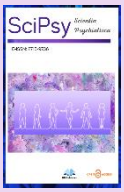

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Takotsubo Cardiomyopathy Related Emotional Stress

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A B S T R A C T

Takotsubo cardiomyopathy (TTC) or Takotsubo syndrome is a syndrome indicated by the presence of temporary left ventricle (LV) regional systolic dysfunction which mimics the symptoms of myocardial infarction. TTS patients have been reported to experience severe and sudden emotional or physical distress and the previous diagnosis of psychiatric disorders may be reported among some of the patients indicating the relationship between an emotional stressor and cardiac dysfunction. The sympathetic nervous system and catecholamines play an essential role to mediate the effect of emotional stressors on the heart. This article briefly discusses the relationship between the emotional stressor and cardiac dysfunction in TTC.

1. Introduction

Takotsubo cardiomyopathy (TTC) or Takotsubo syndrome is a syndrome indicated by the presence of temporary left ventricle (LV) regional systolic dysfunction which mimics the symptoms of myocardial infarction. However, further coronary angiography findings show no sign of coronary blood flow obstruction or acute plaque rupture[1]. The term "Takotsubo" is originated from a Japanese term referring to a container to catch octopus. The container is characterized by a circular bottom and narrow neck, featuring the hear's anatomic change during some extent of the disease[2]. Despite the existence of various subtypes, the classical arrangement of TTS compromises of LV regional wall motion abnormality in concomitant with hypokinesia in the apical and circumferential mid-ventricular, known as apical ballooning. TTS often appears as an acute coronary syndrome (ACS) with significant LV dysfunction, but with spontaneous recovery within days or weeks after the onset[3].

TTS accounts for 0,02% of total hospitalization in the United States4 and importantly, it is predicted that around 2% of patients who undergo core angiography for suspected ACS are having TTS5. The typical profile of TTS patients are post-menopausal women between 66 to 80 years of age with a history of sudden emotional or physical stress prior to admission, which makes up approximately 90% of the cases[3,6,7] Identical prevalence is reported across various ethnic groups[8]. A recent study reported an average in-hospital mortality rate of 4,5%[9], one month after onset mortality rate of 5,9%, and a long haul mortality rate of 5,6%[8]. The mortality rates of TTS are concerning since they are surprisingly higher when compared to

the mortality rate of patients with ACS who have received optimal treatment in the form of percutaneous primary intervention during the event (30-day mortality rate of 4,6% and 1-year mortality rate of experience severe and sudden emotional or physical distress7 and the previous diagnosis of psychiatric disorders may be reported among some of the patients[4,11]. However, one out of five TTS patients does not have any form of stress before the onset of the disease. Additionally, it has been reported that TTS may also occur after a positive life event, thus it comes up with the term happy heart syndrome. This paper will discuss how the mind and the heart are connected in the pathophysiology of the disease and explore whether there is a role of psychiatric drugs to treat the disease[8].

Clinical presentation and diagnosis

The overall symptoms, signs, ECG, and echo findings are suggestive of classic ACS. In most cases, patients with TTS often come with chest pain and dyspnea. Additionally, syncope and pulmonary oedema are also quite often reported. However, cardiac arrest, cardiogenic shock, and ventricular arrhythmia, which are often found in a severe form of ACS, are rarely reported in patients with TTS. Non-cardiac symptoms 2,8%)[10].

Interestingly, TTS patients have been reported to such ac cough, fever, and general weakness have also been reported[8,12]. The most prominent ECG findings in patients with TTS is ST-segment elevation, mostly in the precordial leads. A study by Templin et al[13] which comparing ECG patterns between TTC and STEMI/NSTEMI patients also demonstrated that ST-segment elevation (STE) was prevalent in anterior and anteroseptal leads, and more frequent in aVR which solely produce specificity of 95% and positive productive value of 91%. The specificity to differentiate TTC from STEMI and NSTEMI was reported increased when STe in AVr was combined with STe in anterior leads (specificity of 98%; PPV 91%) or anteroseptal leads (specificity of 100%; PPV of 100%).

Nevertheless, the prevalence of STe among patients with TTC was reported to be only 54% of the total patients[13]. So, other criteria are required to diagnose TTC. To overcome the issue, Mayo Clinic has proposed the widely-accepted diagnosis criteria of TTC as shown in Table 1 below[14]. All of the four criteria must be present for the diagnosis of TTC could be established.

