ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

REVIEW ARTICLE

A narrative review on gender disparities in the pathogenesis and pathophysiology of Takotsubo syndrome: Implications for novel approaches to treatment?

Carola Y. Förster[1]* and Martin J. Herrmann[2]

[1]Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, Würzburg University, Würzburg, Germany

[2]Center of Mental Health, Department of Psychiatry and Psychotherapy, University Hospital Würzburg, Würzburg, Germany

Abstract

Takotsubo syndrome is a type of cardiomyopathy characterized by transient and reversible left ventricular wall motion abnormalities within the ventricle. Depending on the severity of the injury, recovery can occur within a few hours or weeks. According to studies, older people are more likely to be affected by it, and the prevalence is particularly high among postmenopausal women. Stress factors, both physical and emotional, are widely discussed and generally recognized as triggers. The hypothalamic-pituitary-adrenal axis and its glucocorticoid-dependent negative feedback also play important roles in the resulting gender-specific immune response. Transcutaneous vagus nerve stimulation is proposed as a potential novel personalized therapeutic strategy in light of the gender disparities in autonomous nervous system activity and inflammatory response. Considering the modifiable risks involved in this pathology, such as stress which affects the heart and psychology, a strong emphasis should be placed on preventive medicine. In this paper, we propose the use of non-invasive (transcutaneous) vagus nerve stimulation, as a means of dampening sympathetic overdrive with negligible side effects.

Keywords: Takotsubo syndrome; Heart-brain; Inflammation; Gender; Central autonomic network; Stress

***Corresponding author:**
Carola Y. Förster
(foerster_c@ukw.de)

Citation: Förster CY, Herrmann MJ. A narrative review on gender disparities in pathogenesis and pathophysiology of Takotsubo syndrome: Implications for novel approaches to treatment? *INNOSC Theranostics and Pharmacological Sciences.* 2024;7(4):3142. doi: 10.36922/itps.3142

Received: March 11, 2024

Accepted: May 30, 2024

Published Online: September 19, 2024

Copyright: © 2024 This is an Open-Access article distributed under the terms of the Creative Commons AttributionNoncommercial License, permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction: the heart–brain axis

Cardiovascular system regulation is a part of the modulation of the cortical structure throughout the entire body. Although little is known about the mechanism of the "heart-brain axis," various cardiac and neurological diseases have been implicated as being influenced by one another. Insular cortex (IC), anterior cingulate gyrus, and amygdala comprise the cortical modulation network. The central autonomic nervous system (CAN) is regulated by this network, for example, in response to physical stimuli or emotional stressors like excitement, sadness, or anxiety. Functionally, the IC can be separated into the left insula, which is characterized by the parasympathetic tone and causes the heart rate to drop and the depressor responses to rise, and the right insula,

which is linked to sympathetic dominance and causes the heart rate to rise and pressor responses to rise.[1,2] Along with its reciprocal connections to other brain regions such as the limbic system, the IC is also linked to autonomic, sensory, and motor functions. In a series of studies investigating the functional neuroanatomy of sustained fear, defined as a situation of unpredictable threat over a period of time, the IC was co-activated together with the bed nucleus of the stria terminalis, anterior and posterior cingulate cortex, and the periaqueductal gray in healthy controls[3] as well as anxiety disorder patients.[4,5] According to our current understanding about the cortical modulation network, sympathovagal balance is essential for homeostasis and involves major portions of the IC. An imbalance resulting from a damaged IC affects the cardiovascular system, promoting the development of Takotsubo syndrome (TTS). A middle cerebral artery hemorrhage stroke, sexual hormones such as estrogen or emotional processing are some of the various factors that can cause an interruption of the IC.

Different brain nuclei are known to be activated in response to both physical and psychological stressors. Actually, the neuroendocrine and autonomic nervous systems (CAN) are primarily activated, which results in alterations in behavior.[6] Research utilizing brain functional magnetic resonance imaging to track brain functional connectivity during resting states revealed hypoconnectivity of limbic and central brain regions' parasympathetic and sympathetic associated subnetworks in TTS patients when compared to group controls.[7]

