International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
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ARTICLE TITLE	BROKEN HEART SYNDROME (TAKOTSUBO CARDIOMYOPATHY) AND PSYCHOLOGICAL STRESS: A NARRATIVE REVIEW
DOI	https://doi.org/10.31435/ijitss.3(51).2026.6533
RECEIVED	30 May 2026
ACCEPTED	26 August 2026
PUBLISHED	31 August 2026
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BROKEN HEART SYNDROME (TAKOTSUBO CARDIOMYOPATHY) AND PSYCHOLOGICAL STRESS: A NARRATIVE REVIEW

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ABSTRACT

Background: Takotsubo cardiomyopathy (TTC), also known as takotsubo syndrome (TTS) or broken heart syndrome, is an acute reversible cardiac disorder characterized by transient left ventricular dysfunction that mimics acute myocardial infarction. First described in Japan in 1990, TTS is increasingly recognized as a model of psychosomatic cardiovascular disease. However, the mechanisms linking psychological stress with myocardial dysfunction remain incompletely understood.
Objectives: This narrative review summarizes current evidence on the relationship between psychological stress and the onset, clinical course, and prognosis of TTS, with emphasis on neuroendocrine and autonomic mechanisms.
Methods: A structured literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, covering publications from 1990 to 2025, including original research, reviews, meta-analyses, and guidelines addressing psychological stress, neuroendocrine pathways, and psychiatric comorbidities in TTS.
Results: Acute stress triggers a catecholamine surge two- to threefold higher than in myocardial infarction, causing sympathetic overstimulation and cardiomyocyte toxicity. Apical vulnerability reflects increased β2-receptor density, while hypothalamic-pituitary-adrenal (HPA) axis activation may enhance adrenergic sensitivity via cortisol. Anxiety and depression affect up to 56% and 48% of patients, respectively. Women, particularly postmenopausal, account for over 90% of cases and appear especially vulnerable due to estrogen-related alterations in sympathoadrenal regulation.
Conclusions: TTS represents a psychosomatic cardiovascular syndrome in which emotional stress manifests as acute cardiac dysfunction. Integrated psychocardiac management combining cardiac care, psychiatric assessment, and psychological support may improve outcomes and reduce recurrence risk.

KEYWORDS

Takotsubo Cardiomyopathy, Broken Heart Syndrome, Psychological Stress, Catecholamines, Hypothalamic-Pituitary-Adrenal Axis, Autonomic Nervous System, Anxiety, Depression, Psychocardiology, Sympathoadrenal Activation

CITATION

Sylwia Janczak, Maja Śmigielska, Agnieszka Nowosielska-Ogórek, Julia Strumińska-Szularz, Tymoteusz Węgrzyn. (2026). Broken Heart Syndrome (Takotsubo Cardiomyopathy) and Psychological Stress: A Narrative Review. *International Journal of Innovative Technologies in Social Science*. 3(51). doi: 10.31435/ijitss.3(51).2026.6533

1. Introduction

Takotsubo syndrome (TTS) is an acute, reversible syndrome characterized by transient left ventricular dysfunction in the absence of obstructive coronary artery disease. It was first described by Sato et al. in 1990 at Hiroshima City Hospital, Japan, and named after the characteristic apical ballooning of the left ventricle resembling the tako-tsubo, a Japanese octopus trap [1]. TTS accounts for approximately 1-3% of all cases presenting with suspected acute coronary syndrome [2].

The clinical presentation - acute chest pain, dyspnoea, ST-segment changes, and troponin elevation - is indistinguishable from ST-elevation myocardial infarction at initial assessment [3,4]. The diagnosis requires coronary angiography to exclude obstructive coronary artery disease and is confirmed by the characteristic wall motion abnormality on echocardiography or ventriculography. The InterTAK Diagnostic Criteria (2018) provide the most widely used diagnostic framework [3].

More than 90% of TTS cases occur in women, predominantly in the postmenopausal period (typical age 58-75 years) [2,5]. This predilection is attributed to estrogen deficiency, which increases adrenergic receptor density, impairs vascular protection, and heightens sympathoadrenal reactivity [6].

An identifiable trigger is present in the majority of cases. Emotional stressors - bereavement, interpersonal conflict, fear, or acute medical diagnoses - account for approximately 36% of cases in the InterTAK registry; physical triggers for a comparable proportion; and approximately 28% of episodes lack an identifiable precipitant [2]. Positive emotional events may also trigger TTS, a phenomenon termed "happy heart syndrome" [7].

The central pathophysiological mechanism involves a catecholamine surge: plasma epinephrine and norepinephrine concentrations in TTS patients are two- to threefold higher than in acute myocardial infarction [8]. This induces direct cardiomyocyte toxicity, microvascular spasm, and calcium overload. The apical predominance of dysfunction reflects the higher density of β2-adrenergic receptors at the ventricular apex [9].

Psychiatric comorbidities are substantially more prevalent in TTS than in acute myocardial infarction populations: anxiety disorders affect up to 56% and major depressive disorder up to 48% of TTS patients [12, 13]. These comorbidities are associated with higher recurrence risk, estimated at approximately 5% annually [2]. The mechanisms linking pre-existing psychopathology to TTS susceptibility and the direction of this relationship remain incompletely established.

