

REVIEW ARTICLE

Takotsubo Syndrome: Clinical Manifestations, Etiology and Pathogenesis

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Abstract: The purpose of the review is the analysis of clinical and experimental data on the etiology and pathogenesis of takotsubo syndrome (TS). TS is characterized by contractile dysfunction, which usually affects the apical region of the heart without obstruction of coronary artery, moderate increase in myocardial necrosis markers, prolonged QTc interval (in 50% of patients), sometimes elevation of ST segment (in 19% of patients), increase N-Terminal Pro-B-Type Natriuretic Peptide level, microvascular dysfunction, sometimes spasm of the epicardial coronary arteries (in 10% of patients), myocardial edema, and life-threatening ventricular arrhythmias (in 11% of patients). Stress cardiomyopathy is a rare disease, it is observed in 0.6 - 2.5% of patients with acute coronary syndrome. The occurrence of takotsubo syndrome is 9 times higher in women, who are aged 60-70 years old, than in men. The hospital mortality among patients with TS corresponds to 3.5% - 12%. Physical or emotional stress do not precede disease in all patients with TS. Most of patients with TS have neurological or mental illnesses. The level of catecholamines is increased in patients with TS, therefore, the occurrence of TS is associated with excessive activation of the adrenergic system. The negative inotropic effect of catecholamines is associated with the activation of β_2 adrenergic receptors. An important role of the adrenergic system in the pathogenesis of TS is confirmed by studies which were performed using ¹²⁵I-metaiodobenzylguanidine (¹²⁵I-MIBG). TS causes edema and inflammation of the myocardium. The inflammatory response in TS is systemic. TS causes impaired coronary microcirculation and reduces coronary reserve. There is a reason to believe that an increase in blood viscosity may play an important role in the pathogenesis of microcirculatory dysfunction in patients with TS. Epicardial coronary artery spasm is not obligatory for the occurrence of TS. Cortisol, endothelin-1 and microRNAs are challengers for the role of TS triggers. A decrease in estrogen levels is a factor contributing to the onset of TS. The central nervous system appears to play an important role in the pathogenesis of TS.

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1. INTRODUCTION

In 1974, the term “stress-cardiomyopathy” regarding stress-induced injury of the heart (SIH) in animals was first suggested by Johansson *et al.* [1]. In a study performed on pigs, they found that immobilization stress causes morphological changes in the myocardium, including necrosis. According to ECG data, immobilization in pigs causes an inversion of the T wave, transient displacement of the ST segment, and arrhythmias. The first report about “stress cardiomyopathy” in humans was published in 1980 by Cebelin and Hirsch [2]. It should be noted that other investigators also reported on

the possibility of SIH in humans and animals, but they did not use the term stress cardiomyopathy [3-12].

The method of quantitative evaluation of SIH was first proposed by Miller and Mallov [9]. They found that emotional painful stress (EPS) contributes to an increase in accumulation of radioactive ^{99m}Tc-pyrophosphate in the myocardium. In addition, in experiments on the isolated perfused heart, they found that EPS contributed to the release of lactate dehydrogenase from the myocardium, which indicates necrosis of heart cells. It is established that EPS causes a decrease in pressure which is developed by the left ventricle of the isolated heart, and contributes to an increase in end-diastolic pressure [12]. Thus, it was found that stress causes necrosis of the cardiac cells and impaired pumping function of the heart.

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For a long time, there were no methods for the *in vivo* diagnosis of the stress cardiomyopathy in humans. The situation changed in 1990 when a group of Japanese cardiologists, who used the echocardiography method, were able to identify a disease that they called “tako-tsubo syndrome” [13]. The disease was characterized by akinesia/hypokinesia of the distal left ventricle (LV) regions with basal normokinesia. There were no signs of atherosclerosis of the epicardial coronary arteries. The heart took the form of an octopus catch vessel - tako-tsubo. The authors suggested that the cause of the disease is spasm of the coronary vessels. Indeed, spasm of one of the epicardial arteries was discovered, which disappeared after the infusion of nitroglycerin, which was confirmed by an angiographic study. Eleven years later, an article appeared in an authoritative journal that confirmed the existence of takotsubo syndrome (TS) [14]. The term stress cardiomyopathy is applicable to the syndrome so it was first used by Pavin *et al.* [15]. Sometimes stress cardiomyopathy is called the “broken heart syndrome” [16] or “apical ballooning syndrome” [17]. Stress cardiomyopathy is a relatively rare disease, it occurs in 0.6 - 2.5% of patients with acute coronary syndrome [18-24] or 178 (0.018%) cases of TS per 1 million are registered annually in hospitalized patients [25], other authors cite a similar figure - 0.02% of the number of the hospitalized patients [26]. Today, the incidence of TTS is estimated at 2% in patients with an initial diagnosis of acute coronary syndrome (ACS) [27].

2. THE MAIN CLINICAL MANIFESTATIONS OF TAKOTSUBO SYNDROME

The incidence of takotsubo syndrome is 9 times higher in women, who are 60–70 years old, than in men [28-30]. The mortality rate with TS is 3 times higher in men [28]. The daily peak in TS incidence occurs in the morning until noon [31]. The seasonal peak in the incidence of stress cardiomyopathy in Italy and New Zealand is in summer [31, 32].

Chest pain is observed in 63% - 82% of patients with TS [33-35]. Dyspnea occurs in 27% - 50% of patients with stress cardiomyopathy [33, 36]. During the first three days after hospitalization, 39% of patients have systolic blood pressure below 90 mm Hg [37].

The main clinical manifestation of TS is contractile dysfunction (stunning), which usually affects the apical region of the heart in the absence of coronary thrombosis [13]. However, TS can be combined with coronary heart disease (CHD). A combination of CHD and TS is observed in 10-14% of patients with stressful cardiomyopathy [38, 39]. Myocardial stunning in TS usually affects the apical region of the heart, consequently, takotsubo syndrome is often called “apical ballooning syndrome” [17]. Atypical disturbance of cardiac contractility, which affects other parts of the heart, can be observed in 28-40% of patients with TS [40-44]. The left ventricular ejection fraction (LVEF) in TS is comparable to LV EF in patients with ST-segment elevation myocardial infarction (STEMI) and is 33% - 38% [45-47]. Both systolic and diastolic cardiac functions is impaired [48]. Cardiogenic shock can occur in 7% -10% of patients with stress cardiomyopathy [26, 49, 50]. According to other investigators, the incidence of cardiogenic shock in cardiomyopathy stress is 20-27% [33, 51]. The

mortality of patients with TS and cardiogenic shock can be as high as 28% [52]. 45% of patients with TS develop pulmonary hypertension [53]. Contractility dysfunction in TS is persistent. An investigation by Neil *et al.* [54], indicates recovery of LV EF occurs only after 3 months from the onset of the disease.

