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Neurogenic Mechanisms, Takotsubo Syndrome, And Prevention of Stress-Induced Cardiovascular Diseases

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Abstract

This article systematizes the neurogenic and psychophysiological mechanisms of stress-induced cardiovascular diseases, including Takotsubo syndrome, as well as psychological risk factors and preventive directions. It shows that catecholamine release, inflammation, endothelial dysfunction, personality traits, and a lack of social support form a unified pathogenetic framework that should be addressed by psychocardiological and rehabilitation interventions.

Keywords: Stress, catecholamines, Takotsubo syndrome, psychocardiology, psychological risk factors, prevention, cardiovascular diseases.

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1. Introduction

Neurogenic foundations of the development of negative mental states

Psychophysiology of stress

Stress is the body's response to stimulating factors (stressors) that disrupt homeostasis. This response is mediated by the interaction of the nervous, endocrine, and immune systems [8]. The rapid phase of the response is mediated through the sympathoadrenal system (SAS): during acute stress, the hypothalamus stimulates the release of catecholamines (adrenaline, noradrenaline), which leads to an increased heart rate, elevated blood pressure, and greater cardiac workload [8], [9]. At the same time, the hypothalamic–pituitary–adrenal (HPA) axis is activated, releasing corticosteroids (cortisol) that modulate metabolism and immune responses. In short-term stress, these mechanisms are adaptive; however, during prolonged chronic stress, persistently elevated levels of cortisol and adrenaline are maintained. As a result, endothelial dysfunction, increased free radical formation, inflammation, and accelerated progression of atherosclerosis develop [8]. Chronic stress load on the SAS and HPA systems may cause myocyte death, endothelial dysfunction, and sustained elevation of blood pressure. Acute psychogenic stress, in turn, immediately stimulates inflammatory cascades: it has been shown that within minutes after psychological stress (for example, public speaking), the levels of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) in the blood increase [10]. Atrial fibrillation and other acute reactions may occur during such an "adrenaline storm." Thus, stress has a dual effect: short-term episodes increase the work of the heart and blood vessels, whereas long-term stress causes systemic inflammation and metabolic disturbances directly associated with the development of cardiovascular diseases [8].

Takotsubo stress-induced cardiomyopathy

Takotsubo syndrome (TTS) is a poorly studied form of cardiac pathology that was initially regarded as a relatively benign condition [6]. However, subsequent studies have shown that TTS may be accompanied by severe clinical complications, including death, and its prevalence is probably underestimated. In the absence of widely accepted clinical guidelines, the development of an expert consensus statement was timely and necessary. The first part of this document summarizes current concepts regarding the clinical diagnosis and characteristics of TTS, and also addresses controversial issues concerning nomenclature, clinical variants, the role of ischemic heart disease, and presumed etiological mechanisms. In addition, updated diagnostic criteria based on the current level of knowledge were proposed to improve diagnostic accuracy [6].

The diagnosis of TTS is often challenging, because its clinical presentation may resemble acute myocardial infarction in terms of electrocardiographic changes and biomarker levels [6]. At present, there is no widely recognized noninvasive method that can quickly and reliably confirm or exclude TTS; therefore, coronary angiography combined with left ventricular assessment is considered the gold standard for diagnosing this condition [6].

Current understanding of the pathogenesis of stress-induced cardiomyopathy

The pathogenesis of Takotsubo syndrome and related stress cardiomyopathies is considered multifactorial and still not fully understood. A key role is played by hyperactivation of the sympathoadrenal system with catecholamine release at supraphysiological concentrations. In TTS, blood levels of adrenaline and noradrenaline several times higher than normal have been detected [11]. Excess adrenaline causes an "adrenergic storm": myocardial beta-2 adrenergic receptors change conformation and begin to suppress contractility (via Gi mechanisms), leading to myocardial stunning [11]. This is manifested by the typical "ballooning" of the apical region of the left ventricle. In addition to adrenaline, other factors are being studied: estrogen deficiency (although a direct link has not yet been proven), spasm of small coronary vessels, and calcium overload in cardiomyocytes.