Despite growing epidemiological characterization, a coherent psychobiological framework integrating autonomic, neuroendocrine, and psychiatric dimensions of TTS has not been systematically developed at the interface of cardiology and psychiatry. This review aims to synthesize current evidence on these mechanisms and to discuss implications for clinical management [10,11].

2. Materials and Methods

This study was conducted as a narrative review focusing on the relationship between Takotsubo syndrome (TTS), also known as Takotsubo cardiomyopathy (TTC) or broken heart syndrome, and psychological stress. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases. The search covered publications published between 1990 and 2025.

The following keywords and their combinations were used: "Takotsubo cardiomyopathy", "Takotsubo syndrome", "broken heart syndrome", "psychological stress", "emotional trigger", "catecholamines", "hypothalamic-pituitary-adrenal axis", “sympathoadrenal activation”, "autonomic nervous system", "anxiety", "depression", and "postmenopausal women".

Eligible publications included original research articles, systematic reviews, meta-analyses, clinical guidelines, consensus documents, registry-based studies, and case reports containing psychological, psychiatric, stress-related, or clinically relevant data on Takotsubo syndrome. Only studies involving adult populations and published in English were considered.

Studies focusing exclusively on physically triggered Takotsubo syndrome without any psychological, psychiatric, or stress-related component were excluded from the psychological synthesis. However, general clinical studies, consensus documents, and registry-based analyses were included when they provided relevant background information on the definition, diagnostic criteria, epidemiology, clinical presentation, pathophysiology, or outcomes of Takotsubo syndrome. Non-peer-reviewed publications, editorials, letters to the editor, and conference abstracts without full-text availability were excluded.

Due to the methodological heterogeneity of the included studies, a quantitative synthesis was not feasible. Therefore, findings were analysed using a narrative synthesis approach. The selected literature was organized into thematic categories addressing the definition and epidemiology of Takotsubo syndrome, pathophysiological mechanisms, psychological triggers, psychiatric comorbidities, and clinical implications. Particular attention was paid to studies investigating the interaction between emotional stress, neuroendocrine activation, and cardiovascular dysfunction in the development of Takotsubo syndrome.

3. Definition, Epidemiology, and Clinical Presentation

3.1 Definition and Diagnostic Criteria

Takotsubo syndrome (TTS), also known as Takotsubo cardiomyopathy (TTC), stress-induced cardiomyopathy, or broken heart syndrome, is an acute and usually reversible form of heart failure characterized by transient left ventricular systolic dysfunction that cannot be fully explained by obstructive coronary artery disease [10,12]. The condition was first described in Japan in 1990 by Dote and colleagues and derives its name from the resemblance of the affected left ventricle to a traditional Japanese octopus trap known as a “takotsubo” [10,12].

The diagnosis of TTS is currently based on the InterTAK Diagnostic Criteria proposed by the International Takotsubo Registry and incorporated into the 2018 International Expert Consensus Document. These criteria have largely replaced earlier diagnostic approaches, such as the Mayo Clinic Criteria, because they better reflect the heterogeneous clinical presentation of the syndrome [10]. Compared with the Mayo Clinic Criteria, the InterTAK criteria recognize that significant coronary artery disease may coexist with Takotsubo syndrome and therefore should not automatically exclude the diagnosis if the coronary lesions do not adequately explain the observed ventricular dysfunction [10].

According to the InterTAK criteria, the hallmark of TTS is transient left ventricular dysfunction presenting as hypokinesia, akinesia, or dyskinesia. The resulting wall-motion abnormalities typically extend beyond the territory supplied by a single coronary artery and may involve different ventricular regions [10]. Emotional stressors, physical stressors, or a combination of both are commonly identified before symptom onset; however, the absence of a recognizable trigger does not exclude the diagnosis [10].

Additional diagnostic features include new electrocardiographic abnormalities such as ST-segment elevation, ST-segment depression, T-wave inversion, or prolongation of the corrected QT interval (QTc) [10,12]. Cardiac biomarkers, particularly troponins, are usually elevated but often to a lesser extent than would be expected from the severity of ventricular dysfunction observed on imaging studies [10,12]. Elevated concentrations of natriuretic peptides, including BNP and NT-proBNP, are also frequently reported and may reflect the degree of acute ventricular stress [2,10].

Several morphological variants of TTS have been recognized. The classic apical ballooning pattern is the most common form; in the International Takotsubo Registry, it was identified in 81.7% of patients [2]. Other variants include the midventricular, basal (reverse), and focal forms [2,10,12]. Despite differences in the affected myocardial regions, all variants share similar clinical and pathophysiological features and generally demonstrate recovery of ventricular function within days to weeks [10,12].

Because the clinical presentation closely mimics acute coronary syndrome, coronary angiography and cardiac imaging remain essential components of the diagnostic process [10,12]. Accurate diagnosis is particularly important because, despite its reversible nature, Takotsubo syndrome may be associated with severe complications including cardiogenic shock, ventricular arrhythmias, thromboembolic events, and acute heart failure [2,10,13].

3.2 Epidemiology

Takotsubo syndrome is an uncommon but increasingly recognized clinical entity. It is estimated to account for approximately 1-3% of patients presenting with suspected acute coronary syndrome, although its true prevalence may be underestimated due to diagnostic overlap with acute myocardial infarction [10,12]. In women presenting with suspected ST-segment elevation myocardial infarction, the proportion of Takotsubo syndrome may be higher, reaching approximately 5-6% [10].

