REVIEW

Takotsubo syndrome: „between the devil and the deep blue sea"

Serban Balanescu[1]

Abstract: Takotsubo phenotype is defined as an acute, reversible heart failure syndrome precipitated by an acute stressful event occurring mainly in old post-menopausal women. Typical clinical presentation is a form of acute coronary syndrome with apical ballooning. Currently the condition is considered as a syndrome with multiple causes, all associated with acute stress and excess catecholamine release from the pituitary-adrenal axis. Generalized use of coronary angiography lead to increased recognition of this syndrome, as far as a majority of patients has normal epicardial arteries or minor coronary atherosclerosis. Recent data sustain inclusion of Takotsubo syndrome with acute coronary syndromes in between ST-elevation and non ST-elevation ACS.

Although initially regarded as a reversible cause of myocardial dysfunction with complete recovery and good outcome, recently multiple follow-up studies demonstrated that prognosis in Takotsubo syndrome is similar to that of acute coronary syndromes. As far as Takotsubo may arise from extremely different clinical conditions, a recent position paper proposed a sub classification of this condition depending on the offending event. This is sustained by different outcome of Takotsubo related to etiology.

The current paper reviews recent data about causes, mechanisms, outcome and classification of Takotsubo syndrome.

Keywords: Takotsubo syndrome, acute coronary syndrome, catecholamine excess, neuro-endocrine imbalance.

Rezumat: Sindromul Takotsubo reprezintă o formă de insuficiență cardiacă acută reversibilă precipitată de un eveniment stresant acut ce apare mai ales (dar nu numai) la femei vârstnice după menopauză. Forma clinică de prezentare este ca sindrom coronarian acut cu balonizare apicală. În prezent suferința este considerată drept un sindrom cu cauze multiple asociate cu stres acut și eliberare excesivă de catecolamine pe calea hipotalamo-hipofizo-suprarenală. Utilizarea frecventă a coronarografiei diagnostice a dus la creșterea recunoașterii acestui sindrom, deoarece majoritatea pacienților are coronare epicardice normale sau cu ateroscleroză nesemnificativă. Date recente susțin clasificarea sindromului Takotsubo drept un sindrom coronarian acut între cele cu supradenivelare și cu subdenivelare de segment ST.

Deși inițial a fost considerat ca o formă reversibilă de disfuncție miocardică cu recuperare completă și prognostic bun, studiile multiple de urmărire pe termen lung au demonstrat că prognosticul în sindrom Takotsubo este similar cu cel al sindroamelor coronariene acute. Deoarece Takotsubo poate apărea după cauze precipitante foarte diferite, recent a fost propusă o subclasificare în funcție de etiologie, susținută de prognosticul diferit dependent de evenimentul inițial.

Prezentul editorial trece în revistă datele actuale privitoare la cauză, mecanisme, prognostic și clasificarea sindromului Takotsubo.

Cuvinte cheie: sindromul Takotsubo, sindromul coronarian acut, eliberare excesivă de catecolamine, dezechilibru neuro-endocrin.

INTRODUCTION AND DEFINITION: A NECESSARY REAPPRAISAL

Ever since its first description by Sato et al in the early '90s in a Japanese conational[1], Takotsubo syndrome (TS) was viewed as a puzzling Cardiology dilemma despite extensive basic and clinical research[2]. The idiom "between the devil and the deep blue sea", used to express how difficult it is to choose between two undesirable situations reflects the enigmatic appearance and vanishing of this disease. Due to its striking wall motion dyssynergy, mimicking a severe acute coronary syndrome and surprisingly normal angiographic

[1] Department of Cardiology, Elias Emergency University Hospital, „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Contact address:
Serban Balanescu MD, PhD
Department of Cardiology, Elias Emergency University Hospital,
17 Marasti Boulevard, Bucharest, Romania.
E-mail: smbala99@hotmail.com

coronary appearance the disease was named initially "tako-tsubo-like left ventricular dysfunction" by the Japanese group who first identified it[1,3].

The disease occurs mainly in post-menopausal women, aged more than 55 years in their sixth to seventh decade, precipitated mainly by acute negative or positive mental or physical stress. The typical clinical presentation is that of suspected acute coronary syndrome with either ST-elevation or ST-depression associated with acute systolic left ventricular dysfunction[4]. While both ST segment changes and wall motion abnormalities may be striking on admission, they are generally transient and resolve in 6 weeks; they may variably persist up-to 3-to-6 months from the index event[5].

TS differs significantly from acute myocardial infarction, because not only is there no coronary artery stenosis, but segmental dyskinesia extends beyond the distribution territory of a single coronary artery[6]. The presentation mimicking an acute MI with normal epicardial coronary arteries raised the suspicion of an acute form of cardiomyopathy, vigorously denied by some researchers[7]. Up-to-date Takotsubo pathophysiology hypotheses suggest the disease may be viewed as a mix between and abnormal sympathetic cardiomyocyte response and microvascular dysfunction[6].

Mental or physical stress may be recognized as a precipitating factor in more than 80% of Takotsubo patients[8]. The disease was called „stress cardiomyopathy", „broken heart syndrome", „happy heart syndrome" and „voodoo heart" to emphasize the importance of psychological or psychiatric factors in the pathophysiology of this clinical syndrome.

Currently Takotsubo is considered a syndrome that may be induced by a large variety of precipitating factors that have in common sympathetic overstimulation of the myocardium and catecholamine-induced myocardial stunning, myocardial injury and reversible myocardial dysfunction[5,6].

EPIDEMIOLOGY

Today TS occurs in about 2% of patients with an initial diagnosis of ACS, but can reach 5.9-7.5% of ACS in women[9].

There is a major increase in the reported incidence of TS in the last 5-10 years. Data reported from different world regions and health systems demonstrate more and more cases of TS. In the SCAAR Registry of all-comers with an acute coronary syndrome with or without an acute heart failure syndrome TS incidence increased more than 10 times, from 0.16% in 2005 to 2.2% in 2012[10]. In the USA between 2007 and 2012 from a total of 53.947 patients with a Takotsubo discharge diagnosis the prevalence increased from 52 in 2007 to 178 per million discharges in 2012[11].