Recent studies emphasize the importance of inflammatory mechanisms. In the myocardium of patients with TTS, markers of NLRP3 inflammasome activation and elevated levels of cytokines (IL-6, IL-1β, TNF-α) have been identified [7]. Inflammation intensifies oxidative stress and damages cardiomyocytes, leading to fibrosis and remodeling. Thus, TTS is viewed not merely as a "purely hormonal" catastrophe, but as a complex stress-induced heart injury with contributions from neuroendocrine, immune (inflammatory), and microvascular dysfunction [7].

From a neurobiological perspective, chronic stress activates the amygdala—the center of emotional response. PET studies have shown that high amygdala activity during stress stimulates the bone marrow, increasing leukopoiesis and vascular inflammation. In people with elevated amygdala activity, more "vulnerable" atherosclerotic plaques are detected and the risk of cardiovascular events

increases [9]. High amygdala activation is also specifically associated with cases of Takotsubo cardiomyopathy [9]. This suggests that long-term emotional stress triggers a brain-to-heart cascade through the immune system, worsening the progression of atherosclerosis and even directly contributing to the mechanism of TTS.

Thus, current concepts indicate that stress-induced cardiomyopathy is the result of an intersection of neuroendocrine surges (catecholamine "toxicity"), vascular disturbances (spasm and endotheliopathy), and an inflammatory myocardial response [7], [9]. Because of this complex pathogenesis, Takotsubo syndrome is often regarded as a unique "stress-heart" disease.

Mechanisms of CVD induction associated with psychological triggers

Psychological risk factors

Along with physiological factors, psychological predispositions play an important role in the development of stress-induced cardiac events. These include personality traits, mental disorders, and psychosocial conditions. For example, "Type D" personality (distressed personality)—a persistent tendency toward negative emotions and social inhibition—is officially recognized as a risk factor for ischemic heart disease [12]. Type D is associated with high levels of depression, anxiety, and chronic stress reactivity [12]. Early studies also linked CVD with "Type A" personality (dominant character, hostility), but current data emphasize the importance of negative emotional states.

Numerous studies indicate that depression, generalized anxiety disorder, and post-traumatic stress disorder (PTSD) are independent risk factors for cardiovascular disease [13]. The severity and duration of depression correlate with increased cardiovascular mortality. Chronic psychological stress—for example, persistent work overload or family conflict—also increases the risk of myocardial infarction and stroke. Socioeconomic stress factors, loneliness, and insufficient social support further intensify the negative impact.

A relationship has been established between severe life events (death of loved ones, divorce, job loss) and adverse cardiac outcomes. For instance, the loss of a loved one may trigger so-called "acute stress" events followed by myocardial infarction. In addition, adverse childhood experiences (ACEs) increase the likelihood of CVD in adulthood, possibly through mechanisms of a long-activated stress response [13].

Briefly, the key psychological risk factors are as follows:

-Depression and anxiety. There is strong evidence that depressive and anxiety disorders are directly associated with worse prognosis in cardiac patients, reducing adherence and increasing inflammation in the vessels [13], [14].

-PTSD and chronic stress. Severe traumatic experiences (wars, violence, mass disasters) significantly increase the risk of ischemia, stroke, and cardiovascular mortality.

-Personality traits. Type D, hostility, pessimism, and low stress tolerance are all associated with increased cardiac risk [12], [13].

-Social factors. Low socioeconomic status, isolation, family or workplace conflict, and lack of support exacerbate the impact of stress on the heart.

Thus, psychological risks are not the same for everyone; what matters significantly is the combination of stress intolerance, negative affect, and lack of supportive resources [13]. Identifying these factors allows timely attention to be given to the patient.

Mechanisms of neurogenic development of CVD

From a pathophysiological standpoint, TTS and stress-induced CVD develop through a chain of neurogenic reactions. The key component is a sharp release of catecholamines (adrenaline, noradrenaline) during acute stress [2]. Excess sympathetic stimulation leads to "myocardial stunning": damage to cardiomyocytes, calcium imbalance, impaired energy metabolism, and microvascular perfusion [2]. During the acute phase, measured catecholamine levels in patients with TTS significantly exceed those seen in myocardial infarction [2]. High catecholamine concentrations cause direct myocardial toxicity (vasoconstriction, arteriolar spasm, cardiomyocyte dystrophy, and lenticular necrosis) [2]. The density of β-adrenergic receptors in the apical portion of the left ventricle is traditionally considered higher, which explains the tendency for "ballooning" to occur in the apical wall [2].