A characteristic epidemiological feature of Takotsubo syndrome is its strong predominance among women, especially after menopause [10,12,14]. In the International Takotsubo Registry, which included 1,750 patients with Takotsubo syndrome, 89.8% of patients were women, and the reported mean age among women was 66.8 years [2]. Moreover, women older than 50 years constituted the majority of cases, supporting the observation that the syndrome predominantly affects postmenopausal women [2]. This distribution has led to hypotheses suggesting that estrogen deficiency may increase susceptibility to stress-related myocardial dysfunction [14,15].

The predominance of postmenopausal women may be clinically relevant because estrogens are believed to exert protective cardiovascular effects. They may modulate sympathetic nervous system activity, endothelial function, and coronary microvascular reactivity [14,15]. After menopause, reduced estrogen levels may contribute to increased vulnerability to catecholamine-mediated myocardial stunning, which is considered one of the central mechanisms in the pathophysiology of Takotsubo syndrome [15,16].

Although Takotsubo syndrome is commonly associated with emotional stress, epidemiological data indicate that physical triggers are also frequent. In the International Takotsubo Registry, physical triggers were identified in 36.0% of patients, emotional triggers in 27.7%, and no evident trigger was found in 28.5% of cases [2]. These findings show that Takotsubo syndrome should not be understood exclusively as a consequence of emotional distress, despite its popular name, “broken heart syndrome” [2,10].

Some studies have investigated possible chronobiological patterns in Takotsubo syndrome, including variation according to the time of day, day of the week, and season. However, the available evidence is inconsistent: some studies reported morning or afternoon peaks, some suggested a higher frequency on Mondays, and seasonal analyses reported both summer and winter predominance. Therefore, chronobiological patterns in Takotsubo syndrome should be interpreted cautiously [10].

Although Takotsubo syndrome was initially regarded as a benign and reversible condition, contemporary evidence indicates that it may be associated with significant morbidity and mortality [2,10,13]. In the International Takotsubo Registry, serious in-hospital complications occurred in 21.8% of patients [2]. Long-term follow-up demonstrated a rate of major adverse cardiac and cerebrovascular events of 9.9% per patient-year and a mortality rate of 5.6% per patient-year [2]. These findings are consistent with meta-analytic data showing that acute mortality in Takotsubo cardiomyopathy is clinically relevant and should not be underestimated [13]. Therefore, despite the usually reversible nature of ventricular dysfunction, Takotsubo syndrome requires careful acute management and long-term clinical follow-up.

3.3 Clinical Presentation

The clinical presentation of Takotsubo syndrome is often indistinguishable from acute myocardial infarction at first evaluation [2,10]. The most common symptoms include acute chest pain, dyspnoea, and syncope, while palpitations may be more frequent in patients with emotional triggers [10]. Because of this diagnostic overlap, coronary angiography, often combined with left ventriculography, remains an essential diagnostic tool to exclude acute coronary syndrome and support the diagnosis of Takotsubo syndrome [2,10].

Electrocardiographic abnormalities are common but not specific. In the acute phase, ST-segment elevation may be observed, especially in precordial leads [10,12]. Over time, patients may develop deep T-wave inversions and prolongation of the corrected QT interval (QTc) [2,10]. These abnormalities may closely resemble myocardial ischemia and are insufficient on their own to reliably distinguish Takotsubo syndrome from acute coronary syndrome [2,10].

Cardiac biomarkers are usually elevated, particularly troponins; however, the increase is often moderate and disproportionately low compared with the extent of left ventricular dysfunction seen on imaging [2,10]. Natriuretic peptides, such as BNP or NT-proBNP, are frequently markedly elevated and may better reflect the degree of acute ventricular stress [2,10].

Echocardiography and left ventriculography are central to diagnosis. The classic finding is apical ballooning, caused by akinesia or dyskinesia of the apical segments with compensatory hyperkinesia of the basal segments [2,10]. Other variants may involve midventricular, basal, or focal wall motion abnormalities

[2,10,12]. Although ventricular function usually recovers completely within several weeks, the acute phase may be complicated by heart failure, cardiogenic shock, left ventricular outflow tract obstruction, mitral regurgitation, thromboembolic events, or malignant arrhythmias [2,10,12,13].

This diagnostic complexity highlights the importance of evaluating not only cardiovascular findings but also recent emotional stressors, psychiatric history, and neuroendocrine mechanisms that may contribute to the onset of Takotsubo syndrome.

4. Pathophysiology: How Psychological Stress Breaks the Heart

4.1. Catecholamine-Mediated Mechanisms in Takotsubo Syndrome

The catecholamine hypothesis remains the most widely accepted explanation for the pathogenesis of Takotsubo syndrome. Acute psychological stress is initially processed within the limbic system, particularly in brain regions involved in emotional regulation. Emotional stimuli activate the locus coeruleus, the principal noradrenergic nucleus of the brain, which subsequently stimulates both the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Activation of these pathways leads to the release of large amounts of norepinephrine and epinephrine from the adrenal medulla, initiating the neuroendocrine cascade characteristic of Takotsubo syndrome. This mechanism provides a direct biological link between emotional experiences and acute cardiac dysfunction [17].

