Takotsubo Syndrome and Psychosocial Stress Response

Subjects: Others

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Takotsubo syndrome (TTS) is a cardiomyopathy that clinically presents as a transient and reversible left ventricular wall motion abnormality (LVWMA). Recovery can occur spontaneously within hours or weeks. Studies have shown that it mainly affects older people. In particular, there is a higher prevalence in postmenopausal women. Physical and emotional stress factors are widely discussed and generally recognized triggers. In addition, the hypothalamic-pituitary-adrenal (HPA) axis and the associated glucocorticoid-dependent negative feedback play an important role in the resulting immune response.

Keywords: Takotsubo syndrome ; inflammaging ; hypothalamic-pituitary-adrenal axis ; sympathetic nerve action ; central autonomic nervous system

1. Brain-Heart Interaction/Axis

The cardiovascular system is associated with regulation throughout the cortical modulation. Although there is still a lack of knowledge on the mechanism of the “brain-heart axis”, various cardiac and neurological diseases have been discussed to be influenced by each other.

The cortical modulation is a network mainly composed of the insular cortex (Ic), anterior cingulate gyrus, and amygdala. This network plays a crucial role in the regulation of the central autonomic nervous system (CAN), e.g., through physical triggers or emotional stressors such as anxiety, excitement, and sadness. Functionally, the Ic can be divided into the right insula, which is associated with sympathetic dominance, meaning that stimulation leads to an increase in heart rate and pressor responses, and the left insula, which is characterized by the parasympathetic tone, leading to a decrease in heart rate and an increase in depressor responses [1]. In addition, the Ic is associated with autonomic, sensory, and motor functions, as well as its bidirectional connections to other brain areas such as the limbic system. Several studies have attempted to demonstrate a link between activation of the Ic and the processing of emotions such as anxiety, fear, anger, panic, and joy [2][3][4][5]. The anterior part of Ic has been shown to be decisively involved in the processing of emotions [6]. This suggests that the processing of emotions by the anterior part of Ic has an influence on the autonomic nervous system and may shift the sympatho-vagal balance toward a sympatico-dominant status. With regard to the current knowledge of the cortical modulation network, with the involvement of the Ic and main parts of the Ic, sympatho-vagal balance is key for homeostasis. A destructed Ic leads to an imbalance, with effects on the cardiovascular system. Its elimination supports the development of takotsubo syndrome (TTS). Different factors causing a disruption of the Ic may be a hemorrhage stroke of the middle central cerebral artery, sexual hormones, such as estrogen, or the processing of emotions.

It is known that psychological and physical stressors recruit different brain nuclei to respond to stress. In fact, the activation of the autonomic nervous system (ANS) and neuroendocrine system is central and causes behavioral changes [7]. Studies using functional magnetic resonance imaging (fMRI) of the brain to monitor resting-state functional connectivity demonstrated hypoconnectivity of parasympathetic and sympathetic-associated subnetworks of central brain regions and limbic regions in TTS patients compared to control groups [8].

When self-regulation is disrupted, stress becomes harmful and the body’s susceptibility to diseases such as cardiovascular, psychiatric, and immune disorders increases [9][10]. In the stress response, the locus coeruleus (LC), amygdala nuclei, septal-hippocampal complex, paraventricular nucleus of the hypothalamus (PVH), prefrontal and cingulate cortexes, and parabrachial and raphe nuclei play an important role in the stress response. The resulting signals stimulate the hypothalamic-pituitary-adrenal (HPA) axis. In the signaling chain, the PVH is responsible for the release of the corticotropin-releasing factor (CRF), which induces the release of the adrenocorticotropin hormone (ACTH) by the anterior pituitary gland. ACTH in turn initiates the secretion of glucocorticoids (GC) by the adrenal glands [11][12]. Since CRF can be produced in the central nervous system (CNS), but also in the periphery, it is crucial for the coordination of

some physiological systems [13]. Indeed, CRF modulates the stress-induced sympathetic response and is important for the central and peripheral release of norepinephrine (NE) during stress events [14]. This is important to link physiological and behavioral changes and the perception of stress.