Persistent ST-segment elevation can be observed in 13-19% in patients with stress cardiomyopathy [33, 55, 56], and in 60% of patients T-inversion is observed [33]. ST-segment elevation is a predictor of adverse TS events [55]. A prolongation of the QTc interval is observed in 28% - 54% of patients with TS [57, 58]. Patients with a prolonged QTc interval are more often intubated, they often develop cardiogenic shock, and arrhythmias compared with patients with a normal QTc interval [43, 44, 58]. Hospital mortality (25%) was increased in patients in whom QTc did not recover after hospitalization compared with mortality (9%) in patients who had a normal QTc interval after hospitalization [59].

It has now been documented an increased level of markers of necrosis troponin T and troponin I occurred in patients with TS [55, 60, 61]. Some investigators did not find an increase in myocardial necrosis markers in TS patients [46, 62, 63]. The level of necrosis markers in patients with TS is significantly lower than in patients with AMI. Thus, the peak creatine kinase (CK) was 50% lower in patients with TS compared to AMI patients [64]. Other data indicate that the CK peak in patients with AMI is 6 times higher than in patients with stress cardiomyopathy. Troponin T peak in patients with AMI is 6- fold higher than in patients with stress cardiomyopathy [60].

Life-threatening arrhythmias (asystole, ventricular tachycardia and fibrillation) are observed in 11% of TS patients [65]. According to other data, ventricular arrhythmias and AV block are observed in 12% of patients with TS [66].

Magnetic resonance imaging (magnetic resonance imaging) suggests that TS contributes to myocardial edema [67].

The outcome of stress cardiomyopathy can be a complete recovery or death of the patient, usually as a result of cardiogenic shock. Hospital mortality among patients with TS corresponds to 3.5% - 12% [68, 69]. Hospital mortality in patients without cardiopulmonary insufficiency is 1.4%, hospital mortality in patients with cardiopulmonary insufficiency is 18% [70]. According to Perez-Castellanos *et al.* [34], the hospital mortality among male patients with TS is 4.4%, and among women - 0.2%. Hospital mortality in patients with TS and life-threatening arrhythmias is 39%, in patients without arrhythmias - 9%, annual mortality among patients with arrhythmias is 48%, and in patients without arrhythmias - 14% [65]. Thus, the presence of life-threatening arrhythmias significantly worsens the prognosis of TS. Recurrence of TS occurs in 1.8-10% of patients who have experienced the takotsubo syndrome [71, 72]. Surveillance of patients who have had TS, for 5.8 ± 3.6 years, indicated that 9% have re-hospitalization for heart failure [29]. Only 5% patients died from cardiac causes. Cancer is the most common cause of death for TS patients [29].

3. PROBLEM OF DIFFERENTIAL DIAGNOSIS OF PATIENTS WITH TAKOTSUBO SYNDROME

The clinical manifestations of the takotsubo syndrome are similar to AMI. Patients with TS are usually diagnosed with ACS during admission [27]. The problem of differential diagnosis is aggravated by three more reasons. First of all, patients with TS may have atherosclerotic plaques in the coronary vessels [38, 39]. Secondly, in some cases, AMI can proceed without obstruction of the coronary arteries as Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA) [44, 73-75]. Myocardial infarction in the absence of obstructive coronary artery disease is observed in 5% to 6% of all patients with AMI [76]. Investigators believed that the main reasons MINOCA may be epicardial spasm, microvascular dysfunction, plaque disruption, non-angiographically obstructive coronary embolism/thrombosis, and spontaneous coronary artery dissection [44, 76]. Coronary vasospasm was diagnosed in 46% of patients with MINOCA undergoing provocative testing [77]. Some investigators suggest that patients with MINOCA have coronary microvascular dysfunction [76]. Spontaneous coronary artery dissection is a common cause of AMI among women <50 years of age [76]. Intravascular ultrasound and coherence tomography may allow one to identify plaque rupture or erosion as causative mechanisms of AMI with no obstructive coronary arteries [76]. Finally, TS can often occur atypically without apical ballooning [41, 42].

All of these reasons make it difficult to diagnose TS. An important role in the differential diagnosis of TS and AMI is played by BNP and Natriuretic Peptide N-Terminal Pro-B-

Type (NT-proBNP) whose level increases in patients with TS [78-81]. The peak of NT-proBNP is noted 24 h after the onset of the disease [80]. The concentration of NT-proBNP (4702 pg/ml) is 2-fold higher in patients with TS than in AIM patients (2138 pg/ml) [81]. The ratio of NTproBNP/Troponin I and NTproBNP/CK-MB was 2235 and 678 in patients with TS and 82 and 28 in patients with AMI and STEMI ($p < 0.001$) [81] (Table 1). Other investigators obtained similar data [82]. Thus, the ratio NTproBNP/Troponin I and NTproBNP/CK-MB can be used for the differential diagnosis of AMI and TS. Other investigators also point to the importance of identifying biomarkers in the differential diagnosis of TS [83]. Nevertheless, according to some investigators [44] these ratios present low sensitivity (50%). The ST elevation presented only in a minority of patients (12% of cases) with TS [44], that can also help in the differential diagnosis with STEMI. QTc interval prolongation is observed in 48% of patients with TS [58]. Patients with TS generally have normal epicardial coronary arteries at coronary angiography. However, TS can be combined with CHD in 10-14% of patients with TS [38, 39] (Table 1). Although according to some investigators [84], atherosclerotic plaques in coronary arteries can be detected in 70% of patients with TS. It should be noted that plaque rupture is not observed in patients with TS. Serious help in the differential diagnosis of AMI and TS can be angiography and single photon emission computed tomography with a radiopharmaceutical compound ^{99m}Tc -sestamibi, which allows one to identify a perfusion defect in AMI and show that there is no defect in perfusion at TS (Table 1).

Table 1. The differential diagnosis of patients with Takotsubo Syndrome (TS), Acute Myocardial Infarction (AMI) and Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA).