The increased prevalence may be due to a real increase in cases due to progressively higher psychosocial stress of modern life or to increased awareness and

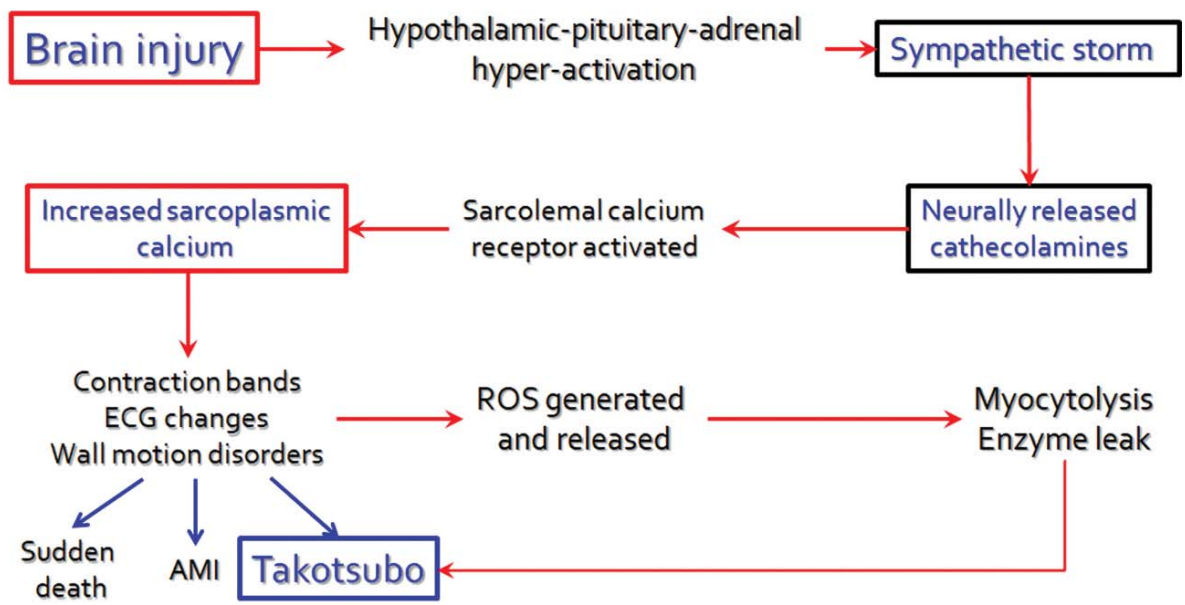

Figure 1. The proposed mechanism of adrenergic-mediated myocardial injury in TS due to central activation of the sympathetic system.

widespread use of coronary angiography in suspected acute coronary syndromes[10]. The constant increase of cases allowed better description of causes, pathophysiological correlates and to establish treatment effect and clinical outcomes[12].

ETIOLOGY

The InterTAK Registry is an international database consisting of a consortium of 26 worldwide centers initiated in Zurich that currently follows-up more than 2000 TS patients all-over the world[4]. Most of the data regarding TS are obtained from this registry[13,14].

The recently published International Expert Consensus on TS enlists the extremely numerous and varied physical and emotional triggers of the disease (Table 1)[6]. As recognized from the initial cases, psychiatric disease has major impact on triggering TS. Mood disorders were diagnosed in 39% of TS cases, anxiety disorders in 27%, while major personality disorders such as schizophrenia occurs in a minority of 1% of Takotsubo patients[15]. Anxiety, negative affectivity and obsessive-compulsive personality are more frequently observed, while isolated depression or neuroticism is seldom found[16]. Resting state functional brain MRI in TS patients demonstrated specific areas with increased connectivity located in the precuneus region as opposed to healthy controls[16]. Other functional MRI studies demonstrated activation of the hippocampus, the brainstem, basal ganglia and prefrontal cortex in acute TS patients that subsided at 30-day follow-up[17]. All these brain regions are involved in stimulation of the locus coeruleus as the main structure responsible for sympathetic hyper activation.

Another frequently observed patient subset presenting with TS are individuals with acute neurological disease. „Neurogenic myocardial injury" associated with myocardial stunning is a condition determined by neurologic events of different significance[18]. In a national US registry of hospitalized patients admitted between 2006 and 2014 comprising 9.146.013 cases with neurologic disease, 5832 patients were discharged with a TS diagnosis[19]. Any acute neurological condition on admission had an OR of developing TS of 1.54 (95% CI: 1.48 to 1.62); the highest risk of developing TS was found in status epilepticus (OR=4.9; 95% CI:3.7-6.3) and subarachnoid hemorrhage (OR=11.7; CI 95%: 10.2-13.4)[19]. However all other acute neurologic disease presented an increased risk for developing TS, starting with ischemic stroke, intracerebral hemorrhage, migraine or meningoencephalitis.

Table 1. Clinical conditions that may trigger the occurrence of TS 6

Neuro-psychiatric triggers		Somatic triggers	
Mood disorders	Depression	Neurologic diseases	Intracranial haemorrhage
	Suicide attempt		Ischemic stroke, TIA
	Divorce		Epilepsy
	Illness of a close relative		Migraine
	Death of spouse		Concussion
	Death of a close family member	Respiratory diseases	Asthma attack
	Death of pet		COPD, bronchitis
Anxiety disorders	Fear of surgery		Pneumonia
	Post-traumatic stress disorder		Pulmonary embolism
	Fear of public speaking	Gastro-intestinal diseases	GI bleeding
	Fear		Inflammatory bowel disease
	Aircraft noise, flights		Incarcerated hernia
	Car accident, no injury	Ob-Gyn	Excessive vaginal bleeds
Psychosocial stress	Job loss		Giving birth
	Debt, bankruptcy	Oncological disease	Active cancer
	Change of domicile, city		Cancer treatment (i.e. checkpoint inh)
	Robbery	Infection and sepsis	Urosepsis
	Loss of money		Peritonitis
	Retirement		Wound infection
	Flooding, earthquake		Influenza
	Hurricanes, tornadoes	Orthopedic conditions	Polytrauma
	Argument with family member		Fractures
Happy heart syndrome	Wedding	Other	Major surgery
	Winning the lottery		General anesthesia
	Positive job interview		Administration of beta-adrenergic drugs
	Birth of child		

