Takotsubo Syndrome: A Review on The Relationship Between The Heart and The Brain

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ABSTRACT

Takotsubo syndrome (TTS), also known as stress cardiomyopathy, causes severe heart syndrome in humans due to extreme physiological and psychological stress events in life. Takotsubo syndrome's critical manifestations of acute chest pain and syncope or dyspnea often imitate an episode of severe myocardial infarction that does not entail coronary artery obstruction. Recent scientific data reveals that the sympathetic nervous system (SNS) stimulation contributes significantly to the pathogenesis of TTS. In detail, emotional stress events in an individual cause SNS activation, leading to an excessive release of catecholamine that inflicts toxicity to myocardial tissues when present at superfluous concentrations. However, the central nervous system (CNS) alterations and the relationship between heart and brain among TTS patients remain vague. Of late, several published studies disclosed the importance of the aforesaid heart-brain relationship in the pathogenesis of TTS. This review examines studies focused on the excessive release of catecholamine, the activation of SNS, and the heart-brain relationship in TTS cases from concurrent systemic and pathophysiological attributes.

Keywords: Heart disease, Takotsubo syndrome, Stress events, sympathetic nervous system, catecholamine

INTRODUCTION

Takotsubo syndrome (TTS) is a physiological and psychological stress condition recognized as stress cardiomyopathy, which causes an acute reversible heart failure [1]. The clinical symptoms of TTS include severe chest pain, dyspnea or syncope, and, in extreme circumstances, it could manifest as cardiogenic shock or ventricular arrhythmia [2]. In the earlier stage of the disease, it is challenging to differentiate TTS from Acute Myocardial Infarction (AMI), since ST-segment elevation with or without elevated levels of creatine kinase-MB (CK-MB) and troponin would show in the electrocardiogram (ECG) of a patient

with TTS [3]. Nevertheless, coronary artery occlusion does not present in the majority of TTS patients, imposing reversible left ventricular dysfunction as a characteristic when the occlusion does exist [3].

In 1991, for the first time, Dote et al. [4] described TTS in a five-cases article. The first case is a woman, 64-year old, who experienced ECG changes and symptoms concordant with Acute Myocardial Infarction. Despite her normal coronary arteries, she presented with an apical ballooning that looked like a traditional Japanese pot known as “Takotsubo”. Her ventricle motions displayed striking irregularities noticeable on left ventriculography and perished after 14-days [5]. The first few unusual cases were reported in Asia, followed by western countries in the late 1990s [6]. In 2006 this condition was termed “stress cardiomyopathy” by the American Heart Association [7]. The European Society of Cardiology (ESC) recommended discontinuing the term “cardiomyopathy” to restore the original term, “Takotsubo syndrome” (TTS) [1].

A progressive increase was observed in global TTS cases. A modern report in epidemiological data reveals that TTS is responsible for 1–3% of total suspected AMI cases, taking 90% into account for postmenopausal women [8]. The observations further report that older women (aged >55 years) are at 11-fold risk of developing TTS than men of equivalent age, and at 6-fold risk than younger women [9]. TTS is held accountable for 0.02% rate of hospitalization in the United States, with a mortality rate of 2% during hospitalization [9-10]. The prognosis of TTS is generally promising, despite potential fatalities and severe complications, such as malignant arrhythmias, cardiogenic shock and heart failure, an early diagnosis of TTS is deemed to be consistently advantageous [11].

CATECHOLAMINE AND STRESS

Even though the pathophysiology of TTS is not fully known, this condition is usually regarded as an intricate reaction of the cardiovascular system induced by acute psychological and physiological stimulation [1]. The essential trigger and stimulation factors of Takotsubo syndrome are physical and emotional stress events. A study by Pelliccia et al., (2015) [12] reported that 35% and 39% of 1109 patients with TTS were triggered by physical and emotional stress, respectively, of which 24% cases had mental disorders [12]. Furthermore, Summers et al. (2010) [13] reported that many women had a history of chronic anxiety prior to the onset of TTS. Likewise, Takotsubo syndrome may be the product of physical stress, as concluded in a study that found that pulmonary vascular disease, nervous system disease, and trauma were apparent in 15%, 7%, and 1% of patients with TTS, respectively [12]. In a different study,

patients with TTS bore the most significant risk factors of death once the disease is followed by chronic kidney disease, malignant tumors, and connective tissue diseases [14].