Indexes	TS	AMI	MINOCA
Symptoms	Chest pain, dyspnea, arrhythmias, heart failure, cardiogenic shock sudden cardiac death. TS patients are usually women	Chest pain, dyspnea, arrhythmias, heart failure, cardiogenic shock-sudden cardiac death	Chest pain, dyspnea, arrhythmias, heart failure, cardiogenic shock sudden cardiac death
ECG	ST-segment elevation (12% of cases) or depression, T-wave inversion, QTc prolongation (50% of cases)	ST-segment elevation (STEMI), ST-segment depression (NSTEMI), T-wave inversion	ST-segment elevation or ST-segment depression and/or T-wave inversion
Echocardiography	Hypokinesia or akinesia may be apical, midventricular, basal or focal	Regional wall motion abnormalities	Regional wall motion abnormalities
Coronary Angiography	Absence of obstructive CAD and/or intravascular imaging suggestive of acute plaque destabilization	CAD with acute plaque rupture and thrombus	Absence of angiographic obstructive CAD
MRI	Myocardial edema and regional wall motion abnormalities	Myocardial edema and regional wall motion abnormalities	Myocardial edema and regional wall motion abnormalities
Biomarkers	NTproBNP/TnI ratio is 2235, NTproBNP/CK-MB ratio is 678 The TnI and CK-MB level is lower than in patients with STEMI	NTproBNP/TnI ratio is 82 NTproBNP/CK-MB ratio is 28	TnI and CK-MB is increased as in STEMI

Note: CAD, coronary artery disease, CK-MB, creatine kinase, MRI, magnetic resonance image, NSTEM, non-ST elevated myocardial infarction, NTproBNP, Natriuretic Peptide N-Terminal Pro-B-Typ, STEMI, ST-elevated myocardial infarction, TnI, troponin I.

4. ETIOLOGY OF TAKOTSUBO SYNDROME

The most common cause of TS is physical or emotional stress. Consequently, a disease is called stress cardiomyopathy. Physical stress is observed in 39% - 55% of cases, while emotional stress has been reported in 17% - 33% of patients with stress by cardiomyopathy [85-87]. However, in 12% - 31% of cases, it is not possible to identify the cause of TS [85-87]. Serum norepinephrine levels were higher in patients with TS who experienced physical stress compared to those patients who had emotional stress or had no apparent reason for the occurrence of stress damage of the heart [69]. Five-year mortality among people undergoing physical stress is 30%, for people who had emotional stress, mortality was 9%, and for patients who could not identify the trigger, mortality over 5 years corresponded to 15% [87].

If stress is the main cause of TS, catecholamine and cortisol levels should be elevated in patients with stress cardiomyopathy. Indeed, it turned out that the plasma epinephrine level in patients with TS in the subacute period was significantly higher ($p = 0.0004$) [88] than in the subsequent study [88, 89]. Performing a mental stress test resulted in a greater increase in the norepinephrine level in patients with TS than in healthy volunteers [90]. The epinephrine level in the plasma of patients with TS during hospitalization was higher than in patients with acute coronary syndrome [91]. The fact that norepinephrine and epinephrine levels increase in plasma of patients with TS has been confirmed by other investigators [92]. It has been shown that sympathetic nervous activity is enhanced in patients with TS compared with patients with chronic heart failure [93]. It should be noted that sympathetic nervous activity is enhanced in patients with chronic heart failure [94]. Apparently, if a comparison was to be made between TS patients and healthy volunteers, the difference in sympathetic activity would be even more significant. It has been shown that in patients with TS, the levels of not only catecholamines, but also cortisol were increased [95].

Consequently, physical and emotional stress is important, but apparently it is not the only etiological factor in stress cardiomyopathy. Thus, according to some data, in 37% of patients with TS, the onset of syndrome was preceded by mental illness [96]. A TS trigger may be status epilepticus [97, 98] or convulsions of a different origin [99-101]. In this regard, it should be noted that bicuculline-induced status epilepticus is accompanied by an increase in the plasma norepinephrine level in dogs [102]. It has been shown that plasma norepinephrine level was increased during the generalization of seizures in a patient [103]. Patients with TS are more likely to have anxiety disorders than patients with acute coronary syndrome [104, 105]. Depression is observed in 20% of patients with TS and anxiety is noted in 31% of patients with stress cardiomyopathy [106]. The occurrence of TS can be preceded by a stroke [36, 107, 108]. It should be noted that hemorrhagic stroke is accompanied by an increase in the plasma norepinephrine and epinephrine levels [109, 110].

Thus, mental disorders and diseases of the central nervous system can be triggers of takotsubo syndrome.

The emergence of TS is associated with over-activation of the adrenergic system [111]. Indeed, TS is often seen in patients with pheochromocytoma [112-114]. There are cases of TS after an injection of adrenergic receptor (AR) agonists [115-117]. TS has been reported after opiate withdrawal [118-120], after the administration of catecholamine re-uptake inhibitors [119]. In this regard, it should be noted that opiate withdrawal syndrome is accompanied by activation of epinephrine release from the adrenal glands [121]. TS has also been reported in people who have used methamphetamine [122, 123]. In this regard, it should be noted that amphetamine and its analogs activate α - and β -AR, which stimulate the release of norepinephrine [124]. It has been documented that thyrotoxicosis can contribute to the occurrence of TS [125-128]. The pathogenic effect of an excess of thyroid hormones appears to be related to the ability of triiodothyronine to increase β_1 -AR density on cell membranes [129, 130].

There is now recent evidence of a genetic predisposition to TS [131]. It is possible that this predisposition is associated with polymorphisms of genes encoding β -ARs. Consequently, a different distribution of β_1 -AR polymorphisms Arg389 Gly is more frequently found in TS [131].

Thus, the main causes of stress cardiomyopathy may be attributed to stress, CNS disease, and effects that increase the level of catecholamines (Fig. 1).