In addition to supraventricular hyperactivation, coronary microangiopathy and endothelial dysfunction are involved in the pathogenesis. Under the influence of catecholamines, the vessels of the coronary microcirculation lose the ability to dilate adequately, and transient vasospasm may occur [2]. These changes worsen local metabolic stress in the myocardium and contribute to discoordinated contraction of the left ventricle.

The central role of the brain–heart axis is emphasized by neuroimaging studies: chronic stress, anxiety, and depression are associated with hyperreactivity of higher regulatory centers of the autonomic nervous system. In patients with TTS, changes have been found in brain regions responsible for stress responses and emotional regulation, confirming the influence of psychological factors on myocardial vulnerability [2].

It is important to note the statistical aspect as well: Takotsubo is traditionally registered in elderly women (60–70 years) after emotional shocks [2]. In our group, the proportion of women with TTS was 6 out of 7 patients, which is consistent with classic data. In international registries, about 80–90% of TTS patients are postmenopausal women [2].

Mechanisms of progression of stress-related CVD

Relationship between stress and cardiovascular events

Stress affects not only Takotsubo. Acute emotional shocks can trigger classical ischemic pathology. It is well known that during natural disasters (earthquakes, hurricanes) and major stress episodes, the number of myocardial infarction cases rises sharply [9]. The mechanism involves a sudden release of adrenaline: heart rate, blood pressure, and contractility increase, which, in the presence of narrowed coronary arteries, leads to oxygen deficiency and plaque rupture [9]. At the same time, stress increases platelet aggregation and blood coagulation, raising the risk of thrombotic complications [9].

Even in the absence of overt thrombosis, psychological stress may provoke cerebrovascular and arrhythmic events. Acute mental stress impairs endothelial function and microcirculation [9], thereby worsening ischemia. For example, episodic mental stress may trigger ischemia with mental stress. In young women, stress may act as a trigger for spontaneous coronary artery dissection (SCAD), leading to myocardial infarction without atherosclerosis [9].

Studies show that stress-induced arrhythmias are also not uncommon: an "adrenaline storm" may cause ventricular or atrial fibrillation, especially in the presence of structural heart disease. In addition, chronic stress accelerates the progression of atherosclerosis by increasing chronic inflammatory markers and increasing the frequency of acute stenosing episodes.

It is important that the stress–CVD relationship is especially pronounced in women. At the same level of psychoemotional impact, women more often develop an acute coronary event or so-called microvascular angina. Studies have shown that under stress, ischemia is detected twice as often in women as in men, and such "stress-related" vascular complications as SCAD and Takotsubo are found predominantly in women [9], [10]. Overall, stress exposures (rage, fear, grief, nausea) systematically increase the risk of myocardial infarction, stroke, and death from cardiovascular causes [9].

Psychological methods for prevention and treatment of stress-induced CVD

The modern approach to cardiac patients involves the active use of psychological methods both for prevention and for rehabilitation after CVD. Physicians and psychologists recommend combining standard drug treatment with psychotherapy and training patients in self-regulation skills. For example, stress-management techniques—meditation, deep breathing, progressive muscle relaxation—help reduce physiological reactivity to stressful situations. Comprehensive cardiac rehabilitation programs increasingly include psychological sessions that teach patients to recognize and control negative emotions.

Cognitive behavioral therapy (CBT) remains one of the foundations of psychocardiological care. CBT helps patients reconsider irrational beliefs ("I will not survive another stress") and develop more adaptive coping strategies. Modern third-wave psychotherapies show great promise. Metacognitive therapy (MCT), which focuses on beliefs about one's own thoughts, has proven effective in cardiac patients: preliminary studies have shown that a short-term MCT seminar significantly reduces anxiety and depression in people with CVD [4]. In the context of the pandemic and a shortage of specialists, digital solutions are emerging: web applications and online MCT or CBT programs are already showing a reduction in anxiety among users [4].

Over the past decade, interest in mindfulness techniques has grown. Numerous studies have confirmed that Mindfulness-Based Stress Reduction (MBSR) or Mindfulness-Based Cognitive Therapy (MBCT) programs in cardiac patients lead to notable improvements in psychological indicators. A 2021 meta-analysis showed that mindfulness training provides a moderate or large effect in reducing anxiety, depression, stress, and even blood pressure in patients with CVD [15]. The authors conclude that mindful breathing and meditation practices can be considered a "first-line" intervention in cardiac rehabilitation [15].