Stress becomes a deleterious factor, in the case of compromised of self-regulation, subjecting the body more susceptible to immune system disease, psychiatric disorder, and cardiovascular disease.[8,9] The paraventricular nucleus of the hypothalamus (PVH), amygdala nuclei, septal-hippocampal complex, parabrachial and raphe nuclei, prefrontal and cingulate cortexes, and locus coeruleus (LC) all play significant roles in the stress response. The hypothalamic-pituitary-adrenal (HPA) axis is stimulated by the signals that follow. The anterior pituitary gland releases adrenocorticotropin hormone (ACTH) in response to the release of the corticotropin-releasing factor (CRF), which is triggered by the PVH in the signaling chain. The adrenal glands then begin secreting glucocorticoid (GC) as a result of ACTH.[10,11] For the coordination of certain physiological systems, CRF is essential because it can be produced both in the peripheral and central nervous systems (CNS). In fact, during stressful situations, CRF plays a crucial role in regulating the sympathetic response brought on by stress and in the peripheral and central release of norepinephrine (NE). It is crucial to note the connection of the alterations in behavior and physiology with the levels of stress experienced. Of note, increased NE synthesis is believed to occur in chronic stress situations when there is a sustained increase in the excitability of the adrenal-medullary axis and the HPA.[12] The issue of whether decreased GC self-regulation in the pituitary and PVH is a major factor in poor stress management emerges. The disruption of negative GC feedback and the resulting prolonged activation and maintenance of elevated systemic GC levels account for the loss of GC self-regulation. The increased availability of these hormones causes alterations in behavior and normal physiology, as well as enhanced activation of the HPA axis in brain structures such as the LC and amygdala.[13-15] Prolonged elevation of systemic GC levels can lead to immunosuppression, as well as facilitate the onset of autoimmune diseases and mood disorders.[16]

In consideration of the above, it is appropriate to discuss the condition of chronic unpredictable mild stress (CUMS). This well-established model explains mood disorders and stress-induced brain plasticity, which are psychological and physical stressors brought on by a brain's inability to adapt to a variety of stressful stimuli that are comparable to stressors encountered in daily life.[17,18] In this context, the connection between loss of HPA self-regulation and NE release is discussed.[19] Using blood samples from TTS patients, a recent study1 was able to demonstrate that patients in various stages of the disease showed several validated biological and psychological indicators of chronic stress, as defined by the trier social stress test.[20] The authors consistently demonstrated the presence of elevated levels of interleukin 6, tumor necrosis factor-α, nuclear factor "kappa-light-chain-enhancer" of activated B-cells, blood cortisol, dehydroepiandrosterone, aldosterone, adrenaline, NE, and dopamine. As a result, chronic psychosocial stress as an underlying factor driving the development of TTS must be recognized.[21]

2. Pathophysiology involving physical and emotional triggers

TTS is believed to be primarily caused by physical and emotional triggers, but psychological and psychosocial stress factors may have a greater influence than previously thought. TTS is associated with several major risk factors.

2.1. TTS triggers

Almost universally, TTS is associated with stress as a major feature of its development. In most cases, an emotional or physical trigger precedes such an event. There is some evidence to suggest that emotional triggers are more prevalent than physical stressors, with the prevalence distribution of these triggers showing gender-specific characteristics. In general, men seem to be more likely to respond to physical events, whereas women are more likely

to be affected by emotional events.[22] By breaking down the total number of TTS cases by gender, it is possible to determine that the notable variation in TTS prevalence between men and women is also a result of the social standing and roles that women play in various nations and cultures. These triggers can happen alone or in combination; for example, a panic attack or an emotional event that follows surgery or an accident can trigger anxiety.

2.1.1. Stressors on an emotional level

Anxiety, fear, anger, earthquakes, floods, interpersonal conflicts, and traumatic experiences are just a few examples of the wide range of emotions and situations that can be described as "stressors".[23-26] An important aspect of this process is the identification of psychological and psychosocial stressors. There is very little information about the living conditions of patients with TTS at the moment. The study by Wallstrom *et al.*[21] examined the psychological and psychosocial stress experienced by postmenopausal women. Many of the patients reported that they felt burdened by responsibility, injustice, and uncertainty long before the onset of TTS. The respondents' defenses were so weakened by this prolonged stress that even minor stressors could cause them to lose their equilibrium. The findings suggest that the respondents' circumstances may also be influenced by the gender-based social structure. The large proportion of female respondents could be a reflection of these factors.

Furthermore, it should be noted that even situations associated with pleasant emotions[27] such as weddings, surprise parties, and employment offers can serve as stressors.[28] These various emotional stressors could all be regarded as TTS triggers. When it comes to stressors, the severity of a single incident or the confluence of multiple relatively insignificant emotions likely matters more than the specific type of emotion.