Clinical evidence strongly supports the central role of catecholamines in Takotsubo syndrome. One of the landmark studies by Wittstein et al. demonstrated that patients with stress-induced cardiomyopathy exhibit plasma catecholamine concentrations several times higher than those observed in patients with acute myocardial infarction. Elevated levels of epinephrine, norepinephrine, and their metabolites indicate an exaggerated sympathetic response rather than myocardial injury driven solely by ischemia. Furthermore, catecholamine exposure may result not only from systemic hormonal release but also from direct local release by sympathetic nerve terminals within the myocardium, potentially explaining why some patients develop the syndrome despite normal circulating catecholamine levels [8,17].

The myocardial response to catecholamine excess appears to be equally important as the catecholamine surge itself. Experimental evidence suggests that the apical myocardium demonstrates increased sensitivity to adrenergic stimulation due to a greater density of β-adrenergic receptors compared with basal ventricular segments. This regional heterogeneity provides a plausible explanation for the characteristic pattern of apical ballooning and transient systolic dysfunction that defines the syndrome [11,17].

Several mechanisms have been proposed to explain catecholamine-mediated myocardial injury. Excessive adrenergic stimulation may directly damage cardiomyocytes through intracellular calcium overload, which disrupts excitation-contraction coupling and impairs myocardial contractility. Alterations in calcium-regulating proteins, including phospholamban, sarcoplasmic reticulum calcium ATPase (SERCA), and sarcolipin, may further exacerbate contractile dysfunction. Histopathological studies have additionally demonstrated contraction-band necrosis and mononuclear inflammatory infiltrates, findings characteristic of catecholamine toxicity and previously described in conditions associated with extreme sympathetic activation, such as pheochromocytoma and subarachnoid haemorrhage [8,11,17].

Beyond calcium dysregulation, catecholamine excess promotes oxidative and nitrosative stress. Intense β-adrenergic stimulation increases the generation of reactive oxygen species and nitric oxide derivatives, leading to the formation of peroxynitrite and subsequent mitochondrial dysfunction. These processes impair myocardial energetics, reduce cellular energy production, and contribute to transient metabolic abnormalities observed during the acute phase of the syndrome. Experimental and clinical studies have further demonstrated intracellular lipid accumulation within affected cardiomyocytes, suggesting profound metabolic stress accompanying adrenergic overstimulation [11].

In addition to direct cardiomyocyte toxicity, catecholamine excess may contribute to transient coronary microvascular dysfunction. Excessive sympathetic stimulation can induce microvascular constriction through activation of vascular α-adrenergic receptors, leading to impaired myocardial perfusion despite the absence of obstructive coronary artery disease. Endothelial dysfunction may further exacerbate this process by reducing nitric oxide-mediated vasodilation and promoting paradoxical vasoconstriction. Evidence from invasive physiological studies, including measurements of coronary flow reserve and the index of microcirculatory resistance (IMR), has demonstrated transient impairment of coronary microvascular function during the acute phase of Takotsubo syndrome, supporting the role of coronary microcirculation as an important contributing mechanism in stress-induced myocardial dysfunction [18].

A particularly important advance in understanding Takotsubo syndrome has been the identification of a functional switch in β2-adrenergic receptor signalling during extreme catecholamine exposure. At very high epinephrine concentrations, β2-receptors shift from the stimulatory Gs pathway to the inhibitory Gi pathway. While this molecular switch reduces myocardial contractility and contributes to transient ventricular dysfunction, it may simultaneously protect cardiomyocytes from irreversible injury by limiting excessive adrenergic stimulation. This observation has led to the hypothesis that Takotsubo syndrome may represent not only a pathological response to stress but also an adaptive cardioprotective mechanism aimed at preserving myocardial viability during periods of extreme neuroendocrine activation [9].

Collectively, current evidence suggests that acute psychological stress triggers a complex neurocardiac cascade involving sympathetic activation, excessive catecholamine release, altered β-adrenergic signalling, calcium dysregulation, oxidative stress, and coronary microvascular dysfunction. These interacting mechanisms provide the biological basis through which emotional stress may lead to the transient but often dramatic cardiac manifestations of Takotsubo syndrome.

4.2. The HPA Axis and Cortisol

The HPA axis represents one of the principal neuroendocrine pathways activated during psychological stress and may contribute to the pathophysiology of Takotsubo syndrome through alterations in circulating stress hormone levels. Acute psychological stress activates the HPA axis through stress-related signals originating in limbic brain regions, including the amygdala and prefrontal cortex. These signals stimulate the paraventricular nucleus of the hypothalamus, resulting in the secretion of corticotropin-releasing hormone (CRH). CRH subsequently triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which stimulates cortisol production by the adrenal cortex. Through this neuroendocrine cascade, emotional stress is translated into systemic hormonal responses that may contribute to the development of Takotsubo syndrome [19,20].

Although the sympathetic nervous system and the HPA axis are often discussed as separate components of the stress response, they function as closely interconnected systems. Activation of the HPA axis occurs in parallel with sympathetic stimulation, suggesting that cortisol may modulate and amplify the cardiovascular effects of catecholamines during periods of acute psychological stress. Patients with Takotsubo syndrome have been shown to exhibit elevated circulating cortisol concentrations, further supporting the involvement of HPA axis activation in the syndrome [20,21].

