarone AICD
LVOT Obstruction	Beta blockers
MR	? Symptomatic
Apical thrombus	LMWH

Flowchart 1. Management of takotsubo syndrome.

(G) Ventricular rupture

Left ventricular rupture in the form of free wall rupture or septal perforation is rare but life threatening. It is associated with LVOT and high intramural pressure. Mortality is 80–90%. Beta blockers have a role in reducing LVOT and preventing cardiac rupture.

17. Prevention of recurrences by drugs

TS is normally regarded as a transient dysfunction of left ventricle with complete recovery in 4–8 weeks in over 90% patients. Recurrence is rare but does occur. In a large study of 1750 patients of TS, a recurrence rate of 1.8% per year was found.[10] In a meta-analysis of 31 studies involving 1664 patients, Singh et al.[55] reported a cumulative recurrence rate of 5% at 6 years with an annual rate of 1.5%. Kato et al.[56] in a recent meta-analysis of 3513 patients, recurrence rate was varying 0–10% in the 16 studies. Factors predictive of recurrence were severe LV dysfunction, increased susceptibility to emotion or physical stress, dynamic variation in the sensitivity of cardiac adrenergic receptors and females under 50 years. Multiple recurrences of TS has also been reported.[57]

The efficacy of various drugs for the prevention of recurrences of TS has been studied in a recent meta-analysis of 8 studies involving 511 patients (Santoro et al.).[58] Beta blockers were most frequently employed for this purpose. The recurrence rate was 1.81% (6 of 331) in those treated with beta blockers compared with 2.86% (4 of 140) in control (OR: 0.44, 95% CI: 0.15–1.31, p-NS). The recurrence rate with ACE inhibitors was 0.5% (1 out of 214) in those treated with ACE inhibitors/ARBs compared with 0% (0 out of 61) in controls (OR:0.42, 95%CI: 0.8–2.36, p-NS). The recurrence rate was 0.5% (1 of 200) in those treated with aspirin compared with 0% (0 of 54) in control (OR 0.33, 95% CI: 0.05–2.17, p-NS). Similarly with statins the recurrence rate was 0% (0 of 107) in those treated with statins compared with 0% (0 of 96) in controls (OR: 0.74, 95% CI:0.07–7.3, p-NS). Thus the study did not find definitive evidence of the efficacy of beta blockers, ACE inhibitors or ARBS, aspirin and statins in preventing recurrence of TS.

In contrast Singh et al.[55] in a meta-analysis concluded that ACE-inhibtors, rather than beta-blockers may reduce the risk of recurrence. In a more recent meta-regression analysis of drug treatment rates with beta-blockers (BB) and ACE-inhibitors (ACEI)/angiotension receptor blockers (ARBs) and recurrences of TS, Brunetti et al.[59] found a significant regression between rates of prescription of ACEI and rate of recurrence of TS. The regression was not statistically significant for beta-blockers. Hence ACEI may be more effective than BB in reducing the recurrence of Takotsubo syndrome.

18. Management of secondary TS

Secondary TS develops in critically ill patients admitted to intensive care unit. The incidence is underestimated because coronary angiography is usually avoided/contraindicated in such patients. Diagnosis is suspected by elevation of NT-proBNP, extensive RWMA beyond distribution of one coronary artery and by cardiac MRI. Dopamine and nor-adrenaline drip for hypotensive state further aggravates TS. Prognosis of secondary TS remains

uncertain and grave. Treatment after suspicion is similar to primary TS.

19. Conclusions

TS can be classified as primary or secondary depending upon the trigger and existing major medical, surgical or psychiatric disease. Primary TS is diagnosed in 1–2% of patients admitted for ACS. The diagnosis should be based on Modified Mayo clinic criteria or European Heart Failure Association criteria. Primary TS commonly affects postmenopausal elderly women. Co-existing neurological or psychiatric illness are encountered frequently in TS. Elevated NT-proBNP and ratio of NT-proBNP and troponin are indicative of TS. Echocardiography, coronary angiography and cardiac MRI are useful tools in the diagnosis of TS. Prognosis of TS is generally good in over 90% patients. Risk stratification and proper management of life endangering complications are essential steps in management. Treatment may include beta blockers, LMWH, levosimedan, IABP, mechanical ventilation, LVAD and ECMO. In-hospital mortality varies 1.1–4.5%. TS has a recurrence rate of 5–10% on 5 year follow-up.