According to the current understanding, the pathogenesis of TTS is influenced by the increasing activity of the sympathetic nervous system (SNS). The activation of SNS is triggered by emotional events, which leads to the release of the catecholamines. In multiple studies, TTS is associated with psychological and physiological events and excessive release of catecholamines. Wittstein et al., (2005) [15] reported a notably higher release of catecholamines in patients with TTS than in patients with Killip class III myocardial infarction. However, instead of plasma catecholamines flood, Madhayan et al., (2009) [16] discovered a significant surge in plasma noradrenaline concentrations in a cohort study of 15 patients. To support, Kume et al., [17] reported an increase in noradrenaline concentrations in the coronary sinuses of patients with TTS. Although earlier studies suggest a strong association of SNS and plasma catecholamines concentrations with TTS, Borodzicz et al., (2020) [18] argued that plasma catecholamines concentration is not necessarily correlated with limited myocardial sympathetic regulation.

Despite conflicting results from previously mentioned studies, intravenous injections of catecholamines have been proved to induce TTS in some clinical cases. In one study, Kido and Guglin (2015) [19] published a study on drug-induced TTS, which involved 157 cases. They reported that 68.2% of the cases were catecholamines-induced, where 8.9% of the cases co-occurred with chemotherapy-induced coronary vasospasm. In another study, Abraham et al., (2009) [20] mentioned that the administration of intravenous beta-receptor agonists or epinephrine could provoke all signs of TTS, such as elevated levels of cardiac isoenzyme, prolonged QTc interval, and rapidly reversible cardiac dysfunction. These observations were supported by several studies on pheochromocytoma and other diseases related to the excessive release of catecholamines. For instance, Giavarini et al., reported 140 patients with paragangliomas (PPGL) and pheochromocytomas and mentioned as much as 11% of the cases which involve the former condition to manifest as acute catecholamine cardiomyopathy (ACC) [21]. In a study of rat models, Redfors et al., (2014) revealed that apical ballooning of the left ventricle in studied rats was provoked by immobilization stress. However, alpha- and beta-receptor blockade plays a role in attenuating the ballooning [22].

The lethal effect of high catecholamines concentrations in the myocardium was observed as a transient left ventricle dysfunction. High levels of catecholamines concentrations could stimulate beta-adrenoceptors and downregulate the expression of genes that encode the calcium regulatory protein, which leads to further disruption of the regulatory channels of

calcium [23]. The upregulation of sarcolipin downregulates the gene expression for sarcoplasmic calcium ATPase (SERCA2a) while the dephosphorylation of phospholamban occurs. The subsequent surge in the ratio of phospholamban and SERCAa reduces Ca^{2+} affinity, which leads to contractile dysfunction. The histopathological hallmarks of TTS involve regional inflammatory cell infiltration, contraction bands, and enhanced fibrosis [24].

THE SYMPATHETIC NERVOUS SYSTEM (SNS) ACTIVATION

The patients who present with TTS have also been reported with many other hallmarks of SNS activation. In the abovementioned study, 90% of patients with TTS were postmenopausal women. During that period, a decline in estrogen levels decreased the support of the parasympathetic nerve in the hypothalamic autonomic center, resulting in intensified reactivity to SNS activation. This intensified reactivity may partially clarify the issue of why TTS affects postmenopausal women more? National Health and Nutrition Examination Survey (NHANES) studied 3,389 TTS patients, 88.9% of whom are women, found that the prevalence of diabetes mellitus in the population was lower than the prevalence in a general population [25]. It is hypothesized that the autonomic neuropathy provoked by diabetes mellitus leads to disconnection on the relationship between the heart and the brain, consequently mitigating the adrenergic storm effect to the myocardium in TTS.

The ECG characteristics between TTS patients and AMI patients are found to be very similar. In both cases, the manifestations are large upright peaked T-waves, T-wave inversion, and prolonged QT interval. The ECG changes seen in TTS patients likely reflect the disruption of the sympathetic nerve terminals [26]. In a review of 24-hour ambulatory electrocardiograms of TTS patients with apical ballooning at two to three days and three months, Ortak et al. [27] noted that the heart rate variability (HRV) indices were meaningfully reduced, suggesting a reduction in the activity of cardiac parasympathetic. Another similar study was performed by Akashi et al., (2007) [28], which concluded a comparable interpretation upon investigating the mean cycle lengths of normal-normal R-R (NN) intervals over 24 h (SDNN) and the standard deviation of the parameter. In that study, the mean value of the difference between NN intervals for each 5-min segment (SDANN) was detected, and the 24-h standard deviation was counted. It was found that the number had improved significantly at the three months post-onset in TTS patients [29]. The role of the SNS in TTS is supported by some evidence gathered from nuclear imaging. For example, an earlier study revealed that a decrease in ^{123}I -metaiodobenzylguanidine uptake on single-photon-emission computed tomography was suggestive of cardiac sympathetic hyperactivity in TTS patients [30].