Cortisol may further enhance the cardiovascular consequences of sympathetic activation by increasing tissue responsiveness to catecholamines. Glucocorticoids have been shown to potentiate the actions of vasoconstrictor hormones, including norepinephrine, and may increase the expression of α-adrenergic receptors. Consequently, elevated cortisol concentrations may strengthen adrenergic signalling and augment the physiological effects of catecholamine release during acute stress, potentially amplifying the myocardial response to sympathetic overstimulation [21,22].

Recent evidence suggests that cortisol itself may play a more important role in Takotsubo syndrome than previously recognized. In a study evaluating dynamic changes in stress hormone levels during the acute phase of the syndrome, patients demonstrated markedly elevated cortisol concentrations, with peak levels exceeding three times the upper limit of normal physiological values. Notably, the increase in cortisol preceded the rise in cardiac biomarkers, suggesting that activation of the HPA axis occurs early in the disease process and may contribute to subsequent myocardial injury. Furthermore, disruption of the normal circadian cortisol rhythm was observed, indicating broader neuroendocrine dysregulation during acute Takotsubo syndrome. These findings support the concept that, alongside sympathetic activation and catecholamine release, cortisol excess may represent an important component of the biological stress response associated with the syndrome [19].

Chronic stress may further contribute to Takotsubo syndrome through persistent activation of the HPA axis and disruption of its physiological negative-feedback mechanisms. Loss of glucocorticoid-mediated feedback may maintain prolonged activation of stress-responsive brain regions and sustained neuroendocrine stimulation. Persistent HPA axis activation has also been associated with enhanced norepinephrine synthesis and prolonged sympathetic activity, highlighting the close interaction between endocrine and autonomic stress pathways. These observations suggest that chronic neuroendocrine dysregulation may increase susceptibility to an exaggerated stress response and thereby predispose vulnerable individuals to the development of Takotsubo syndrome [23].

4.3. Neuroinflammatory Pathways

Beyond its endocrine effects, activation of the HPA axis may also influence immune and inflammatory pathways. Evidence from patients with Takotsubo syndrome demonstrates simultaneous activation of neuroendocrine and inflammatory responses, with elevated circulating cortisol concentrations occurring alongside increased levels of pro-inflammatory mediators, including interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interferon-γ (IFN-γ), and NF-κB. These findings suggest that Takotsubo syndrome is characterized not only by sympathetic and hormonal activation but also by substantial immune dysregulation. Experimental studies have further demonstrated myocardial infiltration by macrophages, neutrophils, and T lymphocytes, accompanied by a shift from resident cardiac macrophages toward monocyte-derived inflammatory macrophages during the acute phase of the disease. Importantly, increased concentrations of inflammatory cytokines have been associated with adverse clinical outcomes, indicating that inflammation may contribute both to disease pathogenesis and prognosis. Collectively, these observations support the concept that Takotsubo syndrome arises from a complex interaction between psychological stress, HPA axis activation, sympathetic stimulation, and immune-mediated mechanisms rather than from isolated neurohormonal activation alone [23,24]

4.4. The Role of the Autonomic Nervous System

Growing evidence suggests that Takotsubo syndrome is not solely a cardiac disorder but rather a manifestation of disrupted communication within the brain–heart axis. Neuroimaging studies have demonstrated structural and functional abnormalities in several brain regions involved in emotional processing and autonomic regulation, including the amygdala, hippocampus, insular cortex, cingulate cortex, ventromedial prefrontal cortex, and brainstem. These interconnected structures form a neural network responsible for integrating emotional experiences with cardiovascular responses to stress. Altered activity within these regions may impair the physiological regulation of autonomic function and contribute to the development of stress-induced cardiac dysfunction [17,25].

Heart rate variability (HRV) is widely regarded as a non-invasive marker of autonomic nervous system function and reflects the balance between sympathetic and parasympathetic activity. A recent systematic review and meta-analysis demonstrated significant alterations of HRV in patients with Takotsubo syndrome, indicating substantial autonomic dysregulation. Overall, HRV indices were reduced compared with healthy controls, suggesting impaired autonomic flexibility and a diminished ability to adapt to stress. Importantly, the available evidence describes an autonomic phenotype characterized by enhanced sympathetic activation and reduced parasympathetic modulation of the heart. This imbalance is consistent with the physiological “fight-or-flight” response and may represent an important mechanism linking psychological stress to myocardial dysfunction in Takotsubo syndrome. Furthermore, several HRV abnormalities appear most pronounced during the acute phase of the disease and partially improve over time, supporting the concept that autonomic dysregulation plays a central role in the pathophysiology of the syndrome [26].

Further support for the brain–heart axis hypothesis comes from neuroimaging studies demonstrating that increased amygdala activity may precede the onset of Takotsubo syndrome by several years. Higher stress-associated neural activity has been linked to an increased future risk of developing the syndrome and a shorter time to disease onset. These findings suggest that some individuals may possess a pre-existing neurobiological vulnerability characterized by enhanced stress responsiveness, making them more susceptible to stress-induced cardiac dysfunction [25].

