Cardiovascular Innovations and Applications

Vol. 7 (2022) 1
ISSN 2009-8618
DOI 10.15212/CVIA.2022.0010

REVIEW

Mechanisms of Myocardial Stunning in Stress-Induced Cardiomyopathy

Quanwei Pei[1,a], Nadine Mbabazi[2,a], Lina Zou[1,a], Junpei Zhang[1], Hongpeng Yin[1], Bin Li[1], Jiaxin Wang[1], Weifa Wang[1], Pengqi Lin[1], Junjie Yang[1], Dechun Yin[1]

[1]*Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China*
[2]*Department of Cardiology, King Faisal Hospital, Kigali, Rwanda*

Received: 11 April 2022; Revised: 10 June 2022; Accepted: 28 June 2022; Published Online: 17 August 2022

Abstract

Stress-induced cardiomyopathy, in contrast to acute myocardial infarction, is a type of acute heart failure characterized by reversible left ventricular dysfunction. Cardiac imaging primarily reveals left ventricle myocardial stunning, 81.7% of which is apical type. Emotional or psychological stress usually precedes the onset of stress-induced cardiomyopathy, which is increasingly being recognized as a unique neurogenic myocardial stunning disease. To distinguish between acute myocardial infarction and acute viral or auto-immune myocarditis, this review summarizes specific mechanisms of myocardial stunning in stress-induced cardiomyopathy, such as calcium disorders, metabolic alterations, anatomical and histological variations in different parts of the left ventricle, and microvascular dysfunction.

Keywords: Stress-induced cardiomyopathy; Myocardial stunning; Calcium disorders; Metabolic alterations; Coronary microvascular dysfunction

Introduction

Stress-induced cardiomyopathy, also known as Takotsubo syndrome (TTS), broken heart syndrome and apical ballooning syndrome, accounts for approximately 5–6% of all suspected cases of acute coronary syndrome in women [1]. This acute heart failure syndrome is characterized by myocardial hypocontractility from the mid-left ventricle to the apex without clear coronary artery stenosis. The classical definition of myocardial stunning is cardiac mechanical dysfunction following complete recovery of coronary blood flow or transient myocardial ischemia. Cardiac systolic function can be restored within hours or days. In stress-induced cardiomyopathy, the left ventricular ejection fraction usually recovers in the short term, whereas electrocardiogram changes and brain natriuretic peptide levels may require 6–12 months to recover. Therefore, stress-induced cardiomyopathy is recognized as a unique neurogenic myocardial stunning disease. The precise pathophysiological mechanism of typical left ventricular stunning in the acute stage of stress-induced cardiomyopathy remains unclear. This review discusses the mechanisms of left ventricular myocardial stunning in stress-induced cardiomyopathy.

[a]Quanwei Pei, Nadine Mbabazi and Lina Zou contributed equally to this article.

Correspondence: **Dr. Dechun Yin**, Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China, E-mail: yindechun@hrbmu.edu.cn

Calcium disorders

Calcium ions are important second messenger in cardiomyocytes and participate in the process of heart contraction, sympathetic stimulation and gene expression, etc. After calcium disorders in ventricular myocytes, myocardial stunning can be caused by several mechanisms, such as altered release and uptake of calcium ions in the sarcoplasmic reticulum, and decreased sensitivity of calcium ions to muscle filaments. Fatal arrhythmias occur in 13.5% of patients with stress-induced cardiomyopathy. These patients typically have a low ejection fraction [2], which may be closely associated with a Ca^{2+} imbalance in cardiomyocyte contraction and relaxation. The influx of calcium ions via an L-type calcium current is critical for the heart's excitation contraction coupling and causes the release of Ca^{2+} from the sarcoplasmic reticulum. The intracellular Ca^{2+} then binds troponin C and causes cardiomyocytes to contract. The calcium balance between the sarcoplasmic reticulum and the cytoplasm is regulated primarily by sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA)/phospholamban (PLB) and RyR2 on the endoplasmic reticulum membrane [3].