Table 1. Criteria for TTC

1.	"Temporary hypokinesis, dyskinesis, or akinesis in LV segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.*"
2.	"Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture. †"
3.	"New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4.	"Absence of: a. Pheochromocytoma b. Myocarditis"

"*There are rare exceptions to these criteria such as those patients in whom the regional wall motion abnormality is limited to a single coronary territory †It is possible that a patient with obstructive coronary atherosclerosis may also develop TTC. However, this is very rare in the published literature, perhaps because such cases are misdiagnosed as ACS. In both of the above circumstances, the diagnosis of TTC should be made with caution and a clear stressful precipitating trigger must be sought"

The mind and heart connection

Stress could be defined as a "physiological response that mediates the action of a stressor on its target organ"[15]. The essential parts of the brain responsible for stress response are the neocortex, limbic system, brainstem, and spinal cord[16].

Observation by Suzuki *et al* on patients with TTS demonstrated an increase in the cerebral blood flow, mainly to the brainstem, hippocampus, and basal ganglia, in concomitant with a decrease of blood flow to the prefrontal cortex area. Interestingly, these blood flow anomaly persists in the chronic phase of TTS when the cardiac wall motion disturbance had perished[17].

Following complex neocortical and limbic interpretation, intense emotional stressors have been demonstrated to increase the concentration of cortisol, epinephrine, and norepinephrine via brain activaion[18]. The primary location for norepinephrine synthesis is the locus coeruleus in the posterior area of the rostral pons in the lateral floor of the 4th ventricle. The locus controls acts as the largest group of noradrenergic neurons in the brain which innervates significant parts of the neuroaxis. It gains afferent signals from the hypothalamus, cingulate gyrus, and amygdala, enabling emotional stressors to generates noradrenergic responses via norepinephrine secretion which finally stimulates the hypothalamic-pituitary-adrenal axos[17,19].

Elevated serum catecholamines (epinephrine, norepinephrine, and dopamine) was observed abundantly in patients with TTS and their concentration were reported to be higher than among with STEMI. Moreover, the concentration remained elevated even after a week following the onset of symptoms[20,21]. The sustained catecholamines concentrations are orchestrated by the hypothalamic-pituitary-adrenal axis. During the chronic phase of the disease, chromaffin cells located in the adrenal medulla are responsible to release epinephrine and norepinephrine in response to the stress[22].

The neural impulses are also transmitted to the posterior hypothalamus apart from the locus coeruleus. The signal is transmitted via the cranial and sacral spinal cords and stimulate norepinephrine release[23]. The sympathetic preganglionic neurons located in the lateral grey column from T1 to L2-3 are the origins of sympathetic cardiac innervation which travel along with the epicardial vascular structures into the underlying myocardium and end up as sympathetic nerve terminals in the myocardium and coronary blood vessels. The sympathetic nerve endings generate norepinephrine into the synaptic cleft which activates α and β postsynaptic adrenoreceptors[24].

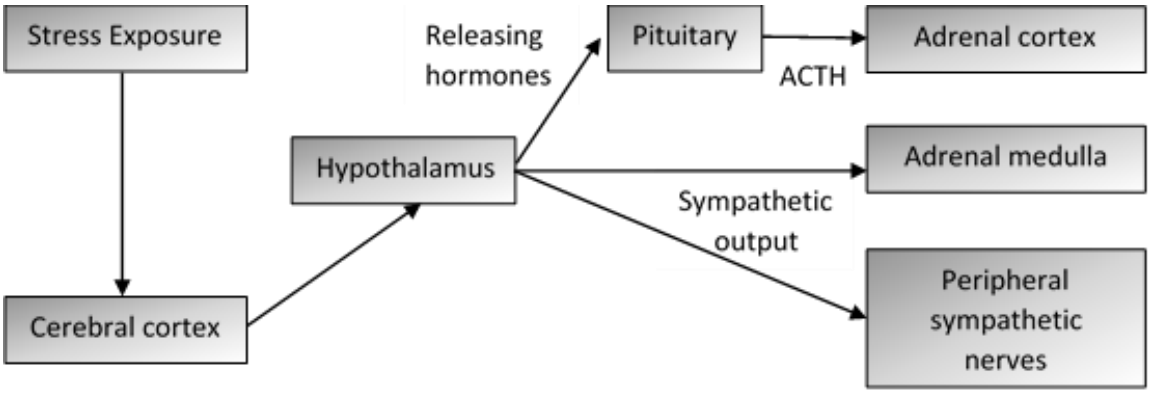

Figure 1. The Physiological response to stress. Stress causes hypothalamus to produce releasing hormones which further stimulates the anterior pituitary to secrete ACTH. ACTH works on the cortex of the adrenal gland to trigger glucocorticoi hormones synthesis and release. Additionally, stress also stimulates the preganglionic sympathetic neurons, prevertebral, paravertebral ganglia, and finally to end organs such as heart and medulla of the adrenal.

