Heart Failure Reviews (2019) 24:101–108
https://doi.org/10.1007/s10741-018-9729-5

Autonomic nervous system in Takotsubo syndrome

Sonia Borodzicz[1,2] · Katarzyna Czarzasta[1] · Grzegorz Opolski[2] · Agnieszka Cudnoch-Jędrzejewska[1]

Published online: 30 July 2018

Abstract
Takotsubo syndrome (TTS) is an acute and usually reversible heart failure syndrome with symptoms resembling acute myocardial infarction, however, without obstruction of coronary arteries. In the majority of cases, TTS is preceded by emotional or physical stress and the disease concerns mainly postmenopausal women. Although several hypotheses have been introduced, the pathogenesis of TTS is controversial and still remains to be determined. As reported in recent studies, the role of the autonomic nervous system (ANS) seems to be pivotal in the pathogenesis of TTS. Therefore, the aim of this article is to summarize and discuss the current knowledge of the pathogenesis of TTS with a special focus on the ANS.

Keywords Takotsubo syndrome · Pathophysiology · Autonomic nervous system · Sympathetic nervous system

Introduction

Takotsubo syndrome (TTS) is an acute and usually reversible heart failure syndrome with symptoms similar to acute myocardial infarction (MI) without coronary artery obstruction [1, 2]. Typically, TTS patients present acute chest pain, breathlessness, and palpitations caused by sinus tachycardia or other types of arrhythmia as well as characteristic ECG changes [1]. Other more serious symptoms may include presyncope or syncope resulting from ventricular tachyarrhythmias, severe left ventricular (LV) outflow tract obstruction, or cardiogenic shock [1]. The estimated number of TTS cases worldwide is between 50,000–100,000 per annum [1, 3, 4]. The average in-hospital mortality rate is 2–5%, mostly due to refractory cardiogenic shock or ventricular fibrillation [1].

TTS was first reported in 1990 in Japan and was named after a Japanese pot called "Takotsubo," whose shape resembles the systolic shape of LV observed in ventriculography [5–8]. The classical pattern described in the first report of TTS and observed in 50–80% of patients is associated with apical and mid-ventricular hypokinesia with basal hyperkinesia of LV [1]. There are two other prevalent variants of TTS: the inverted variant with basal hypokinesia and apical hyperkinesia, and mid-ventricular TTS with mid-ventricular hypokinesia and hypercontractility of both basal and apical segments [1]. Several other rare variants of TTS have been reported, such as biventricular apical hypokinesia, right ventricular TTS, and apical-sparing variant of TTS [9–12].

TTS has a unique predilection for postmenopausal women (which constitute the vast majority of TTS cases), although TTS also occurs in men, younger women, and pediatric patients [1, 13].

Previously, TTS was called "stress cardiomyopathy" and "broken heart cardiomyopathy," because of the stressful events which trigger the symptoms. It has been reported that TTS may be preceded by emotional and physical stress; however, approximately 30% of patients do not present with an identifiable trigger [1, 14]. An analysis of 1750 patients enrolled in the International Takotsubo Registry revealed that 36.0% of cases were preceded by physical factors, 27.7% by emotional triggers, 7.8% both by emotional and physical triggers, and 28.5% by no evident trigger. In the analyzed group of this study, the onset of TTS symptoms in 20 patients was preceded by positive emotions and events [15]. It has been proven that positive emotions may increase the activity of the autonomic nervous system to a comparable level as negative emotions [15]. The authors suggested that both positive and negative events are involved in a common emotional pathway modulating the nervous system which results in the induction of TTS [15].

Several hypotheses concerning the pathogenesis of TTS have been proposed, such as (1) myocardial ischemia, (2)

✉ Agnieszka Cudnoch-Jędrzejewska
agnieszka.cudnoch-jedrzejewska@wum.edu.pl

[1] Department of Experimental and Clinical Physiology, Laboratory of Centre for Preclinical Research, Medical University of Warsaw, 1b Banacha Street, 02-097 Warsaw, Poland

[2] 1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

catecholamine-induced cardiotoxicity, (3) LV outflow tract obstruction, (4) increased ventricular afterload, and (5) enhanced autonomic nervous system activity [1, 2, 16].

The pathogenesis of TTS is controversial and still remains to be determined. As reported in recent studies, the role of the autonomic nervous system (ANS) seems to be pivotal in the pathogenesis of TTS. Therefore, the aim of this article is to summarize and discuss the current knowledge of the pathogenesis of TTS with a special focus on the ANS.