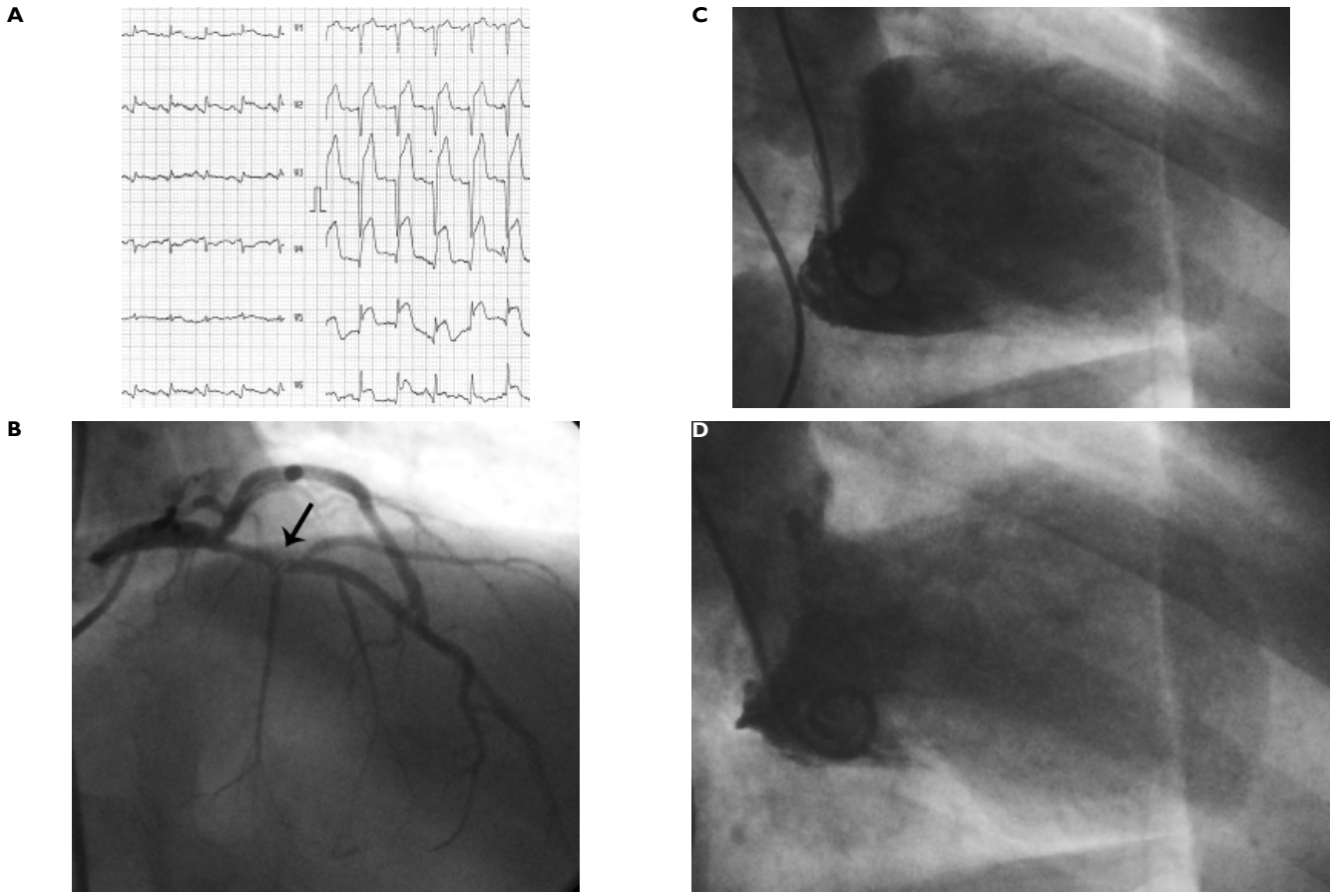

Figure 2. A Takotsubo patient with noncritical coronary artery disease. The 58 year-old patient was admitted because of acute STEMI with significant ST elevation in V2-V6 and infero-lateral leads (**Figure 2A**). Coronary angiography showed a moderate proximal LAD stenosis involving the first major septal branch (black arrow in **Figure 2B**). LV angiogram (in diastole (**Figure 2C**) and in systole (**Figure 2D**) showed a large apical ballooning syndrome involving the inferior wall of LV and hyperkinetic basal segments.

Recently TS was recognized even in patients with coronary artery disease (CAD) (Figure 2). As far as TS is associated with any cause of acute psychic or somatic stress and acute myocardial infarction is a major stress factor associated with increased serum catecolamines, TS and CAD may occur together in the same patient. TS may be diagnosed in a CAD patient if the severely diseased coronary artery responsible for an ACS is distributed to a totally different myocardial territory than the one showing the wall motion anomalies[20]. Some cases are reported with STEMI due to occlusion of a diagonal vessel and a widely patent LAD, with severe apical ballooning and hyperkinetic basal segments[21].

Another supporting argument for the association between TS and CAD is the patient population that can typically develop TS: old post-menopausal women (Figure 3). Advanced age and associated risk factors for CAD may explain concomitant occurrence of TS and coronary atherosclerosis. In an intracoronary imaging study in 23 patients with TS that were investigated by optical coherence tomography (OCT) in the left main and LAD during an ACS, 69.6% of subjects presented atherosclerotic plaques while 26.1% had thin-cap fibroatheromas[22]. No thrombus or properly ulcerated coronary plaques were found by OCT, emphasizing that CAD is an incidental finding in TS.

Various other clinical situations were described in association with TS such as accidental administration of large subcutaneous adrenaline injection[23] or after treatment with check-point inhibitors for different neoplasia[24].

PATHOPHYSIOLOGY

There are four main hypotheses that try to explain the occurrence of TS[25,26]:

- Myocardial impairment due to excessive local catecholamine availability by abnormal epinephrine/norepinephrine release via both hypothalamic-pituitary-adrenal axis and local release from