Financial Support

Nil.

References

1. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on takotsubo syndrome: a position statement from the taskforce on takotsubo syndrome of the heart failure association of the european society of cardiology. *Eur J Heart Fail*. 2016;18(1):8–27.
2. Teske AJ, Verjans JW. Takotsubo cardiomyopathy—stunning views on the broken heart. *Neth Heart J*. 2016;34:508–510.
3. Singh K, Carson K, Shah R, et al. Meta-analysis of clinical correlates on acute mortality in Takotsubo cardiomyopathy. *Am J Cardiol*. 2014;113(8):1420–1428.
4. Sato HTH, Uchida T, Dote K, Ishiara M. Takotsubo like left ventricular dysfunction due to multivessel coronary spasm. In: Kodama K, Haze K, Hori M, eds. *Clinical Aspects of Myocardial Injury: from Ischemia to Heart Failure*. Tokyo, Japan: Kagakuhyoronsha Publishing Co.; 1990:56–64 Article in Japanese.
5. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy—a new form of acute, reversible heart failure. *Circulation*. 2008;118:2754–2762.
6. Sharkey SW, Lesser JR, Maron BJ. Takotsubo (Stress) cardiomyopathy. *Circulation*. 2011;124:e460–e462.
7. Otten AM, Ottervanger JP, Symersky T, Suryapranata H, Boer de MJ. Maas AHEM: Diagnosis of Takotsubo cardiomyopathy is increasing over time in patients presenting as ST-elevation myocardial infarction. *Neth Heart J*. 2016;10.1007/212471-016-0859-x.
8. Deshmukh A, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL. Prevalence of takotsubo cardiomyopathy in the United States. *Am Heart J*. 2012;164(1):66–71.
9. Khera R, Light Mc Groary K, Zahr F, Horwitz PA, Girotra S. Trends in hospitalization for Takotsubo cardiomyopathy in United States. *Am Heart J*. 2016;172:53–63.
10. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med*. 2015;373:929–938.
11. Ghadri JR, Sarcon A, Diekmann J, et al. Happy heart syndrome: role of positive emotional stress in Takotsubo syndrome. *Eur Heart J*. 2016;37:2823–2829.
12. Wittstein IS, Thiemann DR, Lima JAC, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352:539–548.
13. Sattler K, El-Battrawy I, Langh S, et al. Prevalence of cancer in Takotsubo cardiomyopathy: short and long-term outcome. *Int J Cardiol*. 2017;238:159–165.
14. Akashi Y, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. *Nature Reviews Cardiology*. 2015;12:387–397.
15. Nazir S, Lohani S, Tachamo N, Ghirire S, Poudel DR, Donato A. Takotsubo cardiomyopathy associated with epinephrine use: a systematic review and meta-analysis. *Int J Cardiol*. 2017;229:67–70.
16. Bathina J, Weiss S, Weintraub WS. Understanding the pathophysiology of apical ballooning syndrome: a step closer. *Expert Rev Cardiovasc Ther*. 2015;13(1):5–8.
17. Migliore F, Maffei E, Perazzolo Marra M, et al. LAD coronary artery myocardial bridging and apical ballooning syndrome. *JACC Cardiovasc Imaging*. 2013;6(1):32–41.
18. Migliore F, Zorzi A, Marra MP, Iliceto S, Corrado D. Myocardial oedema as a substrate of electrocardiographic abnormalities and life-threatening arrhythmias in reversible ventricular dysfunction of Takotsubo cardiomyopathy: imaging evidence, presumed mechanisms, and implications of therapy. *Heart Rhythm*. 2015;12(8):1867–1877.
19. Migliore F, Zorzi A, Peruzza F, Marra MP, Tarantini SI, Corrado D. Incidence and management of life-threatening arrhythmias in Takotsubo syndrome. *Int J Cardiol*. 2013;166:261–263.
20. Luscher TF, Templin C. Is Takotsubo syndrome a microvascular acute coronary syndrome? Towards a new definition. *Eur Heart J*. 2016;37:2816–2820.
21. Khalid N, Ahmad SA, Umer A. Mechanims of Takotsubo cardiomyopathy; role of microcirculatory dysfunction. *International Cardiovascular Forum Journal*. 2016;5:30–32.
22. Oba Y, Takemoto M, Nakano M, Yamamoto H. Takotsubo cardiomyopathy with left ventricular outflow tract obstruction. *Int J Cardiol*. 2006;107:120–122.
23. Alkhoury J, Lundgren J, Ali A, Mesinovic D, Redfors B, Omerovic E. Updates on publication trends in Takotsubo syndrome. *Int J Cardiol*. 2016;221:283–286.
24. Kumar G, Holmes Jr. DRJr., Prasad A. Familial apical ballooning syndrome (Takotsubo cardiomyopathy). *Int J Cardiol*. 2014;144:444–445.
25. Pison L, De Vusser P, Mullens W. Apical ballooning in relatives. *Heart*. 2004;90:e67.