Autonomic nervous system in the pathogenesis of TTS

It has been proposed that enhanced activity of the sympathetic nervous system (SNS) plays a central role in the pathophysiology of TTS [2, 16, 17]. An acute emotional or physical trigger activates the SNS and induces the release of catecholamines as a physiologic response to the stressful incident. The SNS can act through two mechanisms: (1) sympathoneural, causing local myocardial discharge of norepinephrine, and (2) adrenomedullary hormonal, increasing the level of blood catecholamines. Subsequently, catecholamines may activate several pathophysiologic mechanisms, such as damage to cardiomyocytes and microvascular dysfunction (Fig. 1) [16].

A histopathological analysis of hearts in the acute phase of TTS revealed contraction bands, enhanced fibrosis, and regional infiltration with inflammatory cells, which is in line with the histopathological features of catecholamine toxicity [18]. Moreover, Aoki et al. (2016) reported an autopsy case of a TTS patient in which they observed Lewy body-like eosinophilic cytoplasmic inclusions in neurons in both dorsal nuclei of the vagus nerve in the medulla oblongata, suggesting alterations in the parasympathetic nervous system, which may play a role in the pathogenesis of TTS [19].

Interestingly, TTS may also be induced iatrogenically by intravenous injection of epinephrine in different clinical situations [20–26]. Recently, Kido et al. (2017) analyzed 157 case reports of drug-induced TTS and summarized that 68.2% of cases were associated with the administration of exogenous catecholamines and also with indirect stimulation by drugs with adrenergic vasoconstrictive properties, adrenergic activation due to alcohol or opioid withdrawal, inhibitors of catecholamine reuptake, anaphylactic reaction with concomitant catecholamine release, and psychological or somatic stress corresponding with the administration of a drug which was suspected of inducing the symptoms of TTS [27].

Due to the fact that TTS in clinical practice may be induced by exogenous administration of catecholamines, animal models induced by injection of catecholamines have been established. Rat or mice models of TTS are performed by intraperitoneal injection of isoprenaline (β1/β2-adrenoceptor agonist), epinephrine (β1/β2/α-adrenoceptor agonist), norepinephrine (β1/α-adrenoceptor agonist), dopamine (α/β1/β2-adrenoceptor agonist), and phenylephrine (α-adrenoceptor agonist); however, injection of isoprenaline triggers mainly the apical variant of TTS, whereas other catecholamines induce the basal variant [28–33].

In 2014, Redfors et al. proposed that TTS may be the result of catecholamine-dependent increased ventricular afterload [28]. It has been shown that injection of substances with vasoconstrictive α-adrenergic activity cause high afterload and triggers the basal variant of TTS, while injection of vasodilating β-selective isoprenaline, which lowers systolic blood pressure and ventricular afterload, is associated with the typical apical variant of TTS. On the contrary, it has been reported that exogenous epinephrine administration in patients may induce apical, mid-ventricular as well as the basal variant of TTS [20, 34].

As mentioned above, TTS is characterized by specific wall motion abnormalities, which extend beyond the region of myocardium supplied by a single epicardial vessel. The typical variant of TTS contractile dysfunction corresponds to the sympathetic autonomic innervation of the LV [35–38]. Moreover, it has been suggested that several different variants of wall motion abnormalities in TTS result from the local diversity of sympathetic innervation [34]. Indeed, Zaroff et al. (2000) analyzed patients with LV systolic dysfunction triggered by subarachnoid hemorrhage and observed that, although many of the wall motion patterns were not related to the coronary artery supply region, they matched the distribution of the myocardial sympathetic nerve terminals, confirming the neurogenic background of this disorder [39].

A few studies revealed polymorphisms of the adrenergic receptors which may predispose to an altered response to the sympathetic signaling and therefore lead to higher susceptibility to TTS. Vriz et al. (2011) have shown significant differences in frequencies of the beta-1 adrenergic receptor (β1AR) Arg389 homozygous and beta-2 adrenergic receptor (β2AR) Glu27 homozygous in TTS compared with the control group [40]. It has been assumed that polymorphism *Arg389Gly* alters the human β1AR receptor-Gs coupling, which results in the enhancement of its function for the Arg389 subtype [41]. *Arg389Arg* patients have a higher inotropic response to noradrenaline and dobutamine when compared with G*ly389Gly* patients [42, 43]. Sharkey et al. (2009) did not observe any significant differences in genotype polymorphism frequencies for β1AR or α2AR [44]. It has been shown that the G protein-coupled receptor kinase (GRK)5 L41 variant induces beta adrenergic desensitization and impairs the reaction to sympathetic signals which causes a negative inotropic effect in case of acute catecholamine stimulation [45]. A significant difference for the L41 variant of GRK5 between TTS patients and the control group has been reported [45]; however, a larger study did not reveal any association of the variants of the GRK5, β1AR, and β2AR genes with the occurrence of TTS [45, 46].