4.5. Why Are Postmenopausal Women Particularly Vulnerable?

A striking epidemiological feature of Takotsubo syndrome is its marked predominance among postmenopausal women. The incidence of the syndrome is approximately nine times higher in women aged 60–70 years than in men, suggesting that sex hormones may play an important role in determining susceptibility to stress-induced myocardial dysfunction. Although the exact mechanisms remain incompletely understood, accumulating evidence indicates that estrogen exerts important cardioprotective effects that may protect the myocardium against the adverse consequences of acute stress [21].

Experimental studies have demonstrated that estrogen may increase myocardial tolerance to stress by improving cardiac function and enhancing the expression of protective proteins such as heat shock protein 70 (HSP70). Furthermore, estrogen deficiency has been associated with increased vulnerability to catecholamine-induced cardiac injury. In animal models, ovariectomized females developed more severe myocardial dysfunction and higher troponin concentrations following epinephrine administration, whereas treatment with

17β-estradiol attenuated these effects. These findings suggest that the decline in estrogen levels after menopause may reduce myocardial resistance to catecholamine excess and thereby contribute to the disproportionately high incidence of Takotsubo syndrome among postmenopausal women [21].

Additional evidence indicates that hormonal changes after menopause may also influence autonomic and neuroendocrine responses to stress. Aging is associated with increased sympathetic nervous system activity, while postmenopausal women exhibit a concomitant reduction in vagal tone, resulting in a shift toward sympathetic predominance. This autonomic imbalance may enhance susceptibility to stress-induced cardiovascular responses and facilitate the development of Takotsubo syndrome. Moreover, estrogens appear to attenuate the physiological response to psychological stress. Estradiol supplementation has been shown to reduce the release of cortisol, adrenocorticotropic hormone (ACTH), epinephrine, and norepinephrine during mental stress. Consequently, the decline in estrogen levels after menopause may promote exaggerated activation of both the sympathetic nervous system and the HPA axis, increasing vulnerability to stress-induced myocardial dysfunction [18].

5. Psychological Triggers and Psychiatric Comorbidities

5.1. Classification of triggers

According to the 2018 InterTAK Diagnostic Criteria, an emotional, physical, or combined trigger may precede the onset of Takotsubo syndrome; however, the presence of an identifiable trigger is not obligatory for diagnosis. Therefore, triggers should be understood as clinically relevant precipitating factors rather than mandatory diagnostic criteria [10].

physically triggered, mixed, or without an identifiable precipitant. Emotionally triggered TTS refers to cases preceded by intense affective arousal, such as bereavement, fear, anger, interpersonal conflict, public humiliation, or sudden threatening information. Physically triggered TTS includes cases following medical procedures, trauma, acute neurological disease, sepsis, respiratory failure, or other severe somatic stressors. In clinical practice, the distinction between emotional and physical triggers may be blurred, as many medical events also carry a substantial emotional burden. Examples include receiving a new diagnosis, undergoing an invasive procedure, or experiencing acute dyspnoea or pain. Finally, a relevant proportion of TTS cases occur without an identifiable trigger, which may reflect either a true absence of a recognizable precipitant or the limitations of retrospective trigger assessment [2,10].

Data from the International Takotsubo Registry indicate that physical triggers were identified in 36.0% of patients, emotional triggers in 27.7%, combined emotional and physical triggers in 7.8%, and no evident trigger in 28.5%. These findings are important because they challenge the popular but oversimplified view of TTS as exclusively “broken heart syndrome” [2].

5.2. Types of psychological triggers

Psychological triggers of TTS can be grouped according to the dominant emotional and psychosocial mechanism. The most typical group includes acute negative emotions of high intensity, such as grief, bereavement, sudden loss, fear, anger, and shock. These events are often characterized by abrupt loss of perceived control and intense autonomic arousal [2,10].

A second group consists of interpersonal and social-evaluative stressors, including family conflict, relationship breakdown, public embarrassment, occupational stress, and fear of negative social evaluation. Public speaking and stage fright are clinically relevant examples, as case reports have described TTS after work-related psychological stress associated with giving a lecture [10,27].

A third category includes disaster-related or collective stressors. Increased incidence of TTS has been reported after earthquakes, supporting the concept that acute environmental threat and collective trauma may act as population-level psychological triggers. However, these data are mostly observational and should not be interpreted as proof of simple causality [28].

Finally, positive emotional events may also trigger TTS, a phenomenon described as “happy heart syndrome”. Registry data suggest that intense joy, surprise, celebrations, or receiving good news can precipitate TTS in susceptible individuals. This observation suggests that the key mechanism may not be the negative emotional valence itself, but rather sudden and intense autonomic activation in susceptible individuals [7,10].

5.3. Psychiatric comorbidities

Psychiatric comorbidities are common in patients with TTS, particularly anxiety disorders and mood disorders. In the International Takotsubo Registry, patients with TTS had a higher prevalence of neurologic or psychiatric disorders than patients with acute coronary syndrome. Additional observational studies have reported higher rates of anxiodepressive disorders, chronic psychological stress, and pre-existing psychiatric morbidity in TTS compared with control populations [2,29,30].