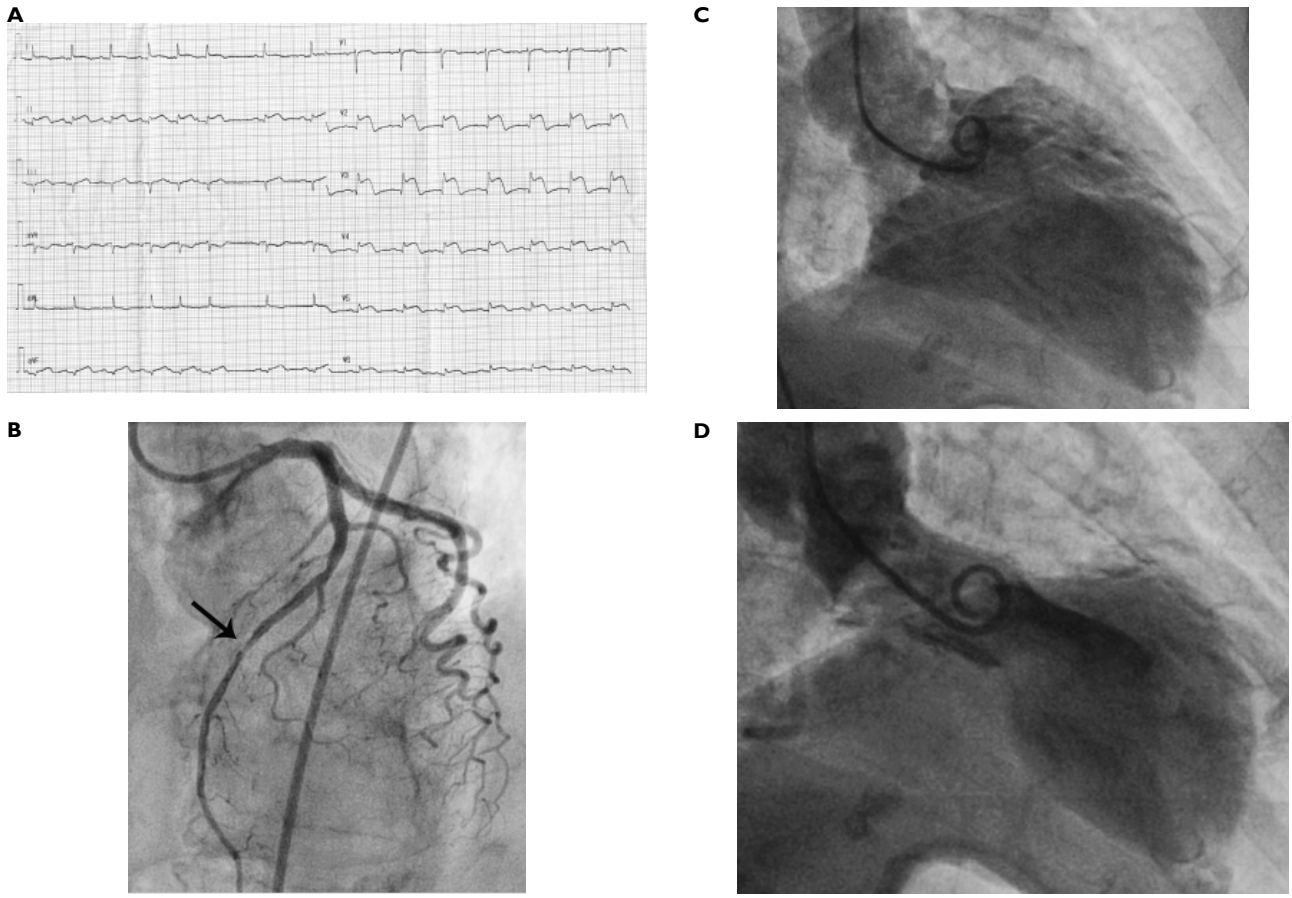

Figure 3. A 67 year-old depressive woman with an acute stressful event presents with chest pain, signs and symptoms of LV failure and ST-elevation in the first 4h from symptom onset (**Figure 3A**). Coronary angiography demonstrates a moderate mid-LAD stenosis (black arrow in **Figure 3A**). Takotsubo syndrome is diagnosed after LV angiogram shows typical apical LV ballooning (**Figures 3C** and **3D**). Coexisting Takotsubo and non-significant obstructive CAD may be identified in old patients with CV risk factors.

sympathetic nerve endings. Patients with TS have a 2-to-3 fold increase of serum cathecolamines versus patients with STEMI[27,28]. The catecholamine excess mediates myocardial injury by direct toxicity, epicardial and microcirculatory vasoconstriction and increased cardiac afterload[2].

- Beta-2 adrenoceptor / Gi-dependent cardio depression. Activation of the beta-2 receptor by epinephrine. Activation of inhibitory G protein. Apical dysfunction due to apex-to-base gradient of beta-2 receptors.
- Focal perfusion defects and microvascular obstruction or coronary spasm. TS was recently included with the acute coronary syndromes due to microvascular dysfunction[29]. Presenting with either ST elevation or depression, positive biomarkers for myocardial injury (higher NT-pro-BNP and lower troponin than in ACS) and typically normal angiographic appearance of coronary arteries, TS is currently considered in the spectrum of ACS together with STEMI, Prinzmetal angina and NSTEMI[29].
- Acute, focal metabolic down-regulation in response to demand / supply mismatches similar to ischemic stunning. Form of protective reaction against malignant arrhythmias and/or necrosis.

The typical neurogenic-mediated myocardial injury is observed in acute stroke. The insular cortex anatomically located in the Sylvian sulcus is responsible for complex functional integrates, both motor and sensory in correlation with the limbic system[18]. It controls autonomic nervous system maintaining the balance between sympathetic and vagal systems[30]. Ischemic lesions of the insula were proven to increase serum catecholamine levels and induce myocardial dysfunction[31]. Interestingly stimulation of the right insula leads to sympathetic hyperactivity, while stimulation of the left insula leads to parasympathetic dominance[32]. Insular cortex is usually involved with the parietal lobe in stroke due to middle cerebral artery occlusion[33].

The main site of noradrenergic production in the brain is the locus coeruleus that concentrate all stimuli from hypothalamus, amygdala and the neocortex, including the insula and the frontal cortex, triggering the systemic sympathetic response[34]. Norepinephrine production in the locus coeruleus activates the hypothalamic-pituitary-adrenal axis[8].

Myocardial cathecolamines are a combination between locally released norepinephrine from the sympathetic nerve endings and the serum epinephrine – norepinephrine released by the adrenal medulla[35]. In normal conditions cathecolamines stimulate beta-1 adrenergic receptors and increase intracellular cAMP intermediated by a second-messenger mechanism through the Gs protein family. Catecholamine excess may switch cellular adrenergic effects from beta-1 receptor stimulation to beta-2 receptor activation coupled with an inhibitory second-messenger Gi protein[36]. Beta-2 receptors are distributed mainly toward the apex: the apico-basal gradient of these receptors is considered responsible for the apical ballooning syndrome, but it does not explain the other middle-segment or basal forms of TS[37]. Calcium sarcoplasmic overload induced by beta-adrenoceptor stimulation results in contractile dysfunction by ATP depletion[38]. Direct negative effects of cathecolamines on the cardiomyocytes are completed by adrenergic-mediated activation of inflammation and oxidative stress[39] (Figure 1).

Neurogenic myocardial injury induces different effects on cardiomyocytes than myocardial ischemia and necrosis. Neurogenic injury produces myofibrillar degeneration and myocytolysis distributed surrounding the epicardial nerve fibers, while myocardial necrosis occurs mainly in the subendocardial layers and respects distribution of a coronary artery[40].