In 2017, Klein et al. [47] performed brain magnetic resonance imaging (MRI) in TTS patients in a median time of 168

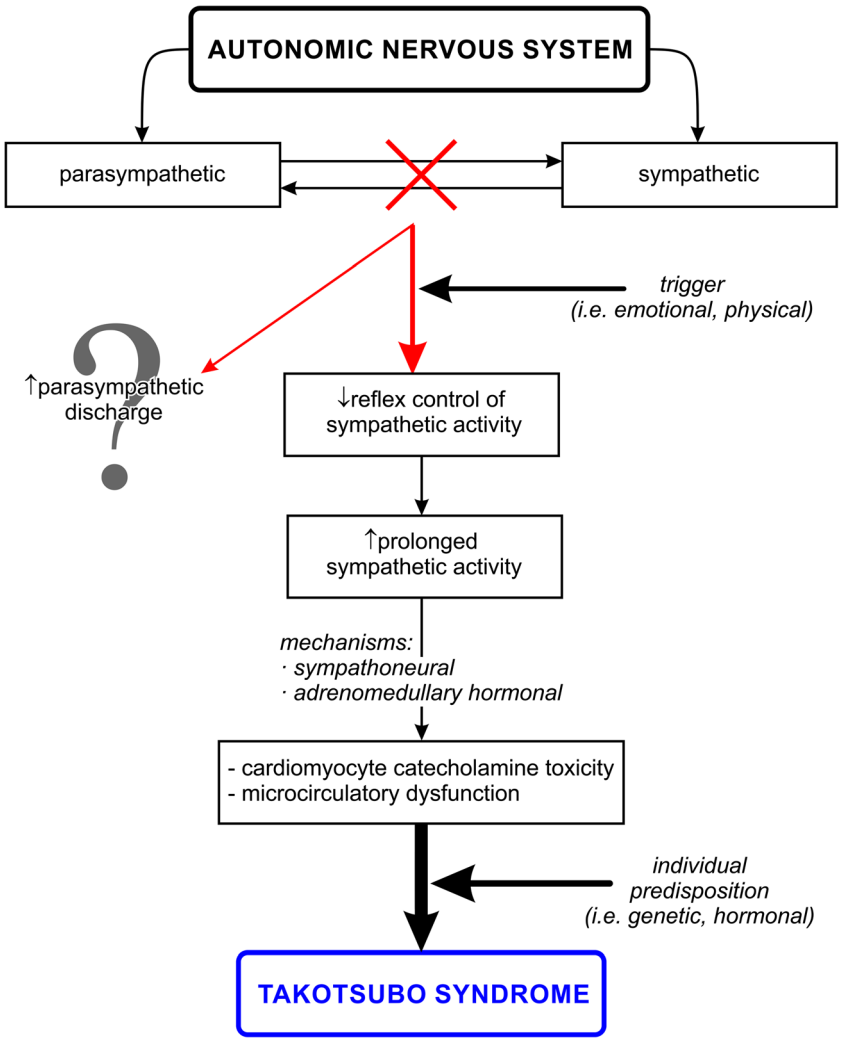

Fig. 1 A suggested mechanism of autonomic nervous system involvement in pathogenesis of Takotsubo syndrome

± 266 days following the onset of TTS symptoms and in age- and gender-matched healthy controls. In comparison with the controls, TTS patients had structural and neurophysiological brain changes in regions involved in the regulation of emotional processing and autonomic control of cardiovascular functions [47]. The authors of the study hypothesize that an abnormal relationship between the sympathetic and parasympathetic nervous system may be a cause of TTS, especially parasympathetic discharge with reduction of the baroreflex control of sympathetic activity (Fig. 1) [47].