2.1.2. Stressors on a physical level

The development of TTS is significantly influenced not only by emotional but also by physical stress factors. These physical stressors therefore include incredibly strenuous activities and illnesses, such as surgery,[29] traumatic injuries, radiotherapy,[30] sepsis,[31] or even pregnancy,[32] drug addiction, and disorders of the neurological system. However, the occurrence of TTS has so far been primarily associated with conditions like intracerebral hemorrhage,[33] seizures,[34] stroke,[29] and head trauma.[35]

Moreover, the following two conditions could be linked to TTS:

(i) An adrenal gland's enterochromaffin cells give rise to pheochromocytoma, a neuroendocrine tumor. It has been proposed that catecholamines are released as a result of this illness. The elevated catecholamine level is thought to be the cause of the left ventricular dysfunction, electrocardiogram abnormalities, band necrosis, and hypercontraction of sarcomas that are indistinguishable from TTS.[36]

(ii) Coronary artery disease (CAD), which has a prevalence of 10 – 29%, is frequently linked to TTS. According to some theories, CAD and TTS coexist or CAD even act as a trigger for the development of TTS.[37-39]

3. Gender disparities in TTS

When comparing the gender distribution of TTS cases in the USA, Europe, and Japan, it is important to note that while the percentage of male cases varies from study to study, TTS affects women more often than men.[40] Of note, TTS affects particularly postmenopausal women.[40]

This is in opposition to how the illness manifests itself: accumulating evidence points out that men are frequently more severely affected by TTS than women. Taking into account the gender disparities in the USA, Europe, and Japan, recent reports suggest that women tend to respond more to emotional stressors, while men respond primarily to physical stressors (Figure 1).

Since TTS is a relatively uncommon disease, the only sources of data available at this time are the Tokyo Cardiovascular Care Unit,[40] the International Takotsubo Registry,[22] the US National Inpatient Sample Registry,[41] and the Cardiovascular Research Consortium-8 Universities.[42] Actually, according to the Tokyo Cardiovascular Care Unit, male patients (50%) are more likely than female patients (31.3%) to have experienced prior physical stress. On the other hand, female patients experience emotional stress at a higher rate than male patients (19.0% vs. 31.0%).[40] In detail, according to reports from the International Takotsubo Registry, 29.2% of females and about 14.5%

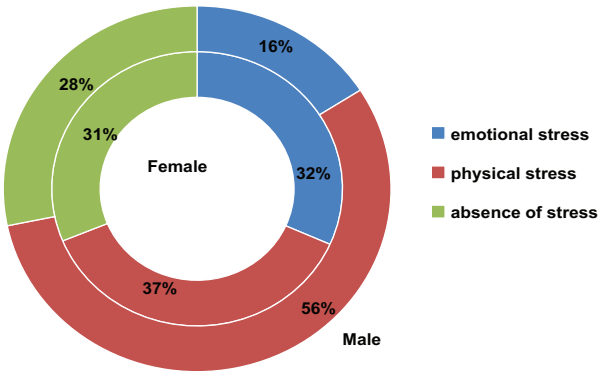


Figure 1. Prevalence of emotion and physical stressors leading to Takotsubo syndrome among female (inner circle) and male individuals (outer circle)

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.[42] These reports suggest that women tend to respond more to emotional stressors, while men respond primarily to physical stressors.

As previously mentioned, TTS is mainly explained by stress responses, even though the pathophysiology of TTS is poorly understood. The sexes' varying reactions to stress could be the cause of this. Remarkably, postmenopausal women make up the majority of patients. The effects of estrogen concentration may be more significant than previously believed in relation to their susceptibility to emotional stress as a trigger for TTS, which calls for more research. Women are thought to have stronger immune responses to both self-antigens and foreign invaders. In addition, autoimmune diseases are more common in women than in men. The distinct role that men and women attribute to sex hormones plays an important part in immune cell activity.[43,44] Through the use of experimental rat models, the Cidlowski group demonstrated that there is a gender difference in the prevalence of numerous major diseases that have an inflammatory component. Interestingly, the sex-specific variations in prevalence may be related to a relationship between inflammatory diseases and the sexually dimorphic effects of GC. These findings suggest that while a lack of GC receptors (GR) may contribute to certain diseases in women, GR's anti-inflammatory effects seem to be more potent in men. This has been observed *in vivo* in the liver in a systemic inflammatory sepsis model.[45] This suggests that in homeostatic female mice, a primary mechanism guarantees a quicker reaction to inflammatory stimuli, which in turn leads to a stronger expression of the most prevalent proinflammatory genes.