It has been postulated that apical ballooning and catecholamine activation of beta-2 receptors and the increased activity of inhibitory G protein may represent a mechanism for cardiomyocyte protection to limit myocardial damage of sudden marked increase in epinephrine[41]. Myocardial dysfunction occurs in the apical region where there is the largest concentration of epinephrine sensitive beta-2 receptors, while the basal regions displaying the largest concentration of beta-1, norepinephrine sensitive receptors remain unaffected[42]. These findings suggest that TS phenotype may be epinephrine specific[43].

Microvascular catecholamine-mediated vasospasm may contribute to pathophysiology of TS[39]. Observed perfusion defects in the acute setting are completely reversible by adenosine injection and at follow-up study[44].

Thus myocardial stunning and systolic dysfunction in TS may represent a protective mechanism against a metabolism/flow mismatch: increased catecholamine normally lead to increased metabolic demands, while microvascular dysfunction reduces supply of oxygen, glucose and free fatty acids. Myocardial stunning would protect cells from self-destruction and would allow complete subsequent recovery when catecholamine levels return to normal.

CLINICAL PRESENTATION

Patients with TS present usually with symptoms, signs and ECG patterns of an ACS[45]. These may occur in a patient with an acute neurological event. Sometimes the neurological event is diagnosed after angiography shows no coronary artery stenosis in a comma patient with cardiac arrest, making differential diagnosis difficult between the causative factors: neurologic disease associated with TS or cardiac arrest with hypoxic neurologic damage. However, prolonged chest pain and dyspnea are the most common symptomatic patterns of TS onset, followed by acute LV failure and pulmonary edema. Syncope, cardiac arrest or cardiogenic shock are also encountered in TS, although not frequently.

When compared with age- and sex-matched patients with acute coronary syndromes (ACS), TS patients have less chest pain, more severe systolic LV dysfunction and significantly less obstructive coronary artery disease 4. There is no difference in the prevalence of cardiogenic shock (10-12% of patients) or 30-days mortality (4-5%) between TS and ACS counterparts[4]. Neurologic (either acute or chronic) or psychiatric disorders are strikingly more encountered in TS patients. Acute neurologic disease is found 9 times more frequently and psychiatric disorders are found three times more in TS patients.

Major complications of TS replicate all common complications of ACS[9]. Mechanical complications extend from overt LV failure and pulmonary edema (12-45% of cases), acute mitral regurgitation (14-25%) or cardiogenic shock (6-20%) to free wall or interventricular septum rupture (less than 1%)[5]. A particular complication of TS is acute LVOT obstruction as far as antero-basal segments are hyperkinetic and the dyskinetic apex pulls the anterior mitral leaflet towards the septum in the LVOT[46]. Apical thrombus formation and

systemic embolization were described in 2-8% of cases. QT prolongation, brady and tachyarrhythmia with sudden cardiac death were also mentioned in 2-5% of patients. Paroxysmal atrial fibrillation occurs in 5 to 15% of TS cases[5].

A plethora of clinical, echocardiographic and serum biological markers were identified to correlate with high risk in TS patients on admission (Table 2)[26].

ECHOCARDIOGRAPHY AND ANGIOGRAPHY FINDINGS

Starting from the initial description of TS as an "apical ballooning syndrome"[47], four different patterns of segmental wall motion anomalies are accepted today as parts of the spectrum of the disease[4,14].

1. The apical, typical pattern with apical ballooning, mimicking antero-apical LV aneurysm is the most frequently encountered in 81.7% of cases.
2. The mid-ventricular pattern is associated with hyperkinetic apical and basal segments while middle segments of the anterior and inferior wall are dyskinetic. This pattern is observed in 14.6% of cases.
3. The basal type is characterized by apical hyperkinesia while the basal segments are dyskinetic. It is found in 2.2% of cases.
4. The focal type is associated with focal dyskinesia of any myocardial segment, i.e. the mid segment of the anterior wall, while all other segments are contracting normally. It is the most seldom found, in 1.5% of cases.

Occasionally a Takotsubo-like wall motion dyskinesia with cardiogenic shock, fully reversible, was described to involve the free wall of the right ventricle without any signs of acute pulmonary hypertension or embolism[48], but this TS presentation was not included with the typical cases yet.

Apparently, the type of acute stressor event may produce different patterns or phenotypes of TS. Negative stressors induce more frequently apical ballooning in the "broken heart syndrome", while positive stressors or "happy heart" may be associated with mid-ventricular TS[49].

Sometimes it is very difficult to differentiate in clinical practice between ACS, myocarditis and TS, mainly when coronary angiography identifies no significant obstructive coronary artery disease. Contrast magnetic resonance imaging should be used to clarify this issue, as apparently there are specific patterns in each and every of these conditions[50].

DIAGNOSIS AND DIFFERENTIATION FROM ACS

Issued in 2008 the modified Mayo diagnostic criteria were used to differentiate TS from other acute heart failure syndromes[47]. The following diagnostic criteria were considered:

- Transient hypokinesis, akinesia or dyskinesia of mid-LV segments with or without apical involvement. Wall segment anomalies extend beyond myocardial distribution of a single coronary vessel. Previous stress factors are frequently found.
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
- New ECG changes (either ST-elevation and/or T-wave inversion) or modest elevation in cardiac troponin.

Table 2. Risk stratification of TS patients according to Heart Failure Association of the ESC (26). (BP – blood pressure; VT-VF – ventricular tachycardia or fibrillation; LVEF – left ventricular ejection fraction; LVOT – left ventricular outflow tract; VSD – ventricular septal defect.)

Risk factor	Higher risk	Lower risk
Age	> 75 years	< 75 years
Systolic BP	<110 mmHg	> 110 mmHg
Pulmonary oedema	Present	Absent
Syncope, VT or VF	Present	Absent
LVEF	< 35%	> 45%
LVOT obstruction	> 40 mmHg	Absent or < 40 mmHg
Mitral regurgitation	Present	Absent
Apical thrombus	Present	Absent
New VSD or contained wall rupture	Present	Absent
QTc	> 500 msec	< 500 msec
ST elevation and pathological Q wave	Present	Absent
BNP	> 600 pg/ml	<600 pg/ml
Bystander obstructive CAD	Present	Absent

- Absence of pheochromocytoma or myocarditis.

The Mayo criteria were reviewed and modified by the *Heart Failure Association* of the ESC in 2016 who added recovery of ventricular function on cardiac imaging at 3-6 months follow-up as a supplemental criterion[26]. The data obtained from the InterTAK registry lead to the recently published International Takotsubo Diagnostic Criteria issued by the ESC in 2018[6].