It is considered that the level of peripheral blood catecholamines reflects sympathetic activity and reactivity, and so several studies have assessed the plasma level of catecholamines in TTS patients. Wittstein et al. (2005) reported higher plasma epinephrine, norepinephrine, and dopamine levels at admission and during 7–9 days after the onset of symptoms in TTS patients in comparison with the MI group [48]. Kume et al. (2008) reported increased levels of norepinephrine and dopamine with decreased concentrations of epinephrine at the coronary sinus in comparison with the levels at the aortic root in TTS patients [49]. Morel et al. (2009) observed elevated levels of plasma noradrenaline in some patients at the onset of TTS symptoms, whereas the levels of adrenaline and dopamine were normal. Interestingly, at the 10-month follow-up, no significant decrease of plasma catecholamines was noted [50]. On the contrary, normal concentrations of plasma epinephrine, norepinephrine, metanephrine, and normetanephrine in 50% or more of TTS patients have been reported [51–53]. It seems that normal values of plasma catecholamines do not exclude the activation of SNS in the development of TTS, since plasma levels of catecholamines do not have to correlate with the activation of local myocardial sympathoneural regulation and local catecholamine release, although it may reflect the enhanced adrenomedullary hormonal activity in some patients [16].

As mentioned earlier, the vast majority of patients with TTS are postmenopausal women. Pinkham et al. (2015) observed that administration of capsaicin on the epicardial surface of the LV in sinoaortic baroreceptor-denervated Wistar rats caused similar cardiac afferent reflex-mediated changes in renal SNA in fertile females when compared to males; however, the maximum sympathetic reflex-driven increase in fertile females' renal SNA was reduced [54]. Moreover,

when compared with fertile female rats, ovariectomized rats had attenuated cardiac vagal afferent reflex-mediated inhibition of renal SNA and augmented cardiac sympathetic afferent reflex-mediated sympathoexcitation which together resulted in significantly increased overall reflex-driven sympathoexcitation [54]. Saleh et al. (2000) revealed that an intravenous bolus of estrogen increased the vagal parasympathetic nerve activity and decreased the renal sympathetic nerve activity which improved the baroreflex sensitivity in estrogen-supplemented ovariectomized female rats [55]. Gautam et al. (2011) assessed cardiac autonomic function in several tests and showed that postmenopausal women had increased sympathetic and decreased parasympathetic tone in comparison with women with a menstrual cycle. Moreover, women receiving hormone replacement therapy (HRT) demonstrated higher parasympathetic and lower sympathetic tone in comparison with postmenopausal women [56]. Hart et al. (2013) measured the muscle sympathetic nerve activity (MSNA) with peroneal microneurography in postmenopausal and young women and revealed that tonic sympathetic activity was higher in postmenopausal women in comparison with young women [57]. Perseguini et al. (2014) assessed the influence of HRT on heart rate variability (HRV) in postmenopausal women and reported that women receiving HRT had higher sympathetic and lower vagal cardiac modulation [58]. Lavi et al. (2007) revealed that in young women, the parasympathetic activity dominates, whereas in postmenopausal women with comparable levels of estrogen, the sympathetic control prevails, suggesting that ageing itself, with no concomitant influence of estrogen levels, is associated with higher enhancement of the SNS [59].

Diseases with altered sympathetic activity and its association with TTS

It has been reported that secondary TTS may occur in the course of some diseases associated with increased sympathetic activity [1, 16]. Pheochromocytoma and paraganglioma (PPGL) are tumors of the paraganglia, the ANS-associated structures arising from the neural crest tissue, the majority of which secrete catecholamines [60]. Interestingly, Takotsubo-like syndrome may be the first clinical manifestation of pheochromocytoma, which, on the other hand, may be the cause of recurrent TTS [61]. A recent analysis of 275 hospitalized patients with PPGL revealed that Takotsubo-like syndrome occurred in 2.6% of patients with secreting-PPGL; however, in 75.0% of patients, the incident was preceded by an acute stressor event, i.e., surgery and infection of the upper respiratory tract [62]. Coupez et al. (2014) reported that the prevalence of catecholaminergic tumors in their analyzed group of TTS patients was 7.5% [63].

Several neurological triggers activating the adrenergic signaling have also been reported to induce TTS, including subarachnoid hemorrhage, acute head injury, acute spinal injury, ischemic stroke, encephalitis, posterior reversible encephalopathy syndrome, epileptic seizures, intracerebral bleeding, and migraine [1, 64, 65]. Other triggers of TTS associated with increased sympathetic tone may be drug and alcohol withdrawal syndrome, electroconvulsive therapy, cocaine abuse, and postural orthostatic tachycardia syndrome [1, 66–70].