5. PATHOGENESIS OF STRESS CARDIOMYOPATHY

The emergence of TS is associated with over-activation of the adrenergic system [23, 43, 44, 111, 132]. Indeed, as we have reported above, in patients with TS, the catecholamines level was increased and the adrenergic system was activated. In addition, it was found that as the concentration of epinephrine increases, its positive inotropic effect gives way to the negative inotropic effect due to the activation of β_2 -AR coupled with G_i -proteins [133], therefore the negative inotropic effect disappears after inhibition of the G_i -proteins by pertussis toxin. The β -AR agonist isoproterenol also had a biphasic effect [134]. The negative inotropic phase disappeared after the blockade of β_2 -AR and the use of pertussis toxin, but persisted after the application of the selective β_1 -AR antagonist CGP 20712A. Injection of large doses of epinephrine caused an apical disturbance of cardiac contractility, which eliminates the administration of the G_i -protein inhibitor pertussis toxin [135] (Fig. 2). The α_2 -AR agonist, xylazine, when administered to immobilized rats, has been shown to impair cardiac contractility, which eliminates pertussis toxin [136]. Isoproterenol (50 mg/kg intraperitoneally) was found to cause the appearance of akinetic regions in the left ventricle of rats 60 min after injection [137].

The important role of adrenergic system hyperactivation in TS is confirmed by the results of studies using AR antagonists. Thus, in a study performed on monkeys, propranolol was shown to prevent the occurrence of SIIH [10]. Propranolol had the same effect on stressed pigs [138]. The non-selective α - and β -AR antagonist labetalol prevented a disturbance of cardiac contractility in rats caused by immobilization for 30 min [139]. Metoprolol also acted [140]. We found that the selective β_1 -AR antagonist nebivolol prevents

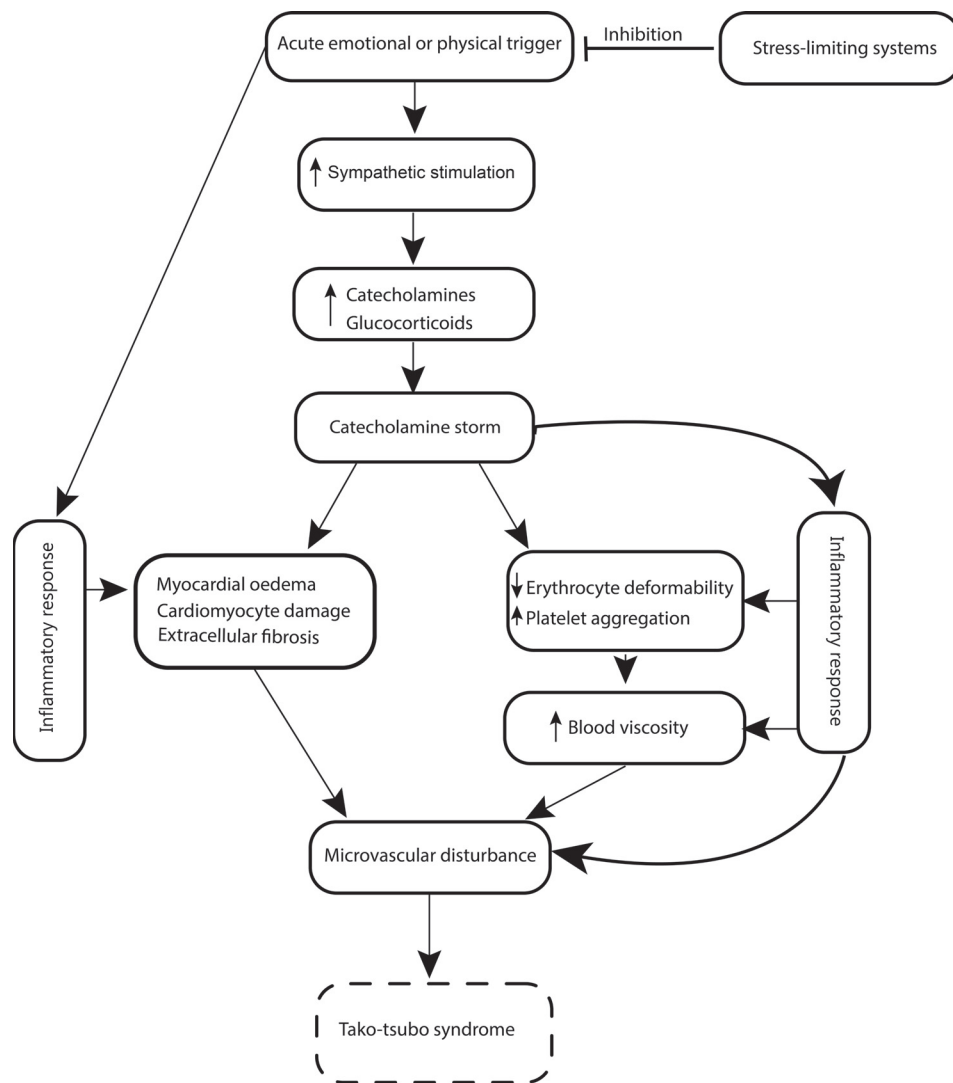


Fig. (1). Hypothetical pathophysiologic mechanisms of takotsubo syndrome.

the occurrence of SIIH. We also found that the β_2 -AR antagonist ICI-118551 exacerbates stress-induced heart's injury and that the β_3 -AR antagonist L748337 does not affect SIIH upon immobilization (unpublished data) (Fig. 2).

An important role of the adrenergic system in the pathogenesis of TS was confirmed by the studies which were performed using ^{125}I -metaiodobenzylguanidine (^{125}I -MIBG), which is an alternative to norepinephrine and, like norepinephrine, is subjected to uptake by sympathetic nerve terminals [141, 142]. Chemical sympathectomy with 6-hydroxydopamine results in impaired uptake of norepinephrine and MIBG in the heart [143]. Norepinephrine and MIBG compete with each other for the system of uptake in sympathetic nerve terminals, therefore reducing the accumulation of MIBG in the heart indicates an increase in the number of norepinephrine in the synaptic cleft, in other words, the higher the sympathetic activity, the less ^{125}I -MIBG accumulates in the heart. Keeping volunteers in hypobaric hypoxia leads to a 2-fold increase in the plasma norepinephrine level, while the level of epinephrine does not change [144]. Twenty minutes after the cessation of hypoxia, the accumulation of ^{123}I -MIBG in the heart was significantly reduced.

The accumulation of ^{123}I -MIBG remained reduced for at least 240 min after the cessation of the hypoxic exposure, until the norepinephrine level returned to normal [144]. Accumulation of ^{123}I -MIBG in the heart is significantly reduced in patients with idiopathic dilated cardiomyopathy compared with volunteers without signs of heart disease [145]. In this regard, it should be noted that the plasma norepinephrine level in patients with dilated cardiomyopathy is 3-fold higher than in the control group [145].