Interestingly, in chronic stress situations, a sustained increase in the excitability of the adrenal-medullary axis and the HPA is thought to result in increased NE synthesis [13]. The question arises as to whether the loss of GC self-regulation in the PVH and pituitary gland is of crucial importance in impaired stress management. The loss of GC self-regulation can be explained by the interruption of negative GC feedback and the associated persistent activation and maintenance of elevated systemic GC levels. Due to the higher availability of these hormones, brain structures such as the amygdala and LC enhance the activation of the HPA axis and promote changes in behavior and normal physiology [15][16][17]. Persistently elevated systemic GC levels can trigger immunosuppression and promote the development of autoimmune diseases and mood disorders as well [18].

In this context, chronic unpredictable mild stress (CUMS) should be mentioned. This is an established model that describes mood disorders and stress-induced plasticity of the brain, which are psychological and physical stressors and are caused by a lack of adaptability to various stressful stimuli that are similar to everyday life stressors [19][20]. In this regard, the role of NE release and loss of HPA self-regulation is under discussion [21]. Interestingly, a recent report [22] was able to highlight that TTS patients in different disease phases exhibited the presence of many validated biological and psychological markers of chronic stress as defined in the Trier Social Stress Test (TSST) [23] using blood biosamples from TTS patients: the authors consistently showed the presence of elevated IL-6, TNF-α, NFkB, blood cortisol, DHEA, aldosterone, adrenaline, noradrenaline and dopamine levels; therefore, chronic psychosocial stress as an underlying factor fueling TTS development needs to be acknowledged [24].

2. Pathophysiology (Physical and Emotional Triggers)

It is currently believed that TTS is primarily caused by physical and emotional triggers, but psychological and psychosocial stress factors may play a greater role than previously thought. The most important risk factors currently associated with TTS are discussed below.

3. Triggers

There is widespread agreement that a major feature of the development of TTS is associated with a stressful event. The most common reason preceding such an event is an emotional or physical trigger. According to some research, physical triggers are more common than emotional stressors, which may also have gender-specific aspects. For example, men seem to be more likely to respond to physical events, whereas women are more likely to be affected by emotional events [25]. Psychological and psychosocial stressors must be identified in this context. Currently, very little is known about the living conditions of patients with TTS. Wallström et al. [24] studied postmenopausal women who were burdened by psychological and psychosocial stress. The patients reported that they felt burdened by responsibility, injustice, and uncertainty long before the onset of Takotsubo syndrome. This long-term stress wore down the respondents' defenses to such an extent that even the smallest stressors threw them off balance. The results indicate that the social structure of gender can also contribute to the respondents' condition. These factors may be reflected in the high number of female respondents. By separating the number of cases of TTS patients by gender, the significant difference in the prevalence of TTS between women and men may also be due to the social position and role of women in some countries and cultures. These triggers do not necessarily occur individually, but can also occur as a combination of triggers (e.g., a panic attack or an emotional event following surgery or an accident).

4. Emotional Stressors

Emotion is a broad term that refers not only to traumatic emotions, i.e., feelings that arise from traumatic events, interpersonal conflicts, anxiety, fear and anger, earthquakes, or floods [26][27][28][29], but also encompasses positive emotions. Examples include weddings, surprises, and job offers [30]. All of these diverse emotional stressors may be considered triggers for TTS.

As far as stressors are concerned, it is probably not the type of emotion that is decisive, but the harshness of a single event or the combination of several emotions that are insignificant in themselves.

5. Physical Stressors

In addition to emotional stressors, physical stressors play an equally important role in the development of TTS. The term physical stressors includes almost any exogenous stress-inducing event. Thus, it includes extremely strenuous activities, medical illnesses (e.g., surgeries [31], traumatic injuries, radiotherapy [32], sepsis [33], or pregnancy [34], to name a few), substance abuse, and nervous system disorders. More specifically, conditions such as head trauma [35], stroke [31], seizures [36], and intracerebral hemorrhage [37] are mainly associated with the onset of TTS.

6. Gender Differences in Takotsubo Syndrome

According to various reports, the severity of TTS is often higher in men than in women. This is in contrast to the prevalence of the disease. Here, women, especially post-menopausal women, are much more frequently affected by TTS [38].