26. Musumeci B, Saponaro A, Pagannone E, et al. Simultaneous Takotsubo syndrome in two sisters. *Int J Cardiol*. 2013;165:e49–e50.
27. Ikutomi M, Yamasaki M, Matsusita M, et al. Takotsubo cardiomyopathy in siblings. *Heart Vessels*. 2014;29:119–122.
28. Falola M, Fonbah W, McGwin JG. Takotsubo cardiomyopathy versus ST—elevation myocardial infarction in a large case control study: proposing a new mechanism. *Int J Cardiol*. 2013;167(3):1079–1081.
29. Ieva R, Santoro F, Ferraretti A, et al. Hyper-acute precipitating mechanism of Tako-Tsubo cardiomyopathy: in the beginning was basal hyperkinesis. *Int J Cardiol*. 2013;167:e55–e57.
30. Santoro F, Ferraretti A, Musaiaca F, et al. Carbohydrate-antigen-125 levels predict hospital stay duration and adverse events at long-term follow-up in Takotsubo cardiomyopathy. *Intern Emerg Med*. 2016;11(5):687–694.
31. Hassan SY. Acute cardiac sympathetic disruption in the pathogenesis of the Takotsubo cardiomyoapthy. *Cardiovasc Revasc Med*. 2014;15:35–42.
32. Wever-Pinzon O, Wever-Pinzon J, Tami L. Recurrent Takotsubo cardiomyopathy presenting with different morphologic patterns. *Int J Cardiol*. 2011;148:379–38110.1016/i.jcard.2010.10.091.
33. Madias C, Fitzgibbons TP, Alsheikh-Ali AA, et al. Acquired long QT syndrome from stress cardiomyopathy is associated with ventricular arrhythmias and torsade de pointes. *Heart Rhythm*. 2011;8:555–561.
34. Santoro F, Tarantino N, Ferraretti A, et al. Serum interleukin 6 and 10 levels in Takotsubo cardiomyopathy: increased admission levels may predict adverse events at follow-up. *Atherosclerosis*. 2016;254:28–34.
35. Bybee KA, Motiei A, Syed IS, et al. Electrocardiography cannot reliably differentiate transient left ventricular apical ballooning syndrome from anterior ST-segment elevation myocardial infarction. *J Electrocardiol, .* 2006;40(1) 38. e1-e6.
36. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Takotsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J*. 2008;155(3):408–417.
37. Budnik M, Kochanowski J, Platkowshi R, et al. Simple makers can distinguish Takotsubo cardiomyopathy from ST segment elevation myocardial infarction. *Int J Cardiol*. 2016;219:417–420.
38. Ctiro R, Rigo F, Ciampi Q, et al. Echocardiographic assessment of regional left ventricular wall motion abnormalities in patient with Takotsubo cardiomyopathy: comparison with anterior myocardial infarction. *Eur J Echocardiography*. 2011;12:542–549.
39. Lee JW, Kim JY. Stress-induced cardiomyopathy: the role of echocardiography. *J Cardiovasc Ultrasound*. 2011;19(1):7–12.
40. Naruse Y, Sato A, Kasahara K, et al. The clinical impact of late gadolinium enhancement in Takotsubo cardiomyopathy: serial analysis of cardiovascular magnetic resonance images. *J Cardiovasc Magn Reson*. 2011;13:67.
41. Kohan AA, Yeyati EL, Stefano LD, et al. Usefulness of MRI in Takotsubo cardiomyopathy: a review of literature. *Cardiovasc Diagn Ther*. 2014;4(2):138–146.
42. Elesber AA, Prasad A, Lennon RJ, Wright RS, Lerman A, Rihal CS. Four year recurrence rate and prognosis of apical ballooning syndrome. *J Am Coll Cardiol*. 2007;50:448–452.
43. Schneider B, Athanasiadis A, Schwab J, et al. Complications in the clinical course of Takotsubo cardiomyopathy. *Int J Cardiol*. 2014;176:199–205.
44. Hagi D, Rohm S, Suselbeck T, Borggree M, Papvassiliu T. Incidence and clinical significance of mitral regurgitation in Takotsubo cardiomyopathy. *Clini Res Cardiol*. 2010;99:93–98.
45. Parodi G, Del Pace S, Salvadori C, Carrabba N, Olivotto I, Gensisin GS. left ventricular apical ballooning syndrome as a novel cause of acute mitral regurgitation. *J Am Coll Cardiol*. 2007;50:647–649.
46. Izumo S, Nalawdi S, Shiota M, et al. Mechanism of acute mitral regurgitation in patients of Takotsubo cardiomyopathy: an echocardiographic study. *Circ Cardiovasc Imaging*. 2011;4:392–398.
47. Yoshida S, Miwa K, Matsubara T, et al. Stress induced Takotsubo cardiomyopathy complicated with wall rupture and thrombus formation. *Int J Cardiol*. 2012;161:e18–e20.
48. Isumi K, Tada S, Yamada T. A case of Takotsubo cardiomyopathy complicated by ventricular septal perforation. *Circ J*. 2008;72:1540–1543.