Apart from emotional stress, postmenopausal women may also be significantly triggered by behavioral stress reactions, psychological stress, and changes in estrogen concentration. Research has demonstrated that premenopausal and postmenopausal women react to psychological stress in quite different ways. Crucially, it seems that estrogen reduces the impact of reactions instigated by stress. This indicates that an imbalance in the levels of androgen and estrogen in TTS could exacerbate the stress response.[46] Furthermore, the dexamethasone/corticotropin-releasing hormone (Dex-CRH) test shows that older women have altered HPA axis negative feedback, as demonstrated by studies on hormonal and psychological reactions to psychosocial stress and Dex-CRH in young, healthy controls and postmenopausal women in good health.[46] Furthermore, the available evidence indicates that supplementing with estradiol seems to alter human HPA feedback sensitivity.[47]

Finally, the impact of catecholamine excess on the different ballooning patterns that are characteristic of TTS has not been fully explained, although there is now substantial evidence that sympathetic activation plays a central role in TTS. Thus far, several rational recommendations have been put forth. For instance, it has been proposed that myocardial damage could result from a catecholamine surge. Various mechanisms that lead to increased cardiac work can be mentioned in this context, including microvascular coronary vasoconstriction and damage mediated by adrenoreceptors.[48]

4. Discussion

4.1. Role of sex steroids in modulation of behavioral and psychological aspects

Stress is recognized to have an impact on the endocrine, behavioral, and molecular responses of stress systems. The implications of rats' sex differences for stress response have been reported, indicating that stress had a distinct sexual dimorphic effect on the behavioral, endocrine, and molecular response of the stress systems in the rats' hypothalamus. Remarkably, this effect is also observed in human data on stress and depression.[49] Interesting findings presented by Dumas *et al.*'s research demonstrate how age and estrogen status affect older women's stress,[50] indicating that estradiol plays a significant role in regulating the emotional response to stressful situations.

Another fascinating study from the field of psychology revealed that older women have altered negative feedback of the HPA axis using the Dex-CRH test.[47] After comparing the behavioral stress responses of premenopausal and postmenopausal women with the effects of estrogen, they were able to draw the following conclusion: premenopausal and postmenopausal women differ significantly in how they respond to psychological stress.[46] The higher risk of cardiovascular disease in women who have gone through menopause may be partially explained by this lack of adaptation. It seems that estrogen reduces the reaction brought on by stress. The TTS framework discussed in the present review may heighten this circumstance, which shows a clear androgen/estrogen imbalance and a strong inflammatory background.

4.2. Possible female sex steroid-mediated modulation of functional cerebral asymmetry

Studies on the gender-specific differences in sympathovagal regulation and functional cerebral asymmetry imply that the female pattern of dominance is characterized by the left hemisphere, which is believed to have parasympathetic predominance, whereas the male pattern indicates dominance of the right hemisphere, which is believed to have sympathetic

predominance. This theory is in line with the concept of decreased magnitude of inter-hemispheric cortical lateralization in premenopausal women compared to men and postmenopausal women. Decrease of endogenous female sex steroid levels in postmenopausal women leads to reduced influence of estrogens on the left hemisphere, which is believed to have parasympathetic predominance. This results in sympathovagal imbalance, increasing sympathetic system activity in postmenopausal women, rendering postmenopausal women more susceptible to sympathetically mediated syndromes such as TTS.

4.3. Role of GCs in modulation of stress response

GCs are hormones produced in response to stress to control inflammatory and immunosuppressive responses as well as the growth and function of CNS, intermediate metabolism, vascular tone, and – most importantly – the process of programmed cell death.[45] The GR acts as a mediator for their action. Hence, GR expression is proposed as a stress-related surrogate marker for a diverse range of stress situations, including post-traumatic stress disorder and chronic stress.[51]