THE HEART-BRAIN RELATIONSHIP

Both the central nervous system and the sympathetic nervous system in humans mediate a physiological response resulting from stressful events. The important anatomic structures involved in the production of stress response comprise of the spinal cord, brainstem, neocortex, limbic system, and reticular formation [31]. In this review, the primary neuroendocrine modifications, which arise in response to strong stimulus manifest in a strong excitation of the locus coeruleus-adrenomedullin axis and hypothalamus-pituitary-adrenocortical (HPA) axis [32]. The primary site of noradrenergic neurons in the brainstem and sympathetic adrenomedullin system is the locus coeruleus, located in the posterior part of the rostral pons in the lateral floor of the fourth ventricle in the brain stem. Afferent signals travel to locus coeruleus from hypothalamus, amygdala, and cingulate gyrus, and are associated with excitement and awareness during stressful events. Furthermore, some emotional responses, such as tension and depression, are affected by locus coeruleus, which activates the noradrenergic responses. This brain structure also helps to manage the acute response to stress by supporting a state of alertness that plays a role in coping with external and internal changes. The secretion of norepinephrine by chromaffin cells of the adrenal medulla is induced by the stimulation from locus coeruleus, sequentially activating the HPA axis [33].

The sacral and cranial parts of the spinal cord are the location where the sympathetic nerve descends. The preganglionic neurons of sympathetic nerve are positioned in the lateral horn of the spinal cord between the level of T1 and L2. These neurons communicate by forming synapses with postganglionic neurons. The synapses move alongside epicardial vessels to interact with the myocardium and coronary arteries. The postsynaptic alpha- and beta-adrenergic receptors are stimulated by the flood of noradrenaline in the synaptic space, which was released by the sympathetic nerve endings [34].

The hypothalamus-pituitary-adrenocortical (HPA) axis, under a mechanism called the limbic system-hypothalamus-pituitary-adrenal (LHPA), controls stress and its consecutive responses. LHPA axis is concentrated adjacent to the paraventricular nucleus, which, as the name implies, involves the hypothalamus, adenohypophysis, and adrenal cortex in its operation. The HPA axis activity induces cortisol synthesis in the adrenal cortex. Primarily known as a stress hormone, cortisol functions on multiple tissues, especially the brain. The combined functions between cortisol and the sympathetic nerve induce the adrenal medulla to synthesize and secrete adrenaline and noradrenaline. The amygdala and hippocampus

physically connect to the hypothalamus. These physical connections between the nuclei of the amygdala and hippocampus additionally stimulate the HPA axis.

The measurement of the cerebral blood flow (CBF), a universally-accepted brain activity index, in TTS patients who display an acute or chronic state, has been done through (99 m)Tc ethyl cysteinate dimer single-photon-emission computed tomography. A remarkable decrease of CBF in the prefrontal cortex accompanied by a significant increase of CBF in the basal ganglia, hippocampus, and brainstem was observed in the acute phase [34]. The hippocampus and basal ganglia are the elements of the limbic system affiliated with the activation of emotion and the sympathetic nervous system. In addition, the origin of descending sympathetic nerves and the sympathetic central nucleus existed in the brainstem. Klein et al. in 2017 showed the brain areas correlated with heart function control in TTS patients [35]. Furthermore, Hiestland et al. in 2018 exposed the connective and structural differences in the limbic networks of patients with TTS and healthy subjects by utilizing magnetic resonance imaging [36]. Hiestland et al. showed that TTS patients develop a cortex covering the limbic area and a notable decrease of connectivity in the autonomic nervous system, which covers the right putamen, the left superior temporal pole, both hippocampi, and the left amygdala. Furthermore, a similar result was reported by a study in which reduced functional connectivity was also observed in the limbic system [37]. Compared to those in a general population, a noticeably higher proportion of individuals with mental disorders were found in TTS patients. Accordingly, changes in the primary structures in the autonomic nervous system of patients with TTS may shrink control in this area.

CONCLUSIONS AND INSIGHTS

This review summarized findings in recent studies regarding the inherent pathophysiological and automatic roles of the sympathetic nervous system activation, the excessive release of catecholamine, and the heart-brain relationship in patients with Takotsubo Syndrome. The pathways through which catecholamine overloads influence direct and indirect myocardial injury have been elucidated continuously. The role of the sympathetic nervous system in TTS pathogenesis has become more apparent. Recent studies reported that structures in the brain that endure stress-induced changes further developed neurophysiological and anatomical changes, starting from the onset of Takotsubo Syndrome. This condition implies that stress-induced changes in the central nervous system may stimulate the activation of the sympathetic nervous system, which subsequently leads to TTS. Considering that all included studies in this review implemented cross-sectional design, interdisciplinary study methods and

supplementary randomized prospective trials are essential to explore further the role of the central nervous system and the heart-brain relationship in the pathogenesis of Takotsubo Syndrome.

DISCLOSURE

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Conflict of Interest

The author declares there is no conflict of interest regarding all aspect of the study.

Author Contribution

PHW is responsible for the study from the literature search, data gathering, data analysis, until reporting the results of the study by a narrative form of literature review.

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