The mechanism of myocardial dysfunction in TTC patients could be divided into three distinct mechanisms: direct catecholamine toxicity, adrenoreceptor-mediated damage, microvascular coronary dysfunction, and increased cardiac workload. The most accepted TTC mechanism of disease is catecholamine-induced cardiotoxicity and microvascular dysfunction. In the acute phase of TTC, there has been evidence of an increasing level of catecholamines at the myocardium[21]. Kume *et al*[25] reported an increased norepinephrine concentration in the coronary sinus, indicating increased local myocardial release of catecholamine. It was also demonstrated in the murine model that a high concentration of epinephrine infusion may generate reversible apical LV ballooning in concomitant with basal hypercontractility which are the characteristics of cardiac abnormalities in patients with TTC[26].

Conditions with high catecholamine levels may affect β2-adrenergig receptors, causing myocyte injury due to calcium leakage via hyper phosphoryl effect on the ryanodine receptor[27]. TTC patients also demonstrated impairment during endothelium-dependent vasodilatation, causing enormous vasoconstriction, and myocardial perfusion abnormality[28]. The apical ballooning feature may be caused by the nature of high β-adrenergic receptors density in the apical-basal making it is more sensitive to catecholamine. The inflated concentration of epinephrine may generate negative inotropic impact and induce conformational change of Gs (stimulatory) protein to Gi (inhibitory) protein signalling[26].

Treatment

No trials have specifically assessing treatment options for patients with TTC. Current treatments largely focus on administering supportive therapy until LV function recovery which usually occurs around the 21st day of the onset[29]. Pulmonary congestion may develop due to declining LV function. Diuretics such as nitroglycerin and nitroprusside could be administered to overcome the issue. Additionally, standard heart failure medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta-blockers have been reported to be advantageous.

During some stage of the disease, TTC patients may develop hypotension and low cardiac output which are caused by either left ventricular outflow tract obstruction (LVOTO) and non-LVOTO which could be defined by echocardiography. Defining the origin of hypotension and low cardiac output is important since patients with no evidence of obstructions may be benefited from inotropic and vasopressors. On the other hand, those with LVOTO should not receive inotropes since inotropes may enhance basal hypercontractility and aggravate the obstruction. As alternatives, beta-blocker and IV fluids should be administered; In severe cases, extracorporeal membrane oxygenation (ECMO) may be initiated[29].

Additionally, patient's risk for getting major cerebrovascular events (MACE) such as stroke and acute myocardial infarction should be mitigated since MACE occurs in 7,1% of the patients in the first month after hospital admission[30]. Anticoagulant administration should be considered, especially in patients with sufficient cardiac hypokinesis[29].

2. Conclusion

In view of the fact that 2% of patients with presenting ACS symptoms are having TTC, and the mortality rate of TTC is more than 5%, one should be cautious and keep TTC on the differential diagnosis list. TTC is an example of a disease that demonstrates the magnificent relationship between emotional stress and clinically significant cardiac dysfunction. Further elaboration on emotional stress and organ dysfunction is suggested.