Anxiety disorders appear to be especially relevant because they are associated with heightened sympathetic arousal, increased vigilance to bodily sensations, and impaired stress regulation. Mood disorders, particularly major depressive disorder and dysthymia, have also been reported more frequently in TTS patients than in patients with acute coronary syndrome. A study using structured lifetime psychiatric assessment found higher rates of pre-existing anxiety and mood disorders in TTS, suggesting that psychiatric morbidity may represent a vulnerability substrate rather than merely a consequence of the cardiac event [30].

Post-traumatic stress disorder and trauma-related symptoms should also be considered, especially in patients with a history of severe life events or chronic psychological distress. Nevertheless, available evidence remains heterogeneous, and the direction of association is difficult to establish. Some patients may have psychiatric symptoms before TTS, whereas others develop anxiety, depressive symptoms, illness-related fear, or reduced quality of life after the acute episode. For this reason, psychiatric assessment in TTS should distinguish between pre-existing psychiatric disorders and post-event psychological sequelae [31].

5.4. Personality and psychological vulnerability

Although several studies have investigated personality traits in TTS, there is currently no clearly established “Takotsubo personality profile”. The most frequently discussed traits include high trait anxiety, neuroticism, alexithymia, emotional suppression, somatization, illness-related anxiety, and maladaptive coping strategies. Some studies suggest that patients with TTS may have difficulties in identifying, expressing, or regulating emotions, which could increase vulnerability to abrupt autonomic dysregulation during acute stress.

However, the evidence is inconsistent. A systematic review indicates that findings on personality and traumatic life events are heterogeneous and often limited by small sample sizes, retrospective designs, and different psychometric tools [31]. Individual studies have nevertheless reported elevated psychological distress and selected personality-related differences in TTS patients [32].

A useful conceptual model is to describe TTS as an acute cardiac event occurring at the intersection of an external trigger and individual psychobiological susceptibility. In this framework, psychological vulnerability does not “cause” TTS alone, but may lower the threshold for developing myocardial stunning when an intense emotional or physical stressor activates the brain–heart axis.

6. Clinical Implications and Management

In the initial phase of the diagnostic process, differentiating Takotsubo syndrome (TTS) from acute ST-segment elevation myocardial infarction (STEMI) poses a tremendous challenge. The clinical presentation of both conditions is often almost indistinguishable in the emergency department setting-patients present with severe chest pain and alarming electrocardiographic changes [10]. Urgent coronary angiography remains the gold standard for establishing the diagnosis, as it is the only method that definitively rules out coronary artery occlusion. In patients with TTS, the vessels are typically fully patent, and the contractility abnormalities visualized in imaging studies (e.g., the typical apical "ballooning" of the left ventricle) always extend beyond the territory supplied by a single coronary artery [2,10].

However, before the patient is transferred to the catheterization laboratory, the attending physician's attention should focus on so-called "red flags". These primarily include: postmenopausal female sex (which is associated with the loss of the protective effect of estrogens on the endothelium) [33], the occurrence of an immediate, severe emotional or physical stress trigger [15], and a characteristic biomarker dissociation. In stress cardiomyopathy, disproportionately low troponin levels are observed in relation to the extensive area of myocardial contractility abnormalities, accompanied by a very rapid and significant release of natriuretic peptides (BNP/NT-proBNP) [34,35].

Although the pathomechanism of TTS is inextricably linked to the overstimulation of the brain-heart axis and a "catecholamine storm" that is destructive to myocytes [8], an in-depth psychological history is routinely omitted in the acute setting of the Emergency Department. The medical staff rightfully concentrates on saving the patient's life and biological stabilization [36]. Unfortunately, completely ignoring this aspect at

a later stage hinders the identification of triggers and the specific psychological profile of the patient, who very often struggles with latent anxiety and emotion dysregulation [37].

To bridge this gap, modern guidelines suggest the routine use of brief screening tools in cardiology. The Patient Health Questionnaire (PHQ-9) allows for a reliable assessment of the severity of depressive symptoms in just a few minutes [38], while the Generalized Anxiety Disorder scale (GAD-7) accurately evaluates anxiety levels [39]. The implementation of these standardized questionnaires does not require advanced psychiatric knowledge; instead, it excellently sensitizes the medical staff to the psychosomatic background of the incident, thereby accelerating psychocardiological intervention [38,39].

The therapeutic strategy in TTS strictly depends on the stage of the disease. In the acute phase, treatment is exclusively supportive. In hemodynamically unstable patients, the administration of exogenous catecholamines (such as epinephrine) is strictly contraindicated. These substances can drastically exacerbate the underlying pathophysiology (the "catecholamine storm") and worsen dynamic left ventricular outflow tract obstruction (LVOTO) [10,33]. For the same reason, classic positive inotropic agents should be avoided; in cases of cardiogenic shock, levosimendan or mechanical circulatory support is preferred [10,40].

In the context of secondary prevention, the use of beta-blockers remains controversial. Although blocking adrenergic receptors seems intuitively a logical way to protect the myocardium from stress, hard clinical data from large registries fail to prove their efficacy in preventing TTS recurrences [2,33]. Considerably greater benefits are associated with the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). These drugs have been proven to support reverse left ventricular remodelling and significantly improve long-term prognosis [2].