Of note, stress can have negative effects and cause diseases in people who exhibit poor self-regulation, such as increased inflammation:[52] it was convincingly presented that male rats exposed to CUMS showed elevated expression of GR in response to CUMS. Malta *et al.*'s study[19] emphasizes that GR is involved in regulating CUMS responses, which are dependent on GC and NE signaling in male rats. The authors provide specific evidence that the 14-day treatment of CUMS to male rats resulted in a persistent hyperactivity of the HPA axis, as demonstrated by an increase in plasmatic corticosterone and hypertrophy of the adrenal glands. These effects were dependent on the increased release of GCs and NE that were generated during each stress session. GR protein levels were shown to be elevated in key brain regions linked to HPA regulation and behavior after exposure to CUMS.[53] In a recent study, these findings were expanded by measuring blood hormone and hormone receptor levels of TTS female patients.[1] While more research is required to investigate additional CUMS-related brain GR expression patterns in TTS patients or animal models, these findings clearly indicated that TTS-prone postmenopausal females have a higher corticosteroid response as compared to healthy individuals, providing a molecular perspective on the gender disparity in stress response.

4.4. Role of GCs and gender aspects in modulation of inflammation

In addition to physical and emotional triggers, female gender, and age-related deficiency of female sex hormones, inflammation emerges as a pathophysiologic factor. Stronger immune responses to foreign and self-antigens are observed in women than in men, providing an explanation regarding the higher prevalence of most autoimmune diseases among women.[54] There have been some investigations suggesting that CUMS leads to the development of GC receptor resistance, which results in its upregulation and failure to inhibit the inflammatory response.

Notably, it has been demonstrated that the sexually dimorphic effects of GC are linked to inflammatory diseases that differ in frequency between genders. With the use of experimental rat models and gene editing techniques, the Cidlowski group demonstrated that the underlying inflammatory components seem to play a crucial role in the recognized gender difference of the prevalence of many major diseases. They emphasized that inflammation is a reflection of the balance between pro- and anti-inflammatory signals and looked into the responses that are specific to gender. They discovered sex-specific GC-regulated genes in a number of canonical pathways linked to the development and susceptibility to pertinent diseases with prevalence differences between genders. Specifically, they opine that either the anti-inflammatory properties of GC are more potent in men or their absence may encourage the onset of specific illnesses in women.[45] In a different article,[55] the same group described a priming mechanism in female mice in homeostatic condition that causes them to respond to an inflammatory stimulus more quickly. This mechanism causes the female mice to express more of the proinflammatory genes that are most frequently regulated. This idea is supported by research from other groups, which recently suggested that CUMS might lead to the development of GR upregulation and resistance impairing the suppression of inflammation.[1]

5. Conclusion

Chronic unpredicted mild stress is reportedly to exert a potentially bigger influence on TTS development than previously thought.[53] Specifically, it pertains to the relationship between the aforementioned reduction in GR and beta-adrenergic receptor sensitivity and persistent psychological stress. GC resistance may cause the HPA axis to be dysregulated and GR to be overexpressed. Increased GC levels and long-term immunosuppression with elevated levels of peripheral proinflammatory markers may be caused by dysregulated negative feedback.[54] As a result, the parasympathetic nervous system becomes less active and the sympathetic nervous system becomes more active.

The HPA axis's GC negative feedback appears disrupted in TTS, causing the GCs to maintain at elevated levels in the system and sustaining their activation in a gender-

disparate manner. Long-term stress might lead to the development of GR resistance, which raises GR levels and impairs the suppression of inflammation. Consequently, a persistent rise in the systemic concentrations of GCs can lead to immunosuppression, metabolic diseases, autoimmune diseases, and mood disorders due to their pleiotropic action, which appears to be more prevalent in women.

In every area of medicine, there should be a strong emphasis on preventive medicine. This is especially true when there are modifiable risk factors involved, such as stress, which affects the heart and psychology. The non-invasive (transcutaneous) vagus nerve stimulation (VNS) therapy, which is beneficial for parasympathetic activity and plays a significant part in lowering chronic inflammation, has high therapeutic value for TTS, according to research by Frank *et al.*[54] It should be highlighted that gender differences must be taken into account with regard to VNS.[56]

Acknowledgments

None.