A decrease in ^{125}I -MIBG accumulation in the apical part of the heart has been reported in patients with TS [146]. ^{125}I -MIBG uptake has been shown to decrease in the hypokinetic regions of the heart of patients with stress cardiomyopathy [147]. ^{125}I -MIBG accumulation defects in the left ventricle of patients with TS have been noted by other investigators [89]. It has also been documented that the ratio of ^{125}I -MIBG uptake in the heart to the mediastinum is lower in the TS subacute phase than with normalization of heart's contractility 4 months after discharge from the hospital or in the control group [88]. The washout rate of ^{125}I -MIBG from the myocardium was increased in patients with TS in the subacute period compared with the control

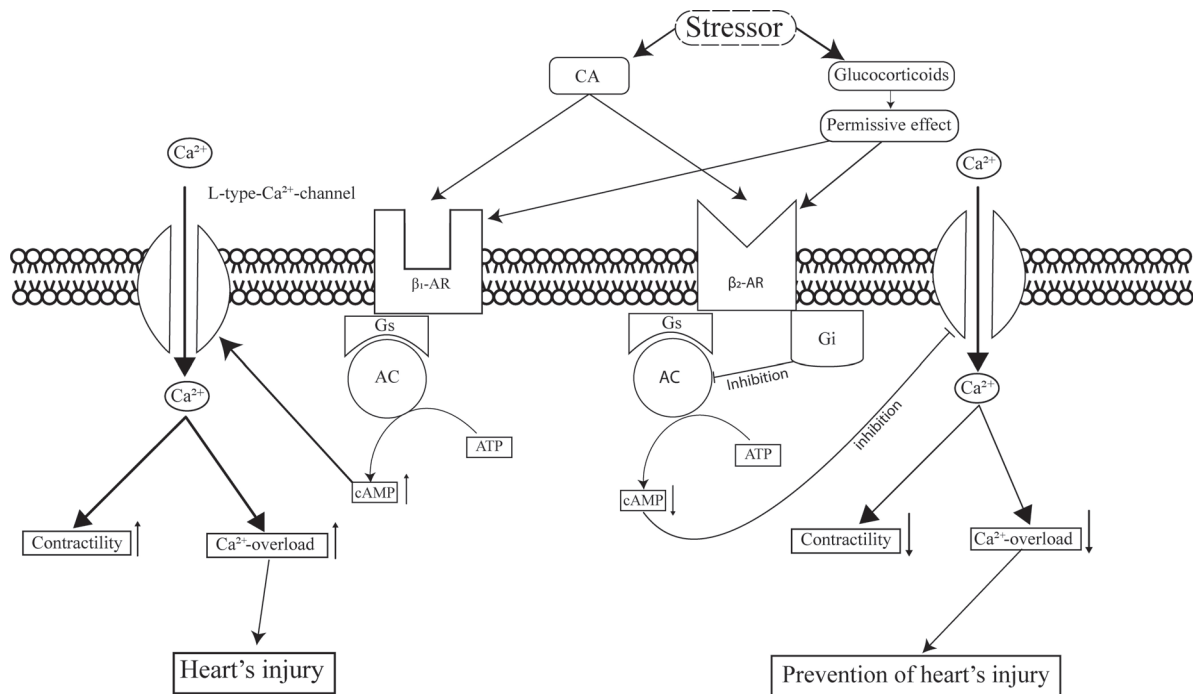


Fig. (2). An involvement of β_1 and β_2 adrenergic receptors in pathogenesis takotsubo syndrome. Abbreviations. AR, adrenergic receptor, G_s, G_i, G-proteins, AC, adenylyl cyclase, cAMP, adenosine 3',5'-cyclic monophosphate.

group [88]. Similar data were obtained by Burgdorf *et al.* [148].

The presented data convincingly show that adrenergic system is activated in patients with TS. What are the consequences of hyperactivation of the adrenergic system? Above, we have shown that it can be a contractile dysfunction of the heart. These can be heart rhythm abnormalities which are caused by catecholamines [149]. Patients with TS may have pathological changes that can also be explained by hyperactivation of the adrenergic system, for example, inflammation and edema of the myocardium. Thus, catecholamine-induced myocarditis has been reported in patients with pheochromocytoma [150-153]. Daily administration of isoproterenol at a dose of 1.2 mg for 14 days has been shown to cause myocarditis in rats [154]. At the same time, some investigators have noted that at the time of diagnosis, many (33%) patients with TS took β -AR antagonists [26]. Among patients with recurrent TS, 51% took β -blockers [26], which contradicts the leading role of catecholamines in the pathogenesis of TS.

An endomyocardial biopsy in patients with TS showed that they had mononuclear infiltration [155] and contraction-band necrosis [155, 156]. In patients with TS, the level of C-reactive protein is increased, which reaches to its maximum 72 hours after the onset of the disease [146]. Other investigators have reported an increase in the high sensitivity of C-reactive protein level patients with TS [157, 158]. Magnetic resonance imaging (MRI) data suggests myocardial edema during stress cardiomyopathy [156, 159, 160]. There is evidence that stress cardiomyopathy leads to myocardial fibrosis [160, 161]. Myocardial edema is persistent, according to Schwarz *et al.* [160], in areas with normal contractility, edema disappears 4 months after disease. It was shown that the levels of tumor necrosis factor (TNF- α) and C-reactive

protein in blood during hospitalization were increased compared to their levels in these patients one year after discharge. The levels of interleukin-6 (IL-6) and interleukin-10 were also increased in patients with TS with adverse events, including death [162]. The IL-6 and chemokine (C-X-C motif) ligand 1 (CXCL1) levels were increased in blood of patients with stress cardiomyopathy compared with the control group [163].

The aforementioned data strongly suggest that TS causes edema and inflammation of the myocardium. The inflammatory reaction in TS is systemic, as evidenced by an increase in C-reactive protein, TNF- α , and IL-6, CXCL1.