In 2016, Madias reviewed 959 currently available studies on 33,894 TTS patients and revealed that the prevalence of diabetes mellitus (DM) in this group of patients is between 10.2 and 17.0%, which is lower in comparison with the percentage reported in the general population [71, 72]. The author suggests that heart-brain disconnection caused by diabetic peripheral autonomic neuropathy may diminish the effect of excessive adrenergic stimulation of the heart and therefore be beneficial in delaying the emergence of TTS [71–73]. Furthermore, local myocardial release of norepinephrine and secretion of adrenal catecholamines are reduced in type 2 DM, which is in line with the hypothesis of the advantageous effect of DM on delaying the development of TTS [71, 74]. However, Stiermaier et al. (2016) reported that DM is a significant predictor of long-term mortality, probably due to the acknowledged complications associated with DM including cardiovascular diseases or nephropathy [75].

Assessment of autonomic nervous system activity in TTS patients

It has been suggested that electrocardiographic changes observed in TTS may reflect the disruption of the sympathetic nerve terminals [76]. Patients with TTS most commonly present with such ECG abnormalities including T-wave inversion, large upright peaked T-waves, and prolongation of the corrected QT interval [2, 76]. Moreover, the features of ECG changes depend on the type of LV wall motion abnormalities. In mid-basal TTS, the ECG recordings show ST depression, peak upright T-waves, and QT prolongation, while in mid-apical TTS, the recordings show ST elevation and giant T-wave inversion [77, 78]. The observed QT prolongation may be the result of sympathetic activation, thus catecholamines may prolong the QT interval [79, 80]. Marra et al. (2013) revealed a linear correlation of the apicobasal ratio of T2-weighted signal intensity for myocardial edema in cardiac magnetic resonance (CMR) with the maximal amplitude of negative T-waves, the sum of the amplitudes of negative T-waves, and the maximum corrected QT interval in TTS patients [81]. Moreover, the ECG abnormalities and myocardial edema were in parallel time course of development and resolution on admission and 3-month follow-up CMR, suggesting that ECG changes in TTS coexist with the apicobasal gradient of myocardial edema [81]. It has been concluded that

dynamic negative T-waves and corrected QT interval prolongation reflect the temporary inhomogeneity and dispersion of repolarization induced by edema between apical and basal segments of the LV [81].

Lee et al. (2016) reported that ECG recordings from the TTS diagnosis phase and from the recovery phase in comparison with the baseline phase (before any cardiac dysfunction) showed higher heart rate, higher frequency of ST segment elevation, ST segment depression, T-wave inversion, and QTc prolongation. Patients with non-recovered QTc interval (QTc in TTS diagnosis phase ≤ QTc in recovery phase) had higher risk of in-hospital mortality in comparison with the QTc recovered group [82]. Santoro et al. (2017) revealed that prolonged QT intervals at admission in TTS patients were related to a higher risk of cardiovascular rehospitalization during follow-up, while the dynamic increase of QTc intervals following admission was associated with a trend toward improved prognosis [83].

Akashi et al. (2007) assessed heart rate variability (HRV) in TTS patients during the acute phase and after 3 months and revealed a significantly lower LF (a marker of sympathetic activity) and LF/HF ratio (a marker of sympathovagal balance) at 0 and 3 months in comparison with the control group, which suggests sudden impairment of cardiac sympathetic nerve function [52, 84, 85]. The authors conclude that decreased LF may result from disorders in central autonomic regulation and impaired sensitivity of beta-adrenergic receptors in spite of high levels of sympathetic activity [52, 84, 85]. Ortak et al. (2009) from an analysis of HRV showed a significant reduction of cardiac parasympathetic activity during the acute phase of TTS; however, the autonomic function recovered between the subacute and chronic phases [85].

Myocardial scintigraphy, which uses ^{123}I-metaiodobenzylguanidine (MIBG), a norepinephrine analogue, is commonly used as an imaging method for the detection of cardiac autonomic sympathetic denervation. Recently, Madias (2016) concluded that regional myocardial uptake of MIBG in TTS patients is markedly decreased in the LV regions with hypo/akinesia with increased washout rates of MIBG, which suggests disturbances in presynaptic norepinephrine uptake and an increased presynaptic catecholamine discharge in the affected LV segments [16, 86]. Interestingly, the majority of studies assessing follow-up MIBG tests reveal that cardiac sympathetic denervation remains present among the previously affected regions of LV; however, some studies show normalization of previously observed disturbances [86]. It has been assumed that exaggerated sympathetic nerve terminal discharge of norepinephrine may cause damage to cardiomyocytes and nerve terminals, subsequently leading to cardiac sympathetic denervation [2].

