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Research Article

Stress Cardiomyopathy (Takotsubo Syndrome): Psychiatric Triggers and Neurocardiac Mechanism

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Abstract

Takotsubo syndrome (TTS), otherwise known as stress cardiomyopathy or broken heart syndrome, is a reversible transient state of acute cardiac dysfunction. There is a systolic impairment in the left ventricle in absence of any obstruction of the coronary artery. A significant association between stress, psychological disorders and TTS suggests a key role of the brain-heart axis in cardiovascular physiology.

Autonomic dysfunction, catecholamine overload, activation of the hypothalamic-pituitary-adrenal axis, inflammation and endothelial dysfunction are likely mechanisms involved in the genesis of TTS. It has been confirmed that depression, panic attacks, anxiety, psychological trauma and chronic stressful lifestyle are correlated with a higher predisposition towards sympathetic overdrive and myocyte damage. Recent advances in psychocardiology and neurocardiology have explained the neurocardiac mechanisms behind stress-induced cardiomyopathy. This narrative review addresses the epidemiology, psychiatric comorbidities, pathogenesis and clinical presentation of TTS, as well as the methods of diagnosis, treatment and future perspective, focusing on the role of psychiatric triggers and neurocardiac pathways.

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INTRODUCTION

Takotsubo syndrome (TTS) is an acute, reversible form of cardiac dysfunction that closely mimics acute coronary syndrome, but where significant obstructions of the coronary arteries are absent. Described for the first time in 1990 in Japan it derived its name from "takotsubo" or the Japanese octopus pot, due to the balloon-shaped apical bulge of the left ventricle that is typically visible during systole.

Patients usually present with chest pain, dyspnea, electrocardiographic changes and cardiac biomarkers.[3]

It was once believed that this condition had no severe consequences, but it is now known that arrhythmias, cardiogenic shock, thromboembolism and heart failure can be very serious consequences.[12]

One of the most characteristic features of the TTS is the association with stressful stimuli and psychological disorders. Grief, fear, domestic conflict, panic attack, and psychological trauma are often reported prior to the presentation of the symptoms. It has been shown that patients with anxiety disorders, depression and chronic stressors present with significantly higher prevalence of the condition.[8]

It has recently become clear that TTS is a disorder of the brain-heart axis where complex neurocardiac relationships between central nervous system, autonomic nervous system, endocrine pathways and the cardiovascular system come into play, resulting in massive sympathetic activation and catecholamine-induced myocyte injury.

In this narrative review we summarize the latest findings concerning the psychological triggers and neurocardiac mechanisms in the development of the Takotsubo syndrome.[23]

Epidemiology

Takotsubo syndrome accounts for 1-3% of patients seeking help with suspected acute coronary syndrome. While men may be affected, women are significantly more likely, almost 90% of patients being female. The decline of estrogen in postmenopausal women is thought to play an important role in this sex difference by impairing endothelium function and autonomic sensitivity.[25]

Many patients with this condition have a history of emotional trauma. The condition may also be precipitated by events such as surgery, infection, trauma or disorders of the nervous system. Psychiatric disorders are far more frequent in TTS patients than in the general population and anxiety and depression are the most common psychiatric illnesses identified in TTS patients.[7]

Ventricular function usually returns to normal within several weeks of presentation. However, it has been suggested that TTS may recurrent in some patients which may reflect ongoing vulnerability related to autonomic or psychological factors.[16]

Psychiatric Triggers and Brain-Heart Axis

The most commonly identified cause of Takotsubo syndrome is a psychologically stressful event. An acute emotional experience triggers massive sympathetic stimulation resulting in acute reversible cardiac dysfunction.

Anxiety disorders, depression, panic attack, extreme shock, loss of a loved one, chronic stress and post-traumatic stress disorder are just a few of the psychiatric conditions that may trigger the illness. Pre-existing psychiatric illness seems to confer a susceptibility because it involves both chronic autonomic imbalance and attenuated stress response.