3. References

1. Ghadri, J. R. et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. Eur. Heart J. 2018;39: 2032–2046.

2. Gianni, M. et al. Apical ballooning syndrome or takotsubo cardiomyopathy: A systematic review. Eur. Heart J. 2006; 27: 1523–1529
3. Sharkey, S. W., Lesser, J. R., Maron, M. S. & Maron, B. J. Why not just call it tako-tsubo cardiomyopathy: A discussion of nomenclature. J. Am. Coll. Cardiol. 2011; 57:1496–1497.
4. Deshmukh, A. et al. Prevalence of Takotsubo cardiomyopathy in the United States. Am. Heart J. 2012; 164: 66-71.e1.
5. Prasad, A., Lerman, A. & Rihal, C. S. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. Am. Heart J. 2008; 155, 408–417.
6. Lyon, A. R. 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.
7. Brinjikji, W., El-Sayed, A. M. & Salka, S. In-hospital mortality among patients with takotsubo cardiomyopathy: A study of the National Inpatient Sample 2008 to 2009. Am. Heart J. 2012;164: 215–221.
8. Templin, C. et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. N. Engl. J. Med. 2015; 373: 929–938.
9. Singh, K., Carson, K., Shah, R. & Sawhney, G. Meta-Analysis of Clinical Correlates of Acute Mortality in Takotsubo Cardiomyopathy. Am. J. Cardiol. 2014; 113: 1420–1428.
10. Rasoul, S. et al. Predictors of 30-day and 1-year mortality after primary percutaneous coronary intervention for ST-elevation myocardial infarction of the Zwolle Myocardial Infarction Study Group. 415–421 https://doi: 10.1097/MCA.0b013e32832e5c4c
11. Summers, M. R. & Prasad, A. Takotsubo Cardiomyopathy: Definition and Clinical Profile. Heart Fail. Clin. 2013; 9: 111–122.
12. Akashi, Y. J., Nef, H. M. & Lyon, A. R. Epidemiology and pathophysiology of Takotsubo syndrome. Nat. Publ. Gr. 13–16 (2015) https://doi:10.1038/nrcardio.2015; 39.
13. Kovac, M., Ruschitzka, F. & Thomas, F. L. ECG Criteria to Differentiate Between Takotsubo (Stress) Cardiomyopathy and Myocardial Infarction. 2016. https://doi:10.1161/JAHA.116.003418.
14. Scantlebury, D. C. & Prasad, A. Diagnosis of takotsubo cardiomyopathy – Mayo Clinic criteria –. Circ. J. 2014; 78: 2129–2139.
15. Camici, F. P. J. C. K. F. C. P. G. Pathophysiology of Takotsubo Syndrome. Circulation. 2017; 135: 2426–2441
16. AR, C. Neuroanatomy. (Churchill Livingston, 2000).
17. Suzuki, H. et al. Evidence for brain activation in patients with takotsubo cardiomyopathy. Circ. J. 2014; 78: 256–258.
18. Steptoe, A. & Kivimäki, M. Stress and cardiovascular disease. Nat. Publ. Gr. 2012; 9: 360–370.
19. Sved, A. F., Cano, G., Passerin, A. M. & Rabin, B. S. The locus coeruleus, Barrington's nucleus, and neural circuits of stress. Physiol. Behav. 2002; 77; 737–742.
20. Akashi, Y. J. et al. 123I-MIBG myocardial scintigraphy in patients with 'takotsubo' cardiomyopathy. J. Nucl. Med. 2004; 45: 1121–1127.
21. Wittstein, I. S. et al. Neurohumoral Features of Myocardial Stunning Due to Sudden Emotional Stress. N. Engl. J. Med.2005; 352: 539–548.
22. Mazeh, H., Paldor, I. & Chen, H. The endocrine system: pituitary and adrenal glands. ACS Surg. Princ. Pract. 2012; 1–13.
23. GS, F. Modulation of peripheral sympathetic nerve transmission. J Am Coll Cardiol 1988; 12: 250–254.

24. Lymperopoulos, A., Rengo, G. & Koch, W. J. Adrenal adrenoceptors in heart failure: fine-tuning cardiac stimulation. Trends Mol. Med. 2007;13: 503–511.
25. Kume, T. et al. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. Circ. J. 2005; 69, 934–939.
26. Paur, H. et al. High levels of circulating epinephrine trigger apical cardiodepression in a β 2-adrenergic receptor/Gi-dependent manner: A new model of takotsubo cardiomyopathy. Circulation 2012; 126: 697–706.
27. Cells, C. S. et al. Acute β-Adrenergic Overload Produces Myocyte Damage through Calcium Leakage from the Ryanodine Receptor 2 but Spares Cardiac Stem Cells. Heart Fail.2008; 282: 11397–11409.
28. Galiuto, L. et al. Reversible coronary microvascular dysfunction: A common pathogenetic mechanism in Apical Ballooning or Tako-Tsubo Syndrome. Eur. Heart J.2010; 31: 1319–1327.
29. Medina de Chazal, H. et al. Stress Cardiomyopathy Diagnosis and Treatment: JACC State-of-the-Art Review. J. Am. Coll. Cardiol. 2018; 72: 1955–1971.
30. Glaveckaite, S., Šerpytis, P., PeČiŪraitĖ, D., Puronaitė, R. & Valevičienė, N. Clinical features and three-year outcomes of takotsubo (Stress) cardiomyopathy: Observational data from one center. Hell. J. Cardiol. 2016; 57: 428–434.