The contraction and relaxation of cardiomyocytes in the acute and convalescent stages of stress-induced cardiomyopathy have been found to be slow, according to confocal microscopy, and to be associated with a slow peak value of the calcium transient and slow recovery of calcium in the sarcoplasmic reticulum, thus resulting in calcium transient stunning [4]. The ratio of SERCA to PLB is the most important factor in sarcoplasmic reticulum Ca^{2+} recovery [5]. SERCA, a Ca^{2+}-ATPase in the myocardial sarcoplasmic reticulum, actively pumps cytoplasmic calcium into the sarcoplasmic reticulum. PLB is a phosphoprotein with 52 amino acid residues that binds the cardiomyocyte sarcoplasmic reticulum. It is found primarily in ventricular myocytes, and it interacts with SERCA via phosphorylation and dephosphorylation, monomer PLB binds to SERCA2a and acts as negative regulator of SERCA2a. Phosphorylated pentamer PLB loses its inhibitory effect on SERCA2a. The SERCA/PLB ratio accurately represents myocardial diastolic and systolic activity, and changes in this ratio directly reflect changes in cardiac function [6]. In a study of ten patients with stress-induced cardiomyopathy, sarcolipin, which is expressed primarily in atrial myocytes, has been found to be highly expressed in left ventricular cardiomyocytes, and to decrease SERCA's activity and affinity for calcium ions by acting in collaboration with phosphorylated PLB; however, the expression of the sodium calcium exchanger NCX and ryanodine receptor 2 (RyR2) has not been found to increase [7]. Under isoproterenol stimulation, pluripotent differentiated stem cells from patients with TTS show elevations in cyclic adenosine monophosphate (cAMP) and subsequently pSer2808-RyR2, thus increasing calcium leakage from the diastolic sarcoplasmic reticulum [8]. In vivo, an increase in Ang II increases the expression of oxidized calmodulin-dependent protein kinase II (oxidized-CaMKII) and consequently the level of pSer2808-RyR2 [9]. Wang et al. have discovered that adult cardiomyocytes, after 24-hour noradrenaline stimulation, show an increase in contraction amplitude to the same extent as that after short-term (10-minute) stimulation. However, this long-term stimulation is dependent not on an increase in protein kinase A (PKA) but on an increase in P-^{17} ThrCaMKII. The spatial conformation of RyR2 is altered by phosphorylated CaMKII [10], thus suggesting that calcium ion disorders in stress-induced cardiomyopathy occur through a multifaceted process. Other pathways in cardiomyocytes that cause phosphorylation and oxidation of RyR2 may exist, involving the participation of various mechanisms, such as direct sympathetic toxicity and excessive catecholamine. MicroRNA (miR)-16 and miR-26a have been identified as blood specific markers in patients with stress-induced cardiomyopathy in recent studies. Liam et al. have discovered that overexpression of miR-16 and miR-26a in apical cardiomyocytes significantly decreases apical cardiomyocyte contractility while increasing the contractility of cardiac basal cardiomyocytes stimulated by isoproterenol. Further research has shown that overexpression of microRNAs associated with stress-induced cardiomyopathy inhibits the voltage dependence of an L-type calcium current β1 protein (voltage dependent L-type calcium channel subunit beta-1, CACNB1), thus decreasing the calcium transient amplitude and calcium concentration in the sarcoplasmic reticulum [11]. Therefore, stress-induced cardiomyopathy ultimately decreases

excitation-contraction coupling and leads to myocardial stunning.