The concept of the brain-heart axis has been widely incorporated into the explanation for stress cardiomyopathy. Emotional stimuli activate brain areas such as amygdala, insular cortex, hippocampus and anterior cingulate cortex which in turn affect autonomic and neuroendocrine pathways and consequently lead to exaggerated sympathetic activity and release of catecholamines into the bloodstream. Brain imaging studies show that areas of the brain responsible for stress response in TTS patients are aberrant. These neural networks are involved in a wide array of activities, including mood, emotion, and behavioral responses to various stresses.

These neuronal networks lead to sympathetic hyperactivation which leads to an outpouring of catecholamines. Psychiatric conditions, itself, have been known to cause sympathetic overactivity, vagal withdrawal, as well as impairment of the HPA axis response and contribute to the vulnerability of the cardiovascular system to emotional stress.[16]

Coronary Microvascular Dysfunction

Coronary microvascular dysfunction is thought to be a key factor in the pathogenesis of TS. Many patients show evidence of abnormal coronary microcirculation and transient myocardial ischemia in the absence of significant obstructive coronary artery disease. A surge in catecholamine output during emotional or physical stress may cause severe vasospasm and/or endothelial dysfunction in the coronary microvasculature.[18]

Microvascular abnormalities may be responsible for the myocardial stunning, ventricle contractility reduction and regional wall motion abnormalities seen in Takotsubo syndrome. A role for endothelial dysfunction and nitrate oxidase reduction in coronary vasoreactivity has been suggested. Growing data regarding a prominent part for coronary microcirculatory abnormalities has pointed out that these may provide the link between autonomic dysfunction and catecholamine-related myocardial damage.[4]

Psychocardiology and Brain-Heart Interactions

Psychocardiology is a new multidisciplinary research field that investigates the symbiosis between mind and heart in the pathophysiology of cardiovascular disease. Of the most dramatic examples of mind-body interaction seen in the medical world to date is the takotsubo syndrome. Mind related phenomena such as emotional stress, psychiatric disease and autonomic imbalance have a prominent role in cardiovascular pathomechanisms producing acute cardiac failure.[23]

The brain-heart axis refers to the interactions of the central nervous system, autonomic nervous system and endocrine and cardiovascular pathways. In response to stress, limbic brain regions activate the sympathetic nervous system and with abrupt catecholamine release can cause transient myocardial dysfunction.[20]

The pathophysiology of psychiatric disease states (anxiety, depression) is characterized by long-term autonomic dysregulation, inflammation and blunted stress-response, which appear to predispose for Takotsubo syndrome. Acknowledgement of these psychocardiological correlations is crucial for appropriate care and encourages multidisciplinary conceptualising representing psychiatry, cardiology and physiology.[21]

The pathophysiology of takotsubo syndrome

The pathophysiology of Takotsubo syndrome is multifactorial and it remains imperfectly elucidated but, in the core, the most probable mechanism involves excessive sympathetic activation and catecholamine induced myocardial damage. Acute emotional and physical stress results in activation of the autonomic nervous system and hypothalamic pituitary adrenal axis with resulting large release of catecholamines (epinephrine, norepinephrine).[14]

This catecholamine is believed to be directly cardiotoxic causing stunning of the myocardium via calcium overload, oxidative stress, coronary artery vasoconstriction and microvascular dysfunction. The apex of the left ventricle is known to be more susceptible to the effects of catecholamines due to high density of beta-adrenergic receptors explaining the characteristic apical ballooning of classical Takotsubo syndrome. Endothelial dysfunction, inflammation, impaired myocardial metabolism and autonomic imbalance might also play an additional role in the transient ventricular dysfunction. Increasing data suggest that Takotsubo syndrome is a disorder of the brain-heart axis, implying an interaction between emotional stress and the physiology of the heart.[4]