49. Brunetti ND, Santoor F, Gennaro LD, et al. Therapy of stress cardiomyopathy: present shortcoming and future perspectives. *Future Cardiology*. 2016;12 (5):563–572.
50. Kurisu S, Kihara Y. Clinical management of Takotsubo cardiomyopathy. *Circ J*. 2014;78(7) 1559-1566.28.
51. Singh K, Akashi YJ, Horowtis JD. Takotsubo syndrome therapy—status and future directions (review). *International Cardiovascular Forum Journal*. 2016;5:23–29.
52. Santoro F, Leva R, Ferraretti A, et al. Safety and feasibility of levosimedan administration in Takotsubo cardiomyopathy—a case series. *Cardiovascular Therapeutics*. 2013;13:E133–E137.
53. Hering D, Jaguszew Ski M. Levosimendan: new hope therapy for Takotsubo syndrome. *Cardiology Journal*. 2016;23(6):616–617.
54. Santoro F, Leva R, Spennati G, et al. Takotsubo cardiomyopathy and spontaneous cardioversion of permanent atrial fibrillation associated with acute hyperkalemia. *Int J Cardiol*. 2013;167:e67–70.
55. 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. *Int J Cardiol*. 2014;174:696–70110.1016/j.ijcard.2014.04.221.
56. Kato K, Kitahara H, Kobayashi Y. Recurrence of takotsubo cardiomyopathy. *International Cardiovascular Form Journal*. 2016;5:50–52.
57. Sager HB, Schunkert H, Kurowski V. Recurrent mid-ventricular Takotsubo cardiomyopathy: three episodes of a uniform cardiac response to varying stressors. *Int J Cardiol*. 2011;152:e22–410.1016/j.icard.2010.09.081.
58. Santoro F, Leva R, Muscaico F, et al. Lack of efficacy of drug therapy in preventing Takotsubo cardiomyopathy recurrence: a meta-analysis. *Clin Cardiol*. 2014;37(7):434–439.
59. Brunetti ND, Santoro F, Gennaro LD, Correale M, Ganglione A, Biase MD. Drug treatment rates with beta-blockers and ACE-inhibitors/angiotensin receptor blockers and recurrences in takotsubo cardiomyopathy: a meta-regression analysis. *Int J Cardiol*. 2016;214:340–342.