It is now hypothesized that coronary artery spasm plays an important role in the pathogenesis of TS [111]. In the first article on takotsubo syndrome, Sato *et al.* [13], presented angiographic evidence that coronary spasm plays an important role in the pathogenesis of stress cardiomyopathy. In 2002, Kurisu *et al.* [164], while were performing coronary angiography, documented spontaneous coronary spasm in three out of 30 patients with takotsubo syndrome. In 6 of the 14 patients which were included in the study, acetylcholine or ergonovine caused spasm of several coronary arteries. Four of these patients had spasm of single coronary arteries. These investigators hypothesized that, although the exact cause of stress for cardiomyopathy remains unclear, simultaneous multi-vascular spasm of the epicardial coronary arteries or microvascular spasm may contribute to the occurrence of TS. Other investigators also emphasize the important role of microvascular dysfunction in the pathogenesis of TS [43,44]. We would like to draw the reader's attention to the fact that spontaneous vasospasm of the epicardial coronary arteries was detected in only 10% of patients, which does not exclude microvascular spasm. One of the causes of impaired

coronary circulation may be attributed to the findings that the myocardial bridging of the left anterior descending artery was detected in 76% of TS [26].

In the last decade, thanks to the possibilities of new diagnostic technologies, in particular, ultrasound study of the coronary reserve and echo contrast myocardial perfusion, investigators have obtained results indicating that the main mechanism in the development of TS may be a microcirculatory dysfunction. Thus, in 2009, investigators [165], while were performing qualitative and quantitative myocardial contrast echocardiography at rest, revealed a disturbance of myocardial perfusion was typical for TS in the apical region of LV, in which an abnormal myocardial contractility was noted. A microcirculatory dysfunction in the acute phase of process was found. A disturbance of microcirculation was transient, followed by recovery within 6 months. Similar results were demonstrated by other investigators [47]. In 2017, Hung *et al.* [166], performing an echocardiographic study in a patient with TS, found indirect signs of global coronary artery vasospasm in the form of a decrease in the deformation characteristics of the left heart chambers.

Stress cardiomyopathy can adversely affect the size of the coronary reserve. Kume *et al.* [167], performed an invasive Doppler study of the coronary reserve with adenosine in the anterior descending, circumflex, and right coronary arteries during coronary angiography. Their study confirmed that coronary microcirculation and endothelial dysfunction were most likely the main origin of TS. Against the background of adenosine-mediated vasodilation, these investigators identified a reduction in coronary reserve in all three main coronary arteries during the acute phase of the process, followed by its recovery after 3 weeks. It was shown by utilizing stress echocardiography with adenosine in patients with TS, that there was a decrease in coronary reserve in the distal segment of the anterior descending artery [168]. At the same time, coronary reserve indicators had an inverse correlation with indicators of contractile and pumping function of LV. The authors regard these changes as manifestation of endothelial dysfunction and impaired coronary microcirculation. Similar data were obtained by other investigators with a similar interpretation [169]. In a study that was performed using dopplerography in the distal segment of the anterior descending coronary artery with contrast enhancement during stress echocardiography with β -AR agonist dobutamine, TS patients also showed a decrease in coronary reserve [170]. According to these investigators, these studies may indicate a coronary microcirculatory dysfunction in TS.

A study performed by Burgdorf [171] included two patients with TS. Evaluation of coronary perfusion was performed using ^{99m}Tc -methoxyisobutylisonitrile (^{99m}Tc -sestamibi), which accumulates in myocardial regions with normal perfusion. The study did not reveal any abnormalities. In another study by Burgdorf *et al.* [148], 10 patients with TS were included. Their study indicated a typical dilatation of the LV apex with hyperkinesia of the LV basal regions and akinesia of the apex of the heart. At the same time, ^{99m}Tc -sestamibi accumulation in the apical region was normal or minimally narrowed. These findings allowed the investigators to conclude that coronary spasm is rare in TS.

In another study, myocardial blood flow and coronary reserve were assessed using positron emission tomography (PET) with ^{13}N ammonium [172]. It was found that myocardial blood flow and coronary reserve were significantly reduced in the area of the apical segments, compared with the middle and basal segments. These changes completely disappeared after 3 months. However, in a study done by Hasbak *et al.* using PET [173], a decrease in myocardial blood flow in the apical region of the heart could not be detected. Perfusion in the apex region of the heart remained within the normal range, and increased in the basal regions [173]. Later on, the same group demonstrated in 25 patients that myocardial beds according to PET data with ^{13}N -ammonium or ^{82}Rb were unchanged in the apical and midventricular regions and increased in basal regions [174]. These investigators concluded that with TS, normal perfusion of certain regions of the myocardium and hyperperfusion of the basal segments takes place [174]. Somewhat different data was provided by Ghadri *et al.* [175] in the description of the clinical case of a patient with TS. Their studies indicated a reduction of perfusion and coronary reserve (PET data with ^{13}N ammonium), as well as glucose metabolism (PET data from ^{18}F -fluorodeoxyglucose) 7 days after hospitalization and full recovery of these processes after 3 months. These investigators observed changes with the development of microcirculatory dysfunction associated with the release of catecholamines into the blood. In addition, these investigators noted that the disturbance of myocardial blood flow and coronary reserve with TS are global [175].

The aforementioned studies suggested that some patients with TS have spasm of the epicardial coronary arteries. Angiographic studies indicate that in patients with stress cardiomyopathy, there is a disturbance of the coronary microcirculation and a decrease in the coronary reserve, but there is no direct evidence of spasm of the coronary arteries in the majority of patients with TS. It has been hypothesized that the over-activation of the adrenergic system plays a key role in the pathogenesis of TS [111]. In a study done by Redfors *et al.* [176], SIIH was induced by injection of the β -AR agonist isoproterenol. Microcirculation in the myocardium was assessed using contrast echocardiography. These investigators failed to detect microcirculation disorders. They concluded that apical perfusion is not impaired in rats with isoproterenol-induced heart injury.

Some investigators [177] have rejected the hypothesis of global vasospasm of the coronary arteries in the origin of stress cardiomyopathy. They consider inflammation, edema of the myocardium and vascular wall with the subsequent compression of small vessels and endothelial dysfunction as the main cause of microcirculatory disorders. It is believed that inflammation plays an important role in the origin of the takotsubo syndrome, which contributes to the slow coronary blood flow [178].

There is reason to believe that blood viscosity may play an important role in the pathogenesis of microcirculatory dysfunction. Increased blood viscosity is one of the factors which causes slower blood flow [179]. It was found that patients with TS, when the cold pressor test was performed, showed an increase in total blood viscosity, plasma viscosity, a decrease in red blood cell deformability compared with the

control group. This study included women of similar age with the same risk factors without coronary artery stenosis [180]. In both groups, a rise in the level of catecholamines was observed after the cold test. One of factors contributing to an increase in blood viscosity is likely to be increased platelet aggregation, which persists 3 months after the onset of disease [91]. Catecholamines are believed to be triggers for increasing blood viscosity in patients with TS [180]. Indeed, the whole blood viscosity has been shown to correlate with the level of epinephrine [181]. Synchronism of the increase in the level of catecholamines and the whole blood viscosity has also been noted by other investigators [182].