Funding

This work is supported by research grant DFG FO 315/5-1 awarded to C.Y.F.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Carola Y. Förster
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Nagai M, Shityakov S, Smetak M, *et al.* Blood biomarkers in Takotsubo syndrome point to an emerging role for inflammaging in endothelial pathophysiology. *Biomolecules.* 2023;13:995.

   doi: 10.3390/biom13060995

2. Ittner C, Burek M, Stork S, Nagai M, Forster CY. Increased catecholamine levels and inflammatory mediators alter barrier properties of brain microvascular endothelial cells *in vitro*. *Front Cardiovasc Med.* 2020;7:73.

   doi: 10.3389/fcvm.2020.00073

3. Herrmann MJ, Boehme S, Becker MP, *et al.* Phasic and sustained brain responses in the amygdala and the bed nucleus of the stria terminalis during threat anticipation. *Hum Brain Mapp.* 2016;37:1091-1102.

   doi: 10.1002/hbm.23088

4. Brinkmann L, Buff C, Feldker K, *et al.* Distinct phasic and sustained brain responses and connectivity of amygdala and bed nucleus of the stria terminalis during threat anticipation in panic disorder. *Psychol Med.* 2017;47:2675-2688.

   doi: 10.1017/S0033291717001192

5. Brinkmann L, Buff C, Neumeister P, *et al.* Dissociation between amygdala and bed nucleus of the stria terminalis during threat anticipation in female post-traumatic stress disorder patients. *Hum Brain Mapp.* 2017;38:2190-2205.

   doi: 10.1002/hbm.23513

6. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci.* 2009;10:397-409.

   doi: 10.1038/nrn2647

7. Templin C, Hänggi J, Klein C, *et al.* Altered limbic and autonomic processing supports brain-heart axis in Takotsubo syndrome. *Eur Heart J.* 2019;40:1183-1187.

   doi: 10.1093/eurheartj/ehz068

8. Béjean S, Sultan-Taïeb H. Modeling the economic burden of diseases imputable to stress at work. *Eur J Health Econ.* 2005;6:16-23.

   doi: 10.1007/s10198-004-0251-4

9. De Kloet ER, Joëls M, Holsboer F. Stress and the brain: From adaptation to disease. *Nat Rev Neurosci.* 2005;6:463-475.

   doi: 10.1038/nrn1683

10. Romier C, Bernassau JM, Cambillau C, Darbon H. Solution structure of human corticotropin releasing factor by 1H NMR and distance geometry with restrained molecular dynamics. *Protein Eng.* 1993;6:149-156.

    doi: 10.1093/protein/6.2.149

11. Trainer PJ, Faria M, Newell-Price J, *et al.* A comparison of the effects of human and ovine corticotropin-releasing hormone on the pituitary-adrenal axis. *J Clin Endocrinol Metab.* 1995;80:412-417.

    doi: 10.1210/jcem.80.2.7852498

12. Henckens MJA, Deussing JM, Chen A. Region-specific roles of the corticotropin-releasing factor-urocortin system in stress. *Nat Rev Neurosci.* 2016;17:636-651.

    doi: 10.1038/nrn.2016.94

13. Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology

of stress. *Eur J Pharmacol.* 2003;463:235-272.

doi: 10.1016/s0014-2999(03)01285-8

14. McEwen BS, Sapolsky RM. Stress and cognitive function. *Curr Opin Neurobiol.* 1995;5:205-216.

doi: 10.1016/0959-4388(95)80028-x

15. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med.* 1998;338:171-179.

doi: 10.1056/nejm199801153380307

16. De Kloet ER, Derijk R. Signaling pathways in brain involved in predisposition and pathogenesis of stress-related disease: Genetic and kinetic factors affecting the MR/GR balance. *Ann N Y Acad Sci.* 2004;1032:14-34.

doi: 10.1196/annals.1314.003

17. Joëls, M, Karst H, Alfarez D, *et al.* Effects of chronic stress on structure and cell function in rat hippocampus and hypothalamus. *Stress.* 2004;7:221-231.

doi: 10.1080/10253890500070005

18. Willner P. Chronic Mild Stress (CMS) revisited: Consistency and behavioural-neurobiological concordance in the effects of CMS. *Neuropsychobiology.* 2005;52:90-110.

doi: 10.1159/000087097

19. Malta MB, Martins J, Novaes LS, *et al.* Norepinephrine and glucocorticoids modulate chronic unpredictable stress-induced increase in the type 2 CRF and glucocorticoid receptors in brain structures related to the HPA axis activation. *Mol Neurobiol.* 2021;58:4871-4885.

doi: 10.1007/s12035-021-02470-2

20. Allen AP, Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Biological and psychological markers of stress in humans: Focus on the trier social stress test. *Neurosci Biobehav Rev.* 2014;38:94-124.