Metabolic alterations

Metabolic alterations are closely associated with myocardial stunning, according to recent research. Patients with stress-induced cardiomyopathy have metabolic alterations, particularly in lipid metabolism and myofibrillar structure destruction, that may decrease ATP utilization, in a crucial aspect in the myocardial stunning process. Fatty acids, which provide 65% of the ATP in cardiomyocytes, are the preferred substrate for myocardial utilization. FDG-PET has revealed abnormal apical metabolism in patients with acute stress-induced cardiomyopathy [12]. The utilization of free fatty acids decreases, and lipid droplets infiltrate into the apical segment of myocardial tissue [13]. The expression of the apolipoprotein B (ApoB) lipoprotein gene, which is involved in intracellular lipid transport, has been found to be diminished in left ventricular endocardial biopsies of patients with stress-induced cardiomyopathy. The cardiac function of the stress-induced cardiomyopathy model caused by isoproterenol has been found to significantly improve in mice overexpressing ApoB [14]. HL-1 cardiomyocytes exposed to high concentrations of epinephrine or to the plasma of patients with stress-induced cardiomyopathy have shown reversible electrical activity inhibition. Excess lipids in cells accelerate cellular lipid oxidation, thus resulting in accumulation of cellular reactive oxygen species (ROS), as well as disruption of intracellular protein homeostasis and biofilm integrity [15]. In stress-induced cardiomyopathy, the left ventricle increases glucose uptake by increasing the expression of the glucose transport receptor, but glucose-6-phosphate, the end product of glycolysis, additionally increases, thus indicating that glucose metabolism is abnormal in stress-induced cardiomyopathy [16]. Carnitine palmitoyltransferase-1b is a key enzyme located on the mitochondrial membrane, where it regulates fatty acid oxidation. Its activity is regulated by malonyl coenzyme A, a product of Krebs cycle regulation. During stress-induced cardiomyopathy, the mRNA level of carnitine palmitoyltransferase-1b significantly increases in the apex of the heart, although the protein level does not change. Malonyl coenzyme A overexpression may eventually result in the down-regulation or modification of fatty acid oxidation pathways. Mitochondria are known as the powerhouse of the cell, and mitochondrial dysfunction is considered the primary mechanism linking myocardial stunning to stress-induced cardiomyopathy. Radionuclide Tc-99m sestamibi myocardial perfusion imaging has revealed that the mitochondrial membranes of cardiomyocytes are damaged in patients with newly diagnosed and recurrent stress-induced cardiomyopathy [17]. Mitochondria isolated from patients with stress-induced cardiomyopathy show diminished mitochondrial area and activity of the NADH-associated respiratory chain in vitro [4]. Tempol is a superoxide dismutase analogue that decreases ROS generated by stress-induced cardiomyopathy, thus decreasing mitochondrial swelling and increasing mitochondrial membrane potential [18]. The key factors in mitochondrial ROS production are oxidative phosphorylation associated with metabolism and mitochondrial respiratory chain dysfunction. Excessive ROS accumulation causes a continual loss of potassium ions and high-energy phosphate, and increases the concentrations of calcium ions in the cytoplasm, thereby resulting in a decrease in cardiomyocyte contractility [15].

Anatomical and histological variations in various parts of the left ventricle

Apical myocardial stunning, which may be the basis of stress-induced cardiomyopathy, is caused by anatomical and histological differences between the apical and basal regions of the heart. In recent research, in isolated single apical and basal cardiomyocytes cultured in vitro, β2AR-dependent cAMP levels have been found to be equal in the cytosol of apical and basal cardiomyocytes, but the reactivity of β2 adrenergic receptor-dependent cAMP has been found to decrease because of the presence of more T-tubes and caveolar densities in cardiac basal cardiomyocytes [19]. Cardiac sympathetic excitation produces cardiotoxicity in the heart, mainly through noradrenaline. MIBG is an analogue of guanidine, an adrenal nerve blocker, which is stored in the vesicles of sympathetic nerve endings. ^{123}I-MIBG myocardial imaging can be used to assess changes in adrenergic nerve function in the

myocardium. The H/M value in patients with stress-induced cardiomyopathy is significantly lower than that in patients with acute myocardial infarction, and it recovers after the onset of myocardial stunning [20].

Activation of the left stellate ganglion and cardiac sympathetic nerves can cause typical apex myocardial stunning, whereas midventricular myocardial stunning may occur after activation of the right stellate ganglion and cardiac sympathetic nerves [21]. The density of the basal sympathetic ganglia at the bottom of normal human hearts is approximately 40% higher than that at the cardiac apex; this finding appears to be inconsistent with the typical TTS-like changes in the left ventricle in stress-induced cardiomyopathy. However, β2 adrenergic receptors are more densely distributed in the heart's apex than the bottom, thus explaining the uneven distribution of β2 adrenergic receptor density, which is an important factor in maintaining sympathetic balance under physiological conditions. When stress-induced cardiomyopathy occurs, this physiological difference may result in apical cardiomyocytes showing a more sensitive response to catecholamine in the blood. When large amounts of norepinephrine and isoproterenol are injected into the jugular vein in rats, injection of isoproterenol induces greater apical myocardial stunning. Thus, increased β-adrenergic receptor density at the apex substantially contributes to left ventricular systolic dysfunction in stress-induced cardiomyopathy.