The final crucial aspect of in-hospital treatment is targeted anticoagulation. Severe apical akinesia predisposes to blood stasis and thrombus formation. The detection of thrombotic material on echocardiography mandates the immediate initiation of anticoagulant therapy, which in turn minimizes the risk of thromboembolic complications, including stroke [41].

Despite the close association between the pathogenesis of TTS and psychological distress, current medical guidelines lack standardized psychotherapeutic care protocols, representing a significant gap in optimal preventive management [42].

The most extensively studied form of psychological support in cardiology remains cognitive-behavioural therapy (CBT). Although strong evidence demonstrates that CBT effectively reduces anxiety and so-called cardiac depression in patients with coronary artery disease, there is still a dramatic lack of rigorous randomized controlled trials (RCTs) specifically dedicated to the TTS population [36,43]. A promising alternative is Mindfulness-Based Stress Reduction (MBSR). This approach is supported by an expanding body of evidence in general cardiac rehabilitation, demonstrating effectiveness in attenuating excessive sympathetic nervous system activity [44].

From a psychobiological perspective, the implementation of targeted emotion regulation training is particularly well justified in TTS. A substantial proportion of patients who have experienced stress-induced cardiomyopathy are found to exhibit an alexithymic profile, characterized by profound difficulty in identifying and expressing their own emotions. Professional therapeutic work addressing these deficits teaches patients how to safely manage and release emotional tension, which may help protect them from another affect-triggered “catecholamine storm” [39].

Optimal management of Takotsubo syndrome requires the implementation of an integrated care model, in which routine psychological or psychiatric evaluation becomes a standard following diagnosis [36,38]. The cornerstone of effective treatment is the close cooperation of a multidisciplinary team, relying on the collaboration of a cardiologist, a mental health professional, and a general practitioner [2,42]. In secondary prevention, the priority is proper patient education aimed at identifying emotional triggers and applying effective stress reduction techniques [39,44]. Furthermore, this condition strictly requires long-term clinical monitoring, especially in the first years after the incident. Studies demonstrate a significant ongoing risk of cardiomyopathy recurrence and major adverse cardiovascular events during this period [2].

7. Limitations

Several limitations of the present review should be acknowledged. The narrative design does not incorporate a formal systematic search protocol or structured quality appraisal, making the synthesis susceptible to selection bias and limiting reproducibility.

Heterogeneity in diagnostic criteria across the included literature complicates cross-study comparisons. Studies published prior to the InterTAK Diagnostic Criteria (2018) used earlier frameworks - including the Mayo Clinic and modified Japanese criteria - resulting in variable case definitions and potentially distinct patient subgroups.

The evidence base is dominated by retrospective registry data, which limits causal inference regarding psychological determinants of TTS onset and recurrence. Prospective designs with standardized psychological assessment at predefined time points are scarce.

Male patients and younger individuals are substantially underrepresented in the literature. Given that men with TTS appear to have higher rates of physical triggers and greater in-hospital complication rates, generalizability to the full TTS population is limited.

Psychiatric assessment methodology is inconsistent across studies, with variation in instruments used, timing of evaluation relative to the acute event, and diagnostic thresholds applied. This limits the pooling of psychiatric comorbidity estimates.

Finally, no randomized controlled trials have evaluated psychological interventions specifically designed for TTS patients. Recommendations regarding cognitive-behavioural therapy and mindfulness-based stress reduction are extrapolated from adjacent cardiac and psychiatric populations.

8. Conclusions

TTS is a psychosomatic cardiovascular syndrome in which acute psychological stress triggers a catecholamine-mediated cascade - involving sympathetic activation, HPA axis dysregulation, and coronary microvascular dysfunction - resulting in transient left ventricular dysfunction. The apical distribution of wall motion abnormality reflects the gradient of β2-adrenergic receptor density within the ventricular wall. Estrogen deficiency in postmenopausal women amplifies sympathoadrenal reactivity and likely contributes to the marked female predominance. Psychiatric comorbidities, particularly anxiety and depression, are present in a substantial proportion of TTS patients and are associated with increased recurrence risk and impaired long-term outcomes. Systematic psychiatric screening using validated instruments - such as the PHQ-9 and GAD-7 - should be considered as part of post-TTS care.

Current evidence supports considering psychological interventions as part of an integrated multidisciplinary approach to TTS management involving cardiology, psychiatry, and primary care. Randomized controlled trials evaluating TTS-specific psychological interventions and prospective studies examining the impact of psychiatric treatment on recurrence rates remain important research priorities.

Author Contributions:

Conceptualization, S.J., J.S. and T.W.; methodology, J.S.; formal analysis, J.S. and M.Ś.; investigation, T.W., A.N.O., and M.Ś.; resources, T.W., A.N.O., and M.Ś.; data curation, T.W., A.N.O., and M.Ś.; writing-original draft preparation, T.W., A.N.O., M.Ś. and S.J.; writing-review and editing, S.J. and J.S.; supervision, S.J., J.S., and M.Ś.; project administration, S.J. All authors have read and agreed to the published version of the manuscript.

Funding Statement: This research received no external funding.

Acknowledgements: The authors thank colleagues for their valuable input.

Conflicts of Interest: The authors declare no conflicts of interest.

Declaration of generative AI and AI-assisted technologies: In preparing this work, the authors used ChatGPT for the purpose of improving academic English language, clarity, readability, consistency, and text formatting. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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