Considering the proportion of gender differences in the USA, Europe, and Japan, although there are varying reports on the proportion of males with TTS, females are predominantly affected by TTS. As TTS is a relatively rare disease, data are currently only being obtained from the US National Inpatient Sample registry [39], The International Takotsubo Registry [25], the Tokyo Cardiovascular Care Unit [38], and the Cardiovascular Research Consortium-8 Universities: CIRC-8U [40]. In fact, the Tokyo Cardiovascular Care Unit claims that prior physical stress is more common in male (50%) than in female (31.3%) patients. In contrast, female patients are more susceptible to emotional stress (male: 19.0% vs. female: 31.0% [38]). According to reports from the International Takotsubo Registry [25], 29.2% of females and about 14.5% of males developed the disease due to emotional stress, whereas 34.3% of females and 50.8% of males developed TTS through physical stress. This is very similar to the Japanese reports [40]. From these reports, it can be assumed that men respond primarily to physical stressors, whereas women tend to respond more to emotional stressors. This is visualized in **Table 1**, which summarizes the data from the abovementioned reports and compares them on a gender-specific basis.

Table 1. Systematic Overview of TTS Trigger Factors on a Gender-Specific Basis.

Country	Registry	Study Period	Age		Preceding Stress						Reference
					Emotional Stress		Physical Stress		Absence of Stress		
			Female	Male	Female [%]	Male [%]	Female [%]	Male [%]	Female [%]	Male [%]	
USA	NI Sample	2009–2010	66.2	59.2	-	-	-	-	-	-	[39]
USA/Europe	Inter TAK Registry	1998–2014	66.8	62.9	29.2	14.5	34.3	50.8	28.8	25.7	[25]
Japan	Tokyo CCU Network	2010–2012	76	72	31.0	19.0	31.3	50.0	37.7	31.0	[38]
Japan	CIRC-8U	1997–2014	71.5	71.8	26.0	10.0	46.0	64.0	28.0	26.0	[40]

Although the pathophysiology of TTS is poorly understood, TTS is primarily explained by stress responses, as previously pointed out. This may be due to differences in stress response between the sexes. Interestingly, most patients are postmenopausal women. With regard to their propensity to emotional stress as a trigger for TTS, the effects of estrogen concentration may have a greater impact than previously thought, which requires further investigation.

It is assumed that women show stronger immune responses against foreign and self-antigens. Furthermore, women show a higher prevalence of autoimmune diseases than men. An important role in the activity of immune cells is due to the different attribution to sex hormones between men and women [41][42]. In experimental rat models, the Cidlowski group was able to show that males and females show a difference in the prevalence of many major diseases that are attributable to inflammatory components. Interestingly, a link between inflammatory diseases and the sexually dimorphic effects of glucocorticoids may be important for the sex-specific differences in prevalence. Based on the outcome of these studies, the anti-inflammatory effects of *glucocorticoid receptors (GR)* appear to be more effective in men, whereas a lack of *GR* may promote certain diseases in women. This has been documented in vivo in the liver in a sepsis model of

systemic inflammation [43]. This indicates that a primary mechanism in homeostatic female mice ensures a faster response to inflammatory stimuli and thus causes a stronger expression of the most common proinflammatory genes.

In addition to emotional stress, behavioral stress reactions, psychological stress, and estrogen concentration can also be an important trigger in postmenopausal women. Studies have shown that there are significant differences between pre- and postmenopausal women in their reactions to psychological stress. Importantly, estrogen appears to attenuate the effect of stress-induced reactions. This means that in TTS, the stress response could be exacerbated as there is an imbalance in androgen/estrogen levels [44].

In addition, the dexamethasone/corticotropin-releasing hormone (Dex-CRH) test indicates, that the negative feedback of the HPA axis is altered in older women. This is shown by studies of psychological and endocrine responses to psychosocial stress and Dex-CRH in healthy postmenopausal women and young controls. In addition, the current data suggest that estradiol supplementation appears to modulate HPA feedback sensitivity in humans [45].

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