The neuroimaging findings in Takotsubo syndrome

With the advent of neuroimaging, several findings were brought into the light about the neurocardiac mechanisms of Takotsubo syndrome. Using functional magnetic resonance imaging and positron emission tomography, abnormalities have been found in brain regions which are known to play a role in emotion processing and regulation of autonomic function.[19]

Changes in activities were reported in the amygdala, hippocampus, insular cortex, anterior cingulate cortex and prefrontal cortex in patients suffering from Takotsubo syndrome. Amygdala, which plays a critical role in response to fear and stress, seems to play an integral part in mediating sympathetic activation in the context of emotional stress.[20]

These findings support the hypothesis that chronic stress and psychiatric diseases could result in dysregulated brain network activity which in turn might lead to increased risk of developing stress induced myocardial dysfunction. Neuroimaging studies seem to establish that Takotsubo syndrome is a disorder of the brain heart axis and psychocardiology in the future seems to play a vital role in dealing with cardiovascular diseases.[22]

Catecholamine Hypothesis

The catecholamine hypothesis is the most broadly accepted explanation for the pathophysiology of Takotsubo syndrome. Following intense emotional or physical stress the secretion of large amounts of catecholamines such as epinephrine and norepinephrine occurs.[10]

High concentrations of catecholamines cause myocyte toxicity in multiple ways, including calcium overload, free radicals, coronary vasospasm and microvascular dysfunction. Cathecholamines can directly damage myocytes, impair cardiac energy metabolism.

The apex of the left ventricle, particularly the segment within it, is most vulnerable to catecholamine mediated injury due to the higher beta-adrenergic receptors. This fact possibly explains why the apex of the left ventricle shows a prominent ballooning in conventional TTS.[4]

Animal models show similar changes seen with catecholamine mediated damage with stress cardiomyopathy and it does confirm the sympathetic hyperactivation theory.

Autonomic Dysfunction: The autonomic nervous system imbalance is the second hypothesis regarding the pathophysiology of TTS. Sympathetic system overactivity combined with vagal withdrawal leads to dysfunction of the heart.[14]

Heart Rate Variability (HRV) is the measure of the autonomic nervous system and is consistently reduced in patients with TTS and these are often indicative of sympathovagal balance where sympathetic is more dominant, it's like those with depression and anxiety, where reduced HRV is more common.[17]

Excessive sympathetic activity would explain the many physical symptoms, and would be accompanied by the loss of parasympathetic stimulation, to make the Heart rate increase, cause coronary vasospasm, arrhythmia and cause myocardial stunning and can result in recurrent attacks in patients and cardiac compromise in the longer run. The relationship between psychiatric disorders and autonomic function confirms the brain-heart axis, with an obvious involvement in this aspect.

Hypothalamic-Pituitary-Adrenal Axis and Inflammation:

The hypothalamic-pituitary-adrenal (HPA) axis is also of importance in stress cardiomyopathy; psychological stress leads to excitation of hypothalamus, activating anterior pituitary to release corticotropin, which stimulates adrenal cortex to release cortisol. Chronic HPA axis activation is associated with sympathetic excitation, endothelium dysfunction, inflammation and metabolic abnormalities. Patients with depression, and chronic anxiety tend to have blunted cortisol response, failing to adequately adapt to stress. [11]

Inflammation has increasingly been implicated in the pathogenesis of TTS. High levels of inflammatory mediators including interleukin-6 and C-reactive protein have been found in patients. Inflammation causes endothelium dysfunction and compromises microcirculation leading to reduced oxygen supply and myocardial damage. [4]

Psychological stress causes inflammatory activation of the brain which can in turn activate other immune pathways to induce inflammation and thereby compromise heart health; these can be referred to as neuroimmune pathways and it adds to the link between psychiatric disorder and cardiovascular disease.[23]