doi: 10.1016/j.neubiorev.2013.11.005

21. Wallstrom S, Ulin K, Maatta S, Omerovic E, Ekman I. Impact of long-term stress in Takotsubo syndrome: Experience of patients. *Eur J Cardiovasc Nurs.* 2016;15:522-528.

doi: 10.1177/1474515115618568

22. Templin C, Ghadri JR, Diekmann J, *et al.* Clinical features and outcomes of takotsubo (Stress) cardiomyopathy. *N Engl J Med.* 2015;373:929-938.

doi: 10.1056/NEJMoa1406761

23. Chan C, Elliott J, Troughton R, *et al.* Acute myocardial infarction and stress cardiomyopathy following the Christchurch earthquakes. *PLoS One.* 2013;8:e68504.

doi: 10.1371/journal.pone.0068504

24. Sharkey SW, Windenburg DC, Lesser JR, *et al.* Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J Am Coll Cardiol.* 2010;55:333-341.

doi: 10.1016/j.jacc.2009.08.057

25. Tagawa M, Nakamura Y, Ishiguro M, *et al.* Transient left ventricular apical ballooning developing after the Central Niigata prefecture earthquake: Two case reports. *J Cardiol.* 2006;48:153-158.

26. 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.

doi: 10.1093/eurheartj/ehy076

27. Nagai M, Kobayashi Y, Kobatake H, *et al.* Happy heart syndrome: A case of Takotsubo syndrome with left internal carotid artery occlusion. *Clin Auton Res.* 2020;30:347-350.

doi: 10.1007/s10286-020-00696-z

28. 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.

doi: 10.1093/eurheartj/ehv757

29. Scheitz JF, Mochmann HC, Witzenbichler B, Fiebach JB, Audebert HJ, Nolte CH. Takotsubo cardiomyopathy following ischemic stroke: A cause of troponin elevation. *J Neurol.* 2012;259:188-190.

doi: 10.1007/s00415-011-6139-1

30. Modi S, Baig W. Radiotherapy-induced Tako-tsubo cardiomyopathy. *Clin Oncol* (*R Coll Radiol*). 2009;21:361-362.

doi: 10.1016/j.clon.2009.01.005

31. Y-Hassan S, Settergren M, Henareh L. Sepsis-induced myocardial depression and takotsubo syndrome. *Acute Card Care.* 2014;16:102-109.

doi: 10.3109/17482941.2014.920089

32. Brezina P, Isler CM. Takotsubo cardiomyopathy in pregnancy. *Obstet Gynecol.* 2008;112:450-452.

doi: 10.1097/AOG.0b013e3181662cfe

33. Hjalmarsson C, Oras J, Redfors B. A case of intracerebral hemorrhage and apical ballooning: An important differential diagnosis in ST-segment elevation. *Int J Cardiol.* 2015;186:90-92.

doi: 10.1016/j.ijcard.2015.03.187

34. Stöllberger C, Wegner C, Finsterer J. Seizure-associated Takotsubo cardiomyopathy. *Epilepsia.* 2011;52:e160-e167.

doi: 10.1111/j.1528-1167.2011.03185.x

35. Riera M, Llompart-Pou JA, Carrillo A, Blanco C. Head injury and inverted Takotsubo cardiomyopathy. *J Trauma.* 2010;68:E13-E15.

doi: 10.1097/TA.0b013e3181469d5b

36. Samuels MA. The brain-heart connection. *Circulation.* 2007;116:77-84.

doi: 10.1161/circulationaha.106.678995

37. Napp LC, Ghadri JR, Cammann VL, Bauersachs J, Templin C. Takotsubo cardiomyopathy: Completely simple but not so easy. *Int J Cardiol.* 2015;197:257-259.

doi: 10.1016/j.ijcard.2015.06.043

38. Redfors B, Råmunddal T, Shao Y, Omerovic E. Takotsubo triggered by acute myocardial infarction: A common but overlooked syndrome? *J Geriatr Cardiol.* 2014;11:171-173.

doi: 10.3969/j.issn.1671-5411.2014.02.001

39. Y-Hassan S, Böhm F. The causal link between spontaneous coronary artery dissection and takotsubo syndrome: A case presented with both conditions. *Int J Cardiol.* 2016;203:828-831.