G protein coupled receptor kinase (GRK), a key regulator of β-AR signal transduction and desensitization, promotes and activates β-AR phosphorylation. β-arrestin, which acts in membrane translocation, effectively binds β-adrenergic receptors, thus restricting the distribution of β-AR on the cell membrane. In patients with acute TTS, endocardial biopsy has revealed overexpression of GRK2 and β-arrestin2, which is more prevalent in the cell membrane in stress-induced cardiomyopathy than in dilated cardiomyopathy. Decreased GRK2 and β-arrestin2 have been observed in the second biopsy during cardiac function recovery, thus indicating that GRK2 and β-arrestin2 play important roles in left ventricular dysfunction in stress-induced cardiomyopathy [22]. However, findings regarding whether GRK5 is involved in the progression of stress-induced cardiomyopathy are inconsistent across studies, and more research is needed to confirm this possibility [23, 24]. Circulating norepinephrine and epinephrine interact with β1 and β2 under physiological conditions. Adrenaline binds the β1 adrenergic receptor, which in turn activates the Gs protein-enzyme adenylyl cyclase-PKA pathway, thus resulting in a positive inotropic effect. Patients with stress-induced cardiomyopathy are stimulated by supraphysiological catecholamine concentrations in the blood and subsequently produce large amounts of PKA via stimulation of the β1 and β2 adrenergic receptors, thereby resulting in β2 adrenergic receptor phosphorylation, further phosphorylation of GRK and recruitment of Gβγ. As a result of the change in β2 receptor binding from Gs to Gi, the binding of the β2 adrenergic receptor and Gi protein decreases adenylyl cyclase production and muscle strength [25]. This change is reversed when the concentration of circulating catecholamine decreases [26, 27]. The histological differences between the apex and the bottom of the heart make the apex more responsive to catecholamine in the acute stage of stress-induced cardiomyopathy. In this stage, changes in the β-adrenergic receptor signaling pathway have important roles in the occurrence of myocardial stunning. When the circulating catecholamine concentration falls bellow that in early stages of the disease, left ventricular myocardial stunning is ameliorated. This aspect is the critical distinction between this decease and irreversible ventricular wall motion abnormalities caused by myocardial infarction.

Microvascular dysfunction

Patients with stress-induced cardiomyopathy experience emotional stress and physical injury, which primarily result in a sharp increase in blood catecholamine levels, owing to abnormal activation of the brain cardiac axis and sympathetic adrenal system [28]. Wittstein et al. have discovered that the plasma catecholamine concentration is several times higher in patients with acute TTS than in patients with ST-segment elevation myocardial infarction. One week after the onset of TTS, patients' plasma catecholamine levels have been found to remain higher than those in patients with ST-segment elevation myocardial infarction [29]. The rapid release of catecholamine causes transient ischemia of the

myocardium via multiple coronary artery spasms and coronary microvascular dysfunction, thus resulting in local myocardial systolic dysfunction. In the autopsies of five patients with stress-induced cardiomyopathy, endocardial or transmural myocardial necrosis has been discovered. The International Center for stress-induced cardiomyopathy has registered the coronary angiography results of 1,016 patients with stress-induced cardiomyopathy, 64.2% of whom had coronary atherosclerosis. Notably, 41.2% of the patients had non-obstructive coronary atherosclerosis, and 23% had obstructive arteriosclerosis and clearer slow blood rheology of the anterior descending branch [30–32]. In patients with stress-induced cardiomyopathy, the fractional flow reserve and thrombolysis in myocardial infarction frame counts have been measured. The findings have indicated no major abnormalities in coronary artery function, thus demonstrating that stress-induced cardiomyopathy fundamentally differs from the irreversible phased dyskinesia caused by severe vascular occlusion. Noninvasive microvascular assessment, such as myocardial perfusion magnetic resonance imaging, has indicated that microvascular dysfunction may play a major role in the pathogenesis of stress-induced cardiomyopathy. Microvascular dysfunction is unevenly distributed in three coronary artery territories, among which anterior descending artery microvascular dysfunction is more common and clearer than others. The area of abnormal myocardial stunning is approximately the same as that of microvascular dysfunction in the acute stage of stress-induced cardiomyopathy [31]. Increasing evidence indicates that stress-induced cardiomyopathy cannot be clearly distinguished from coronary artery obstructive disease. The original coronary atherosclerosis of stress-induced cardiomyopathy, particularly in the anterior descending branch, may cause transient and severe myocardial ischemia due to vasospasm resulting from high plasma catecholamine, thus leading to myocardial stunning at the apex of the left ventricle.

Conclusion

Although left ventricular systolic function can be largely restored in most patients with stress-induced cardiomyopathy, the risk of serious in-hospital complications is comparable to that in patients with acute coronary syndrome. Because of the complex mechanisms of brain-heart interaction, the differences between myocardial stunning caused by the acute stage of stress-induced cardiomyopathy versus myocardial infarction include not only the short-term recovery of systolic function in the former, but also the association between the long-term presence of diastolic dysfunction and the prognosis of stress-induced cardiomyopathy [33]. Consequently, better understanding of stress as a distinct myocardial stunning disease is critical to differentiate it from the typical myocardial stunning caused by severe coronary artery stenosis. This review discussed the causes of transient systolic dysfunction of the left ventricular apex, including calcium ion disorders, metabolic alterations, coronary artery spasms, and microvascular dysfunction. However, because clinical samples from patients with stress-induced cardiomyopathy are difficult to obtain, and animal models have limitations, the pathological mechanism of left ventricular systolic dysfunction cannot be fully explained. More research is needed to establish the pathogenesis of stress-induced cardiomyopathy.