The aforementioned studies present substantial evidence indicating that catecholamines may act as TS triggers. However, there is the possibility that other humoral factors, such as endothelin, are involved in the TS pathogenesis. Endothelin-1 can cause spasm of the coronary arteries [183–185]. The coronary arteries of small diameter are most sensitive to endothelin-1 [183]. It is generally accepted that endothelin has a positive inotropic effect [186, 187]. However, there is evidence that endothelin-1 may reduce contractility of isolated mouse cardiomyocytes [188]. Endothelin receptor antagonists have been reported to increase the survival rate of heart failure rats [189,190], therefore endothelin may be a potential trigger point TS. It was found that the level of endothelin-1 in plasma of patients with TS is 2-fold higher than in healthy subjects [191]. These investigators believed that their data confirm microvascular spasm hypothesis of TS. However, in another clinical study, the differences in endothelin-1 levels were not found in those patients with TS compared the control group of people of similar age, gender, cardiovascular risk factors and medications [192]. Thus, the question of the involvement of endothelin-1 in the pathogenesis of TS remains open.

We hypothesize that cortisol may be another candidate for the role of a trigger in the pathogenesis of TS. Indeed, the cortisol levels are elevated in patients with TS [95]. Immobilization stress is commonly used to model TS in rats [139, 140, 193]. Immobilization causes an increase in serum not only in the corticosterone levels, but also in cortisol in these animals [194]. Glucocorticoids are known to have a permissive effect, that is, they enhance the effect of catecholamines [195, 196]. We found that the glucocorticoid receptor antagonist mifepristone reduces heart damage during immobilization stress (unpublished data).

It has been shown that microRNAs may be involved in the pathogenesis of TS [191, 197, 198]. MicroRNAs are generally considered small noncoding RNA sequences (20–23 nucleotides) that suppress the expression of various genes in eukaryotic cells [199]. MicroRNA formation occurs as a result of RNA transcription by RNA polymerase II enzyme [200], sequential processing of primary transcripts by Drosha and DGCR8 complexes (inside the cell nucleus) [201], and migration of microRNA precursors (pre-microRNA, 70 nucleotides) from the nucleus to the cytoplasm with the exportin-5 protein [200]. In the cytoplasm, pre-microRNA is hydrolyzed with RNase III and then bound to the RISC (microRNA-induced silencing complex) complex, forming a mature microRNA (miRNA) molecule. According to some investigators [202, 203], mature miRNAs together with a

complex of RISC proteins, binding to complementary sites on mRNA, blocks the translation of mRNA. Due to this ability, miRNAs participate in the regulation of a number of cellular functions and processes, such as growth, differentiation, proliferation, metabolism and apoptosis [204, 205]. It is now believed that miRNA exert their effects by migration with the blood flow to target cells inside exosomes (microvesicles) [206]. Microvesicles, in turn, can be released from cells whose tissue has undergone transient ischemia/reperfusion [206].

The aforementioned study which was performed in 2010 included patients with normal coronary arteries, stable angina STEMI, non-STEMI, takotsubo syndrome, dilated cardiomyopathy [197]. miRNA miR-1 levels were elevated only in STEMI. The miR-133a level was elevated in all patients except patients with normal coronary arteries and stable angina. These investigators tried to find out the reason for the increase. They incubated H9c2 cardiomyoblasts with calcium ionophore A23187. It turned out that A23187 leads to the appearance in the culture medium of exosomes containing miR-133a. The maximum increase in miR-133a level was at concentrations of A23187 that cause the death of cardiomyoblasts. The investigators concluded that miR-133a appears in blood of patients as a result of myocardial damage and death of cardiomyocytes [197]. The investigators of another study found that miRNA125a-5p level decreases in blood of patients with TS [191]. This miRNA inhibits the expression of endothelin-1, the level of which is elevated in patients with stress cardiomyopathy. It is possible that a decrease in the level of miRNA125a-5p is the cause of an increase in the concentration of endothelin-1 in the blood of patients with TS. The level of other miRNAs (miR-16, miR-26a, miR-1, miR-133a) was, on the contrary, increased in patients with TS compared to healthy subjects. The physiological significance of this increase in miRNA remains unclear.

Takotsubo syndrome mainly affects women who are in a state of menopause. Consequently, some investigators believe that one of the factors contributing to the onset of TS is a decrease in estrogen levels [17, 207]. Indeed, estrogen increases the tolerance of the heart to the ischemia/reperfusion [208, 209], therefore, it is likely that it can increase cardiac tolerance to stress. A study was performed on ovariectomized female rats, some of animals received estrogen [210]. Animals were subjected to immobilization stress. Chronic estrogen supplementation has been shown to improve stress-induced cardiac dysfunction and significantly increase blood pressure [210]. In addition, estrogen supplementation contributed to a threefold increase in heat shock protein 70 (HSP70). Heat shock proteins are known to increase cardiac tolerance to adverse effects, such as ischemia/reperfusion [211]. It can be assumed that such an increase in the HSP70 level contributes to increased tolerance of the heart to stress. In a study that was performed on sham-operated and the ovariectomized rats, it was shown that epinephrine resulted in more serious cardiac dysfunction and higher plasma troponin I concentration in ovariectomized rats than in the sham-operated group [212]. 17 β -Estradiol eliminated hypersensitivity to epinephrine in ovariectomized rats. The selective β_2 -AR antagonist ICI118,551 eliminated the negative inotropic effect of epinephrine in ovariec-

tomized rats. An increase in the cAMP level in the myocardium and the amount of phosphorylated protein kinase A (p-PKA) in myocardium after epinephrine injection was lower in ovariectomized rats than in the sham-operated rats. The administration of 17 β -estradiol to ovariectomized rats promoted a rise in the cAMP level and an increase in the amount of p-PKA after administration of epinephrine [212]. Thus, the presented data indicates that ovariectomy increases the sensitivity of the heart to stress and the cardiotoxic effect of epinephrine. Estradiol eliminates these disorders. In addition, these data suggest that the negative inotropic effect of ovariectomy after epinephrine injection is associated with the activation of β_2 -AR. These facts suggest that a low level of estrogen may contribute to the occurrence of TS due to the activation of β_2 -AR. However, these data do not explain the fact why TS is less common in men. It is possible that testosterone prevents the development of TS.