An important factor in successful care is the interdisciplinary approach. Major clinical guidelines emphasize that almost all updated CVD recommendations recognize the need to address depression and anxiety. For example, a review of CPGs showed that 71% of such guidelines recognize depression as a significant risk factor, and approximately 29% recommend cognitive behavioral therapy for depression in cardiac patients [14]. However, practical implementation is still in its infancy—only about a quarter of guidelines include specific algorithms for screening and treating depression [14]. Newer consensus statements insist on the mandatory participation of psychotherapists in the cardiac team.

In addition to psychotherapy, modern measures include psychoeducation and the development of "stress resilience." This may involve training in problem-solving skills, principles of a healthy lifestyle (sleep, physical activity, socialization), and so on. In emergency situations (in ACS or stroke), psychologists provide crisis intervention to reduce the impact of acute stress on the heart. Biofeedback and neurofeedback, as well as heart rate variability training, are also used for direct physiological control of stress. Some clinics are experimenting with mobile applications and virtual reality to reduce anxiety in cardiac patients.

Taking into account the psychogenic component of CVD, prevention and treatment extend beyond purely cardiological correction. Recommendations include a combination of lifestyle modification, psychological, and pharmacological measures.

Stress management and psychotherapy. Cognitive behavioral methods and stress-control training have proven effective in reducing anxiety and depression in cardiology patients [1], [2]. It has been established that structured psychotherapy (for example, CBT) combined with cardiac rehabilitation improves functional outcomes after TTS [2] and may reduce the risk of cardiovascular events [1]. International and domestic experts recommend including psychological rehabilitation of CVD patients in the complex of primary and secondary prevention measures [1].

Physical activity. Regular aerobic exercise (walking, therapeutic exercise, swimming) reduces the impact of stress, improves vascular reactivity, and decreases anxiety symptoms [1]. According to meta-analyses, physical activity reduces the risk of developing coronary artery disease and overall mortality in patients with CVD [1].

Social support. Increasing social support (support groups, family psychotherapy) is also an important component of prevention of post-stress consequences [1]. It is known that people with sufficient support have less cardiac anxiety and better adherence to treatment. Drug therapy. In the presence of clinically significant depression or generalized anxiety, the use of SSRIs (for example, sertraline, escitalopram) or serotonin-norepinephrine reuptake inhibitors (SNRIs) is justified [1]. These drugs effectively relieve depressive and anxiety symptoms and are considered relatively safe in cardiac patients [1]. Although some studies note an increased risk of bleeding with SSRIs in patients receiving anticoagulants, in general SSRIs do not increase the number of deaths or cardiovascular events in coronary artery disease [1]. In certain cases, anxiolytics (short courses of benzodiazepines) may be useful for situational relief of acute anxiety, but long-term use is undesirable because of the risk of dependence.

As for the specific treatment of TTS, the role of beta-blockers remains controversial. Theoretically, beta-blockers can reduce catecholamine shock; however, systematic reviews have not found a statistically significant reduction in mortality with their use in the acute phase of TTS [3]. Nevertheless, beta-blockers may be prescribed for hypertension or pronounced tachycardia, especially in patients with concomitant arrhythmias or marked sympathicotonia.

In summary, the preventive protocol should be interdisciplinary: in addition to standard cardiological measures (blood pressure control, CHD, lipids), regular assessment of patients' mental status (screening for depression and anxiety) should be carried out, and behavioral interventions and, when necessary, psychopharmacotherapy should be implemented [1], [2].

2. Conclusions

As a result of many years of experience and research, a paradigm of "psychocardiological care" has emerged: recognition that, alongside hypertension and cholesterol, physicians must also control psychological risks. Screening for depression and anxiety is being introduced widely in all patients with CVD, and methods such as CBT, MCT, and mindfulness are increasingly incorporated into rehabilitation programs [5], [15]. These approaches improve patients' quality of life, restore psychoemotional well-being, and may reduce the frequency of recurrent cardiac events, although statistical evidence of a direct effect on mortality is still limited [15], [16]. Nevertheless, modern psychocardiology is aimed at "retraining" patients to perceive stress as a manageable factor, weakening its

influence on the heart in order to achieve long-term improvement in prognosis.

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