Clinical Features and Diagnosis

The clinical presentation of TTS usually resembles that of an acute myocardial infarction. Common symptoms are sudden chest pain, dyspnea, palpitations or syncope. Usually, the illness is preceded by an emotional or physical stressor. Electrocardiogram shows evidence of anterior STEMI, T-wave inversions and QT prolongation; troponin will be elevated but disproportionate to the extent of ventricular dysfunction. On echocardiography there is usually apical wall motion abnormality resulting in the characteristic ballooning. Coronary angiogram does not show significant obstruction and distinguishes TTS from ischemic heart disease. [15]

Cardiac MRI may be useful in differentiating the condition from myocarditis and also helps to determine the amount of edema without significant necrosis of heart muscle. Modified Mayo clinic criteria remain in use for the diagnosis.[16]

Management

There is no specific treatment for Takotsubo syndrome. Treatment should initially be similar to that of acute coronary syndrome until an obstruction in the coronary arteries is ruled out. Patients may benefit from treatment with beta-blockers, ACE inhibitors, diuretics and/or hemodynamic support dependent on their clinical status. Beta-blockers may also be used to decrease sympathetic overactivity, however there are conflicting data on the role they may have in preventing subsequent recurrence. A psychiatric assessment and stress management approach is key in the management of patients.[3]

Anxiety, depression and chronic stress need to be adequately managed by counselling, psychotherapy, relaxation techniques and in some cases drug therapy. Improvement in the long-term prognosis is believed to involve lifestyle modification such as ensuring optimal sleep, providing psychological support, practicing mindfulness, and reducing sources of stress. The majority of patients achieve full recovery of left ventricular function within days to weeks, but complications such as arrhythmias, thromboembolism, cardiogenic shock and recurrence can arise.[25]

Complications and Prognosis

Takotsubo syndrome is usually reversible. Nevertheless, acute phase of Takotsubo syndrome may have serious complications such as heart failure, pulmonary edema, arrhythmias, cardiogenic shock, left ventricular thrombus and thromboembolic events. Prolongation of QT interval may cause the susceptible patients susceptible to ventricular arrhythmias and sudden cardiac death.

The left ventricular systolic function usually returns to normal in days to weeks; however, about 5% to 10% of patients suffer recurrence. Chronic stress, anxiety disorders, and autonomic disorders may be predisposing factors for recurrence.[12]

The prognosis is generally favorable, however, some patients may have post- Takotsubo syndrome complications like fatigue, decreased quality of life, and chronic stress-related psychopathology. However, early diagnosis and proper cardiovascular and psychiatric treatment are of vital importance for better clinical outcome and the long term cardiovascular event prevention.[16]

Future Perspectives

The last few years have witnessed exciting developments in the fields of psychocardiology and neurocardiology, which have brought a better understanding of the pathophysiology of Takotsubo syndrome. Research continues in terms of using functional brain imaging, monitoring autonomic functions and using artificial intelligence and digital biomarkers in an effort to identify those who are at greater risk of developing Takotsubo syndrome. Wearable devices that are able to measure heart rate variability and autonomic activity may provide the earliest clues to an impending stress induced cardiovascular dysfunction. [20]

More research is required to assess the usefulness of psychiatric intervention in preventing recurrent episodes. Close integration of psychiatry, cardiology and physiology could aid in development of individualised treatment strategies.21

CONCLUSION

Takotsubo syndrome remains a key example of how psychological stress interacts with cardiovascular physiology. A multitude of psychological factors and disorders trigger autonomic dysfunction, catecholamine release, inflammation and subsequent transient myocardial dysfunction. There is now substantial evidence for a brain-heart axis involved in the generation of Takotsubo syndrome.

Awareness and consideration of both psychological and autonomic influences are important when caring for the patient. Continued interdisciplinary investigation by psychocardiologists, neuroscientists and cardiovascular physiologists will further enhance our knowledge of stress cardiomyopathy and promote innovative strategies of treatment.

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