The central nervous system appears to play an important role in the pathogenesis of TS. The aforementioned studies indicate that TS is common in patients with CNS diseases (subarachnoid hemorrhage, status epilepticus, anxiety disorders, depression). According to some studies, 37% of TS patients were preceded by a mental illness [96]. In a study which was performed by Belcour *et al.* [98], stress cardiomyopathy was detected in 56% of patients with status epilepticus. According to Porto *et al.* [213], TS patients often suffered from neurological disorders. The most frequent neurological disorders were subarachnoid hemorrhage, followed by stroke/transient ischemic attack, and less often seizures. According to Wagdy and El Maghawry [26], mental and neurological disorders occur in 56% of patients with TS. Other investigators cite a similar figure [214]. Back in 1969, before the discovery of the “broken heart syndrome” in the UK, it was demonstrated that mortality among widowers is higher than that of their married peers [7]. The investigators considered that the cause of the increased mortality was a “broken heart,” that is heart disease. In 1980, autopsy results of people who died suddenly as a result of physical violence were published [2]. All victims of violence had myofibrillar degeneration of the heart, which could have occurred only as a result of psychological trauma. The authors of the discovery suggested to name this disease as stress cardiomyopathy. It was later known as takotsubo syndrome [13]. The most recent work has shown the important role of emotional stress in TS pathogenesis [106, 155, 215-217]. As we noted above, depression was observed in 20% of patients with TS, and anxiety in 31% of patients [106]. According to other data, anxiety disorders occur in 53% of TS patients [104].

The presented data show the important role of CNS in the pathogenesis of TS. In 2017, Tavazzi *et al.* [218] hypothesized the existence of neurogenic stress cardiomyopathy, which is similar to takotsubo syndromes. In their opinion, these are two different syndromes with common pathways. They report that abnormalities in cardiac contractility are present in 30% of patients with severe brain damage without a known history of cardiac disease. According to Tavazzi *et al.* [218], patients with severe brain damage experience an “autonomic storm,” which is responsible for cardiac stunning (Fig. 1). We have attempted to compare TS and neurogenic stress cardiomyopathy, as presented by the authors of the hypothesis. The only difference between these diseases was

that with TS, a disturbance is local (apical, basal with mild-ventricular), and with neurogenic stress cardiomyopathy, contractility dysfunction is global. A similar view is held by Marafioti *et al.* [219], who hypothesized that in severe brain diseases promote Takotsubo-like cardiac pathology development. In the occurrence of this pathology, the insula cortex lesion seems to play a pivotal role. Some investigators do not share this view [220]. We also do not share this view. In our opinion, for a more feasible hypothesis of neurogenic stress cardiomyopathy, the differences between these two syndromes should be larger.

6. THE PROBLEM OF TREATMENT OF TAKOTSUBO SYNDROME

There is currently no consensus on the most appropriate TS therapy. In the absence of randomized clinical trials, there is no evidence for highly effective treatment of TS. It is believed that in most cases, this therapy should be conservative [44]. However, some investigators suggest using intra-aortic balloon pumping to treat TS [43, 221]. In the first days after hospitalization, the risk of arrhythmias and cardiogenic shock is high, consequently, treatment should be aimed at preventing these disorders. It is suggested that the following pharmacological agents should be used for TS: β -blockers, diuretics, anticoagulants, antiarrhythmics, and levosimendan [132, 221]. In our opinion, the issue of using β -blockers cannot be considered to be resolved. On the one hand, according to our unpublished data, β_1 -AR antagonists are able to prevent stress injury of the heart in rats. On the other hand, it is well known that β -AR antagonists have the negative inotropic effect. Consequently, one cannot rule out the possibility that they will exacerbate heart failure in patients with TS. Therefore, some investigators recommend the use of short-acting intravenous β -blockers in patients without severe heart failure and bradycardia [43, 132]. Moreover, it is now recommended to use catecholamines in patients with TS and cardiogenic shock, but keeping aware that they can exacerbate heart damage [132]. Levosimendan has been suggested as an alternative to catecholamines, but there is a lack of convincing data on its effectiveness in patients with TS [132]. It is believed that in the absence of obstruction, drugs with positive inotropic action (*i.e.*, dobutamine, milrinone, dopamine, or levosimendan) can be used to increase cardiac output [43]. Some investigators recommend the use of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers for treatment of TS [44, 132]. Other investigators recommend that prophylactic anticoagulants should be used to prevent apical thrombus formations [132].

CONCLUSION

The presented data indicate that emotional and physical stress plays a triggering role in the onset of takotsubo syndrome. Indeed, in patients with TS plasma norepinephrine and epinephrine level are increased, which proves the stressful nature of TS. However, in 12% - 31% of cases, it is not possible to identify the main cause of TS. It would be interesting to compare the level of catecholamines in those patients with TS who have undergone stress, and in patients with takotsubo syndrome, in whom the cause of cardiomyopathy has not been identified. In 37% of patients with TS,

the mental illness preceded stress cardiomyopathy. The trigger for TS may be status epilepticus, stroke, pheochromocytoma, adrenergic injection, opiate withdrawal syndrome. These conditions are accompanied by an increase in the level of catecholamines, which play a trigger role in TS. Catecholamines in toxic doses have a negative inotropic effect, which confirms their role in the pathogenesis of takotsubo syndrome. It has been documented that patients with TS have signs of myocarditis and systemic inflammation, microcirculatory dysfunction, some patients have coronary spasm. Whether catecholamines can cause all these disturbances is still unknown. The mystery is the fact that countless millions of people endure stress each year, but only a few thousand develop stress cardiomyopathy. Apparently, there are the certain mechanisms in the body of most individuals that limit the stress response. In this regard, we should recall the hypothesis of Professor Meerson about the existence of stress-limiting systems to which he attributed endogenous antioxidants, GABA, and endogenous opioids [222, 223]. The ability of opioids to limit the adrenergic effect on the heart is a known fact [224]. In our opinion, a comparative determination of the level of opioid peptides in patients with TS, patients with acute coronary syndrome and healthy volunteers could help in fully understanding the pathogenesis of TS.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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