Because TS has a significant presentation overlap with acute coronary syndromes and acute heart failure, accurate diagnosis is mandatory in order to prescribe appropriate investigations and treatment. Data from the InterTAK Registry allowed development of a clinical score ("InterTAK diagnostic score") that should ease differentiation between TS and acute coronary syndromes[51] (Table 3). There are 7 major criteria included, female sex and emotional trigger being the most significant. When a cut-off value of 70 points is considered, there is a high probability (more than 90%) of TS over 70 points and a low-intermediate probability of TS with a score of less than 70 points[5].

When compared with ACS, TS patients have lower troponin and higher BNP serum levels; the extent of ventricular motion anomalies greatly exceeds necrosis biomarker increase, reflecting the stunned, recoverable myocardium[5].

Some research teams demonstrated that circulating micro-RNAs (19-25 nucleotides) that are non-coding transcriptional regulators of complex cellular functions (such as apoptosis, proliferation or differentiation) could be used to distinguish between TS and acute MI[52]. Eight micro-RNAs were selected for verification by real-time quantitative reverse transcription PCR. In this trial patients with TS had a significant up-regulation of miR-16, miR-26a and let-7F, while patients with STEMI had miR-1 and miR-133a up regulated with respect to TS. Interestingly the identified micro-RNAs are up regulated by stress and depression confirming the close relationship between TS and neuropsychiatric disease.

Consequently establishing the diagnosis of TS evolved from excluding major coronary disease or myocarditis to specific criteria[53].

TREATMENT OF TS

There are no prospective randomized trials in TS patients. Thus all recommendations are based on clinical experience and have a class C (expert consensus) level of evidence. Current data based on retrospective studies, meta-analysis and small case series were gathered in a recently published International Expert Consensus Document[5].

There is general consensus to admit all patients with TS in the Coronary Care Unit where prompt full clinical, ECG, echocardiographic, angiographic and serum biomarkers should allow classification of risk (Table 2)[26].

Lower risk patients with LVEF higher than 45% need no specific treatment and should be closely followed-up until recovery. Low-risk patients with LVEF between 35-45% should be treated with progressively increasing doses of beta-blockers and ACE-inhibitors. Early discharge strategy may be considered in these low-risk category patients. Complex cardiac imaging by echocardiography and cardiac MRI should be performed at follow-up to confirm myocardial recovery and exclude myocardial infarction or myocarditis[26].

High-risk patients should be kept in CCU for at least 72h. Beta-blockers should be carefully initiated although LVEF may be lower than 45%; patients with ventricular tachycardia or fibrillation and those with paroxysmal atrial fibrillation also benefit from beta-blockers. LVOT obstruction with a maximum gradient more than 40 mmHg is another indication for beta-blockers. ACE-inhibitors should be given in all patients with LVEF lower than 45%. Apical thrombus needs

Table 3. The InterTAK diagnostic score components, their relative value and respective odds ratio as resulted from multiple logistic regression analysis in TS patients (n=218) vs acute coronary syndrome patients (n=436) 51

Criterion	Points	OR (95% CI)
Female sex	25	68 (29.0-163.7)
Emotional trigger	24	65 (20.3 – 205.8)
Physical trigger	13	8.7 (4.6-17.3)
Absence of ST-segment depression	12	7.2 (3.1-16.8)
Psychiatric disorder	11	7.0 (3.1-15.5)
Neurologic disorder	9	4.9 (2.2-11.3)
QTc prolongation	6	2.8 (1.3-5.7)
TOTAL	100	--

low-molecular weight heparin (LMWH) acutely and subsequent oral anticoagulation for at least 3 months. High-risk patients should be treated however with a LMWH for 7 days, even when no intraventricular thrombosis can be found. Acute pulmonary edema should be treated with standard doses of IV loop diuretics and nitroglycerine.

Cardiogenic shock is the most difficult clinical presentation with TS as systemic cathecolamines are spontaneously high, are implicated in the pathogenesis of the disease and may worsen myocardial dysfunction when administered as therapeutic measure to increase LV systolic function. TS patients treated with cathecolamines have a 20% mortality rate[4]. An ECMO machine and/or LVAD or Impella device may be necessary to properly support heart function and systemic oxygenation until LV function recovers. Levosimendan as a calcium-sensitizer, non-beta-receptor-dependent positive inotropic drug may be empirically used to increase LV systolic function[54]. Shock TS patients with LVOT obstruction cannot be treated with beta-blockers and may benefit from ivabradine as bradycardia-inducing drug in sinus rhythm[55].

Long-term treatment comprises ACE-inhibitors or sartans, while no benefit of chronic beta-blocker use could be demonstrated even on the recurrence of TS[4,56]. If CAD is present at angiography, but it cannot be held responsible for clinical presentation while the patient is diagnosed with TS, appropriate doses of a statin and aspirin should be started and continued indefinitely.

There are no data regarding the effect of treating anxiety, mood disorders or any associated psychiatric disease on the occurrence of TS, which is another topic for controversy.

OUTCOME

TS is far from being a benign condition, despite the fact it is regarded as an acute reversible heart failure syndrome. Initial reports considered the disease as benign, based on the rapid recovery of left ventricular function when compared with ACS[57].

Cardiogenic shock occurs in TS with the same prevalence as in atherothrombotic ACS[4]. Cardiogenic shock in TS was observed at admission in 11.4% of 711 patients enrolled in the RETAKO Registry[58]. In-hospital mortality of TS is 4-5% similar with that of STEMI reperfused by primary PCI[59,60]. 30-day mortality is 5.9% and the long-term mortality rate is 5.6%/patient/year[4].

Long-term outcome of TS patients is similar to those with CAD and worse than matched control subjects as demonstrated in a group of 505 patients from the SCAAR Registry[60]. TS patients have a 2.1 times higher risk for mortality at 5 years when compared to control subjects without CAD, despite having low cardiovascular risk profile.

Despite prompt (sometimes spontaneous) recovery of left ventricular function long-term outcome in TS may not be as benign as previously thought. In a trial on 37 patients with previous TS more than 1 year from acute presentation they had impaired cardiac deformation indices and lower cardiac energetic markers[61]. Thus it is currently considered that TS patients may develop a persistent subclinical heart failure phenotype.

Recently data from the InterTAK Registry showed that the long-term outcome of TS depends on the initial trigger[12]. Patients with a pure emotional trigger and no other major comorbidity have the best 5-year outcome, while TS patients due to neurologic disorders have the highest 5-year mortality that may reach 20%[12]. Based on this difference in outcome depending on the triggering factor, the InterTAK Registry investigators recently proposed a new classification of TS. Class I is considered TS due to emotional triggers. Class II consists of TS patients due to physical stress; class IIa is due to medical conditions or interventions and intense physical activities; class IIb is due to neurologic disease and has the worst outcome. Class III is TS without any identifiable cause. Time will tell if this classification confirms its usefulness in TS patients.