Funding

This work was supported primarily by the Distinguished Young Foundations of the First Affiliated Hospital of Harbin Medical University (HYD2020JQ002 to Dr Yin) and The Science Foundation of the First Affiliated Hospital of Harbin Medical University (2018 L001 to Dr Yin).

Conflicts of interest

The authors declare they have no conflicts of interest.

REFERENCES

1. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018;39(22):2032–46.
2. Stiermaier T, Eitel C, Denef S, Desch S, Schuler G, Thiele H, et al. Prevalence and clinical significance of life-threatening arrhythmias in takotsubo cardiomyopathy. J Am Coll Cardiol 2015;65(19):2148–50.
3. Kushnir A, Wajsberg B, Marks AR. Ryanodine receptor dysfunction in human disorders. Biochim Biophys Acta Mol Cell Res 2018;1865(11 Pt B):1687–97.
4. Willis BC, Salazar-Cantú A, Silva-Platas C, Fernández-Sada E, Villegas CA, Rios-Argaiz E, et al. Impaired oxidative metabolism and calcium mishandling underlie cardiac dysfunction in a rat model of post-acute isoproterenol-induced cardiomyopathy. Am J Physiol Heart Circ Physiol 2015;308(5):H467–77.
5. Stammers AN, Susser SE, Hamm NC, Hlynsky MW, Kimber DE, Kehler DS, et al. The regulation of sarco(endo)plasmic reticulum calcium-ATPases (SERCA). Can J Physiol Pharmacol 2015;93(10):843–54.
6. Raguimova ON, Aguayo-Ortiz R, Robia SL, Espinoza-Fonseca LM, Dynamics-driven allostery underlies Ca^{2+}-mediated release of SERCA inhibition by phospholamban. Biophys J 2020;119(9):1917–26.
7. Nef HM, Möllmann H, Troidl C, Kostin S, Voss S, Hilpert P, et al. Abnormalities in intracellular Ca^{2+} regulation contribute to the pathomechanism of Tako-Tsubo cardiomyopathy. Eur Heart J 2009;30(17):2155–64.
8. Borchert T, Hübscher D, Guessoum CI, Lam TD, Ghadri JR, Schellinger IN, et al. Catecholamine-dependent β-adrenergic signaling in a pluripotent stem cell model of takotsubo cardiomyopathy. J Am Coll Cardiol 2017;70(8):975–91.
9. Erickson JR, Joiner ML, Guan X, Kutschke W, Yang J, Oddis CV, et al. A dynamic pathway for calcium-independent activation of CaMKII by methionine oxidation. Cell 2008;133(3):462–74.
10. Wang W, Zhu W, Wang S, Yang D, Crow MT, Xiao RP, et al. Sustained beta1-adrenergic stimulation modulates cardiac contractility by Ca^{2+}/calmodulin kinase signaling pathway. Circ Res 2004;95(8):798–806.
11. Couch LS, Fiedler J, Chick G, Clayton R, Dries E, Wienecke LM, et al. Circulating microRNAs predispose to Takotsubo syndrome following high-dose adrenaline exposure. Cardiovasc Res 2022;118:1758–70.
12. Eitel I, Behrendt F, Schindler K, Kivelitz D, Gutberlet M, Schuler G, et al. Differential diagnosis of suspected apical ballooning syndrome using contrast-enhanced magnetic resonance imaging. Eur Heart J 2008;29(21):2651–9.
13. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, Carbone I, Muellerleile K, Aldrovandi A, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. J Am Med Assoc 2011;306(3):277–86.
14. Shao Y, Redfors B, Ståhlman M, Täng MS, Miljanovic A, Möllmann H, et al. A mouse model reveals an important role for catecholamine-induced lipotoxicity in the pathogenesis of stress-induced cardiomyopathy. Eur J Heart Fail 2013;15(1):9–22.
15. Fineschi V, Michalodimitrakis M, D'Errico S, Neri M, Pomara C, Riezzo I, et al. Insight into stress-induced cardiomyopathy and sudden cardiac death due to stress. A forensic cardio-pathologist point of view. Forensic Sci Int 2010;194(1–3):1–8.
16. Godsman N, Kohlhaas M, Nickel A, Cheyne L, Mingarelli M, Schweiger L, et al. Metabolic alterations in a rat model of takotsubo syndrome. Cardiovasc Res 2022;118:1932–46.
17. Miyajima K, Tawarahara K, Saito N. Serial changes of myocardial perfusion imaging in takotsubo and reverse takotsubo cardiomyopathy. J Nucl Cardiol 2021; Online ahead of print. doi: 10.1007/s12350-021-02755-y. PMID: 34427859.
18. Qi C, Liu X, Xiong T, Wang D. Tempol prevents isoprenaline-induced takotsubo syndrome via the reactive oxygen species/mitochondrial/anti-apoptosis /p38 MAPK pathway. Eur J Pharmacol 2020;886:173439.
19. Wright PT, Bhogal NK, Diakonov I, Pannell LMK, Perera RK, Bork NI, et al. Cardiomyocyte membrane structure and cAMP compartmentation produce anatomical variation in β2AR-cAMP responsiveness in murine hearts. Cell Rep 2018;23(2):459–69.
20. Ito K, Sugihara H, Kinoshita N, Azuma A, Matsubara H. Assessment of Takotsubo cardiomyopathy (transient left ventricular apical ballooning) using 99mTc-tetrofosmin, 123I-BMIPP, 123I-MIBG and 99mTc-PYP myocardial SPECT. Ann Nucl Med. 2005 Sep;19(6):435-45.
21. Bonnemeier H, Demming T, Weidtmann B, Ortak J, Burgdorf C, Reppel M, et al. Differential heart rate dynamics in transient left ventricular apical and midventricular ballooning. Heart Rhythm 2010;7(12):1825–32.
22. Nakano T, Onoue K, Nakada Y, Nakagawa H, Kumazawa T, Ueda T, et al. Alteration of β-adrenoceptor signaling in left ventricle of acute phase takotsubo syndrome: a human study. Sci Rep 2018 24;8(1):12731.
23. Figtree GA, Bagnall RD, Abdulla I, Buchholz S, Galougahi KK, Yan W, et al. No association of G-protein-coupled receptor kinase 5 or β-adrenergic receptor polymorphisms with Takotsubo cardiomyopathy in a large Australian cohort. Eur J Heart Fail 2013;15(7):730–3.