doi: 10.1016/j.ijcard.2015.11.047

40. Murakami T, Yoshikawa T, Maekawa Y, *et al.* Gender differences in patients with takotsubo cardiomyopathy: Multi-center registry from Tokyo CCU network. *PLoS One.* 2015;10:e0136655.

doi: 10.1371/journal.pone.0136655

41. Krishnamoorthy P, Garg J, Sharma A, *et al.* Gender differences and predictors of mortality in Takotsubo cardiomyopathy: Analysis from the national inpatient sample 2009-2010 database. *Cardiology.* 2015;132:131-136.

doi: 10.1159/000430782

42. Yoshizawa M, Itoh T, Morino Y, *et al.* Gender differences in the circadian and seasonal variations in patients with Takotsubo syndrome: A multicenter registry at eight university hospitals in East Japan. *Intern Med.* 2021;60:2749-2755.

doi: 10.2169/internalmedicine.6910-20

43. 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.

doi: 10.1002/ejhf.424

44. Angelini P, Tobis JM. Is high-dose catecholamine administration in small animals an appropriate model for takotsubo syndrome? *Circ J.* 2015;79:897.

doi: 10.1253/circj.CJ-15-0099

45. Duma D, Collins JB, Chou JW, Cidlowski JA. Sexually dimorphic actions of glucocorticoids provide a link to inflammatory diseases with gender differences in prevalence. *Sci Signal.* 2010;3:ra74.

doi: 10.1126/scisignal.2001077

46. Lindheim SR, Legro RS, Bernstein L, *et al.* Behavioral stress responses in premenopausal and postmenopausal women and the effects of estrogen. *Am J Obstetr Gynecol.* 1992;167:1831-1836.

doi: 10.1016/0002-9378(92)91783-7

47. Kudielka BM, Schmidt-Reinwald AK, Hellhammer DH, Kirschbaum C. Psychological and endocrine responses to psychosocial stress and dexamethasone/corticotropin-releasing hormone in healthy postmenopausal women and young controls: The impact of age and a two-week estradiol treatment. *Neuroendocrinology.* 1999;70:422-430.

doi: 10.1159/000054504

48. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo syndrome. *Circulation.* 2017;135:2426-2441.

doi: 10.1161/circulationaha.116.027121

49. Lu J, Wu XY, Zhu QB, *et al.* Sex differences in the stress response in SD rats. *Behav Brain Res.* 2015;284:231-237.

doi: 10.1016/j.bbr.2015.02.009

50. Dumas JA, Albert KM, Naylor MR, Sites CK, Benkelfat C, Newhouse PA. The effects of age and estrogen on stress responsivity in older women. *Am J Geriatr Psychiatry.* 2012;20:734-743.

doi: 10.1097/JGP.0b013e31825c0a14

51. Gonzalez Ramirez C, Villavicencio Queijeiro A, Jiménez Morales S, *et al.* The NR3C1 gene expression is a potential surrogate biomarker for risk and diagnosis of posttraumatic stress disorder. *Psychiatry Res.* 2020;284:112797.

doi: 10.1016/j.psychres.2020.112797

52. Wirtz PH, von Känel R, Mohiyeddini C, *et al.* Low social support and poor emotional regulation are associated with increased stress hormone reactivity to mental stress in systemic hypertension. *J Clin Endocrinol Metabol.* 2006;91:3857-3865.

doi: 10.1210/jc.2005-2586

53. Li Y, Jiang W, Li ZZ, *et al.* Repetitive restraint stress changes spleen immune cell subsets through glucocorticoid receptor or β-adrenergic receptor in a stage dependent manner. *Biochem Biophys Res Commun.* 2018;495:1108-1114.

doi: 10.1016/j.bbrc.2017.11.148

54. Frank N, Herrmann MJ, Lauer M, Förster CY. Exploratory review of the Takotsubo syndrome and the possible role of the psychosocial stress response and inflammaging. *Biomolecules*. 2024;14:167.

doi: 10.3390/biom14020167

55. Quinn MA, Cidlowski JA. Endogenous hepatic glucocorticoid receptor signaling coordinates sex-biased inflammatory gene expression. *FASEB J.* 2016;30:971-982.

doi: 10.1096/fj.15-278309

56. Yaghouby F, Jang K, Hoang U, Asgari S, Vasudevan S. Sex differences in vagus nerve stimulation effects on rat cardiovascular and immune systems. *Front Neurosci.* 2020;14:560668.

doi: 10.3389/fnins.2020.560668