Data obtained from 371 patients with TS enrolled in an Italian registry and followed-up for a mean of 26+/-20 months demonstrated that CHA_2DS_2-VASc score could be used to predict death, MI or stroke in a similar way with cardioembolic risk prediction in patients with atrial fibrillation[62]. The patients were divided in three groups with respect to the calculated CHA_2DS_2-VASc score on enrollment: 0-1, 2-3 and higher than 4. Patients with CHA2DS2-VASc score ≥4 had a MACCE prevalence of 17% while those with a CHA_2DS_2-VASc score £ 1 had a MACCE prevalence of 6% (p=0.033).

The recurrence rate of TS is a topic of controversy; it is considered TS may recur in up-to 22% of all TS patients[45]. The triggering factor and TS phenotype may be different from the those seen with the first TS occurrence[63].

CONCLUSION

Takostubo syndrome is an acute reversible heart failure syndrome with various segmental wall motion anomalies, mostly with apical ballooning according to the originally described, typical pattern. Some form of acute stress is always elicited in personal history and there is a complex interaction with neuro-psychiatric disorders and increased plasma cathecolamines.

TS may be associated with coronary disease commonly non obstructive and stable. In some cases Takotsubo may occur associated with an acute coronary syndrome (as a major stressful event), with wall motion anomalies extending beyond coronary distribution of the responsible artery.

Although generally reversible between 2 to 6 months after the index event, TS has the same complex prognosis and complications as all other acute coronary syndromes. The worst recognized outcome occurs when TS is associated with any acute neurologic disease. Risk stratification should identify higher risk patients (i.e. cardiogenic shock or severe acute left ventricular failure), needing intensive treatment and supervision. Standard treatment of acute heart failure is recommended, while avoiding beta-mimetic drugs in this condition associated anyway with serum catecholamine excess.

Financial support: none declared.
Conflicts of interest: none declared.

References

1. 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;21:203-14.
2. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo Syndrome. Circulation 2017;135:2426-2441.
3. Kurisu S, Sato H, Kawagoe T et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. Am Heart J 2002;143:448-55.
4. Templin C, Ghadri JR, Diekmann J et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. N Engl J Med 2015;373:929-38.
5. Ghadri JR, Wittstein IS, Prasad A et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. Eur Heart J 2018;39:2047-2062.
6. Ghadri JR, Wittstein IS, Prasad A et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. Eur Heart J 2018;39:2032-2046.
7. Pelliccia F, Sinagra G, Elliott P, Parodi G, Basso C, Camici PG. Takotsubo is not a cardiomyopathy. Int J Cardiol 2018;254:250-253.
8. Ranieri M, Finsterer J, Bedini G, Parati EA, Bersano A. Takotsubo Syndrome: Clinical Features, Pathogenesis, Treatment, and Relationship with Cerebrovascular Diseases. Curr Neurol Neurosci Rep 2018;18:20.
9. Schlossbauer SA, Ghadri JR, Scherff F, Templin C. The challenge of Takotsubo syndrome: heterogeneity of clinical features. Swiss Med Wkly 2017;147:w14490.
10. Redfors B, Vedad R, Angeras O et al. Mortality in takotsubo syndrome is similar to mortality in myocardial infarction - A report from the SWEDEHEART registry. Int J Cardiol 2015;185:282-9.
11. Khera R, Light-McGroary K, Zahr F, Horwitz PA, Girotra S. Trends in hospitalization for takotsubo cardiomyopathy in the United States. Am Heart J 2016;172:53-63.
12. Ghadri JR, Kato K, Cammann VL et al. Long-Term Prognosis of Patients With Takotsubo Syndrome. J Am Coll Cardiol 2018;72:874-882.
13. Ghadri JR, Templin C. The InterTAK Registry for Takotsubo Syndrome. Eur Heart J 2016;37:2806-2808.
14. Ghadri JR, Cammann VL, Napp LC et al. Differences in the Clinical Profile and Outcomes of Typical and Atypical Takotsubo Syndrome: Data From the International Takotsubo Registry. JAMA Cardiol 2016;1:335-40.
15. Nayeri A, Rafla-Yuan E, Farber-Eger E et al. Pre-existing Psychiatric Illness is Associated With Increased Risk of Recurrent Takotsubo Cardiomyopathy. Psychosomatics 2017;58:527-532.
16. Sabisz A, Treder N, Fijalkowska M et al. Brain resting state functional magnetic resonance imaging in patients with takotsubo cardiomyopathy an inseparable pair of brain and heart. Int J Cardiol 2016;224:376-381.
17. Suzuki H, Matsumoto Y, Kaneta T et al. Evidence for brain activation in patients with takotsubo cardiomyopathy. Circ J 2014;78:256-8.
18. Biso S, Wongrakpanich S, Agrawal A, Yadlapati S, Kishlyansky M, Figueredo V. A Review of Neurogenic Stunned Myocardium. Cardiovasc Psychiatry Neurol 2017:2017:5842182. doi: 10.1155/2017/5842182. Epub 2017 Aug 10.
19. Morris NA, Chatterjee A, Adejumo OL et al. The Risk of Takotsubo Cardiomyopathy in Acute Neurological Disease. Neurocrit Care 2018:doi:10.1007/s12028-018-0591-z.
20. Hurtado Rendon IS, Alcivar D, Rodriguez-Escudero JP, Silver K. Acute Myocardial Infarction and Stress Cardiomyopathy Are Not Mutually Exclusive. Am J Med 2018;131:202-205.
21. Redfors B, Ramunddal T, Shao Y, Omerovic E. Takotsubo triggered by acute myocardial infarction: a common but overlooked syndrome? J Geriatr Cardiol 2014;11:171-3.
22. Eitel I, Stiermaier T, Graf T et al. Optical Coherence Tomography to Evaluate Plaque Burden and Morphology in Patients With Takotsubo Syndrome. J Am Heart Assoc 2016;5.
23. Spina R, Song N, Kathir K, Muller DWM, Baron D. Takotsubo cardiomyopathy following unintentionally large subcutaneous adrenaline injection: a case report. Eur Heart J - Case Reports 2018;2:1-7.
24. Ederhy S, Cautela J, Ancedy Y, Escudier M, Thuny F, Cohen A. Takotsubo-Like Syndrome in Cancer Patients Treated With Immune Checkpoint Inhibitors. JACC Cardiovasc Imaging 2018;11:1187-1190.
25. Redfors B, Shao Y, Ali A, Omerovic E. Current hypotheses regarding the pathophysiology behind the takotsubo syndrome. Int J Cardiol 2014;177:771-9.
26. 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;18:8-27.
27. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Musha H, Sasaka K. 123I-MIBG myocardial scintigraphy in patients with «takotsubo» cardiomyopathy. J Nucl Med 2004;45:1121-7.
28. Wittstein IS, Thiemann DR, Lima JA et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005;352:539-48.
29. Luscher TF, Templin C. Is takotsubo syndrome a microvascular acute coronary syndrome? Towards of a new definition. Eur Heart J 2016;37:2816-2820.
30. Naidich TP, Kang E, Fatterpekar GM et al. The insula: anatomic study and MR imaging display at 1.5 T. AJNR Am J Neuroradiol 2004;25:222-32.
31. Zhang ZH, Rashba S, Oppenheimer SM. Insular cortex lesions alter baroreceptor sensitivity in the urethane-anesthetized rat. Brain Res 1998;813:73-81.

32. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology 1992;42:1727-32.
33. Rincon F, Dhamoon M, Moon Y et al. Stroke location and association with fatal cardiac outcomes: Northern Manhattan Study (NOMAS). Stroke 2008;39:2425-31.
34. Sved AF, Cano G, Passerin AM, Rabin BS. The locus coeruleus, Barrington's nucleus, and neural circuits of stress. Physiol Behav 2002;77:737-42.
35. Florea VG, Cohn JN. The autonomic nervous system and heart failure. Circ Res 2014;114:1815-26.
36. Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy--a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. Nat Clin Pract Cardiovasc Med 2008;5:22-9.
37. Eitel I, Lucke C, Grothoff M et al. Inflammation in takotsubo cardiomyopathy: insights from cardiovascular magnetic resonance imaging. Eur Radiol 2010;20:422-31.
38. Nguyen H, Zaroff JG. Neurogenic stunned myocardium. Curr Neurol Neurosci Rep 2009;9:486-91.
39. Galiuto L, De Caterina AR, Porfidia A et al. Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in Apical Ballooning or Tako-Tsubo Syndrome. Eur Heart J 2010;31:1319-27.
40. Chalela JA, Ezzeddine MA, Davis L, Warach S. Myocardial injury in acute stroke: a troponin I study. Neurocrit Care 2004;1:343-6.
41. Paur H, Wright PT, Sikkel MB et al. High levels of circulating epinephrine trigger apical cardiodepression in a beta2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy. Circulation 2012;126:697-706.
42. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. Circulation 2008;118:397-409.
43. Borchert T, Hubscher D, Guessoum CI et al. Catecholamine-Dependent beta-Adrenergic Signaling in a Pluripotent Stem Cell Model of Takotsubo Cardiomyopathy. J Am Coll Cardiol 2017;70:975-991.
44. Ito K, Sugihara H, Kinoshita N, Azuma A, Matsubara H. Assessment of Takotsubo cardiomyopathy (transient left ventricular apical ballooning) using 99mTc-tetrofosmin, 123I-BMIPP, 123I-MIBG and 99mTc-PYP myocardial SPECT. Ann Nucl Med 2005;19:435-45.
45. Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. Nat Rev Cardiol 2015;12:387-97.
46. De Backer O, Debonnaire P, Gevaert S, Missault L, Gheeraert P, Muyldermans L. Prevalence, associated factors and management implications of left ventricular outflow tract obstruction in takotsubo cardiomyopathy: a two-year, two-center experience. BMC Cardiovasc Disord 2014;14:147.
47. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 2008;155:408-17.
48. Sumida H, Morihisa K, Katahira K, Sugiyama S, Kishi T, Oshima S. Isolated Right Ventricular Stress (Takotsubo) Cardiomyopathy. Intern Med 2017;56:2159-2164.
49. 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.
50. Nakamori S, Matsuoka K, Onishi K et al. Prevalence and signal characteristics of late gadolinium enhancement on contrast-enhanced magnetic resonance imaging in patients with takotsubo cardiomyopathy. Circ J 2012;76:914-21.
51. Ghadri JR, Cammann VL, Jurisic S et al. A novel clinical score (InterTAK Diagnostic Score) to differentiate takotsubo syndrome from acute coronary syndrome: results from the International Takotsubo Registry. Eur J Heart Fail 2017;19:1036-1042.
52. Jaguszewski M, Osipova J, Ghadri JR et al. A signature of circulating microRNAs differentiates takotsubo cardiomyopathy from acute myocardial infarction. Eur Heart J 2014;35:999-1006.
53. Scantlebury DC, Prasad A. Diagnosis of Takotsubo cardiomyopathy. Circ J 2014;78:2129-39.
54. Santoro F, Ieva R, Ferraretti A et al. Safety and feasibility of levosimendan administration in takotsubo cardiomyopathy: a case series. Cardiovasc Ther 2013;31:e133-7.
55. Madias JE. If channel blocker ivabradine vs. beta-blockers for sinus tachycardia in patients with takotsubo syndrome. Int J Cardiol 2016;223:877-878.
56. 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;174:696-701.
57. Elesber A, Lerman A, Bybee KA et al. Myocardial perfusion in apical ballooning syndrome correlate of myocardial injury. Am Heart J 2006;152:469.e9-13.
58. Almendro-Delia M, Nunez-Gil IJ, Lobo M et al. Short- and Long-Term Prognostic Relevance of Cardiogenic Shock in Takotsubo Syndrome: Results From the RETAKO Registry. JACC Heart Fail 2018.
59. Singh K, Carson K, Shah R et al. Meta-analysis of clinical correlates of acute mortality in takotsubo cardiomyopathy. Am J Cardiol 2014;113:1420-8.
60. Tornvall P, Collste O, Ehrenborg E, Jarnbert-Petterson H. A Case-Control Study of Risk Markers and Mortality in Takotsubo Stress Cardiomyopathy. J Am Coll Cardiol 2016;67:1931-6.
61. Scally C, Rudd A, Mezincescu A et al. Persistent Long-Term Structural, Functional, and Metabolic Changes After Stress-Induced (Takotsubo) Cardiomyopathy. Circulation 2018;137:1039-1048.
62. Parodi G, Scudiero F, Citro R et al. Risk Stratification Using the CHA2DS2-VASc Score in Takotsubo Syndrome: Data From the Takotsubo Italian Network. J Am Heart Assoc 2017;6.
63. Ghadri JR, Jaguszewski M, Corti R, Luscher TF, Templin C. Different wall motion patterns of three consecutive episodes of takotsubo cardiomyopathy in the same patient. Int J Cardiol 2012;160:e25-7.