24. Novo G, Giambanco S, Guglielmo M, Arvigo L, Sutera MR, Giambanco F, et al. G-protein-coupled receptor kinase 5 polymorphism and Takotsubo cardiomyopathy. J Cardiovasc Med (Hagerstown) 2015;16(9): 639–43.
25. Feldman AM, Cates AE, Veazey WB, Hershberger RE, Bristow MR, Baughman KL, et al. Increase of the 40,000-mol wt pertussis toxin substrate (G protein) in the failing human heart. J Clin Invest 1988;82(1):189–97.
26. Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy–a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. Nat Clin Pract Cardiovasc Med 2008;5(1):22–9.
27. Paur H, Wright PT, Sikkel MB, Tranter MH, Mansfield C, O'Gara P, et al. High levels of circulating epinephrine trigger apical cardiodepression in a β2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy. Circulation 2012;126(6): 697–706.
28. Templin C, Hänggi J, Klein C, Topka MS, Hiestand T, Levinson RA, et al. Altered limbic and autonomic processing supports brain-heart axis in Takotsubo syndrome. Eur Heart J 2019;40(15):1183–7.
29. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005;352(6): 539–48.
30. Napp LC, Cammann VL, Jaguszewski M, Szawan KA, Wischnewsky M, Gili S, et al. Coexistence and outcome of coronary artery disease in Takotsubo syndrome. Eur Heart J 2020;41(34):3255–68.
31. Y-Hassan S. Coronary microvascular dysfunction in Takotsubo syndrome: cause or consequence. Am J Cardiovasc Dis 2021;11(2):184–93.
32. Slomka P, Hung GU, Germano G, Berman DS. Novel SPECT Technologies and Approaches in Cardiac Imaging. Cardiovasc Innov Appl 2016;2(1):31–46.
33. Scally C, Rudd A, Mezincescu A, Wilson H, Srivanasan J, Horgan G, et al. Persistent long-term structural, functional, and metabolic changes after stress-induced (Takotsubo) cardiomyopathy. Circulation 2018;137(10):1039–48.