Controversial findings are provided by microneurographic recordings of muscle sympathetic nerve activity (MSNA) which is used to measure directly the sympathetic action potentials from efferent postganglionic unmyelinated "C" nerve fibers [87]. Sverrisdóttir et al. (2012) revealed lower MSNA from both acute (24–48 h) and recovery phase (1–6 months) in TTS patients in comparison with healthy controls [87]. The authors suggest that excessive release of catecholamines in the acute phase of TTS enhances the rate of discharge from unmyelinated cardiac c-fiber afferents causing sympathetic inhibition. On the contrary, Vaccaro et al. (2014) in the acute phase (within 72 h) of TTS onset observed a significant increase in MSNA in comparison with the group of control patients with acutely decompensated chronic heart failure [88]. Moreover, the authors detected a decrease in spontaneous baroreflex control of sympathetic activity in TTS patients. Norcliffe-Kaufmann et al. (2016) observed a higher pressor response to the Stroop test and emotional stimulation and decreased indexes of parasympathetic modulation of heart rate during respiration and cardiovagal baroreflex gain during autonomic assessment in TTS patients when compared with the controls [89]. Ali et al. (2015) proposed that baroreflex dysfunction may predispose to TTS due to the sustained sympathetic activity, which causes extremely high intraluminal pressures and wall tension in the apical regions of the LV, causing the apical wall motion abnormalities [90].

Conclusions

Currently available studies suggest the essential role of ANS in the pathophysiology of TTS. Most of the studies confirmed the activation of SNS in TTS patients, although the alterations in parasympathetic centers have also been observed. It is suggested that further research evaluating the function of ANS in TTS patients and the role of risk factors leading to increased individual predisposition to TTS may improve the prevention and therapy of TTS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The manuscript does not contain clinical studies or patient data.

References

1. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, Ruschitzka F, Filippatos G, Mebazaa A, Omerovic E (2016) Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on Takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 18(1):8–27. https://doi.org/10.1002/ejhf.424

2. Y-Hassan S, De Palma R (2017) Contemporary review on the pathogenesis of Takotsubo syndrome: the heart shedding tears: Norepinephrine churn and foam at the cardiac sympathetic nerve terminals. Int J Cardiol 228:528–536. https://doi.org/10.1016/j.ijcard.2016.11.086
3. Deshmukh A, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL (2012) Prevalence of Takotsubo cardiomyopathy in the United States. Am Heart J 164(1):66–71 e61. https://doi.org/10.1016/j.ahj.2012.03.020
4. Brinjikji W, El-Sayed AM, Salka S (2012) In-hospital mortality among patients with Takotsubo cardiomyopathy: a study of the National Inpatient Sample 2008 to 2009. Am Heart J 164(2):215–221. https://doi.org/10.1016/j.ahj.2012.04.010
5. Sato HTH, Umemura T, Dote K, Ishihara M (1990) Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. In: Kodama K, Haze K, Hori M (eds) Clinical aspect of myocardial injury: from ischemia to heart failure. Kagakuhyoronsha Publishing Co, Tokyo, Japan, pp 56–64
6. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M (1991) Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. J Cardiol 21(2):203–214
7. Komamura K, Fukui M, Iwasaku T, Hirotani S, Masuyama T (2014) Takotsubo cardiomyopathy: pathophysiology, diagnosis and treatment. World J Cardiol 6(7):602–609. https://doi.org/10.4330/wjc.v6.i7.602
8. Sharkey SW, Lesser JR, Maron MS, Maron BJ (2011) Why not just call it tako-tsubo cardiomyopathy. J Am Coll Cardiol 57(13):1496–1497
9. Haghi D, Athanasiadis A, Papavassiliu T, Suselbeck T, Fluechter S, Mahrholdt H, Borggrefe M, Sechtem U (2006) Right ventricular involvement in Takotsubo cardiomyopathy. Eur Heart J 27(20):2433–2439
10. Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Mitsuba N, Hata T, Nakama Y, Kisaka T, Kijima Y (2005) Takotsubo-like transient biventricular dysfunction with pressure gradients. Intern Med 44(7):727–732
11. Novak G, Kross K, Follmer K, Brofferio A, Shirani J (2007) Transient biventricular apical ballooning: a unique presentation of the "broken heart". Clin Cardiol 30(7):355–358
12. Abdulla I, Kay S, Mussap C, Nelson G, Rasmussen H, Hansen P, Ward M (2006) Apical sparing in tako-tsubo cardiomyopathy. Intern Med J 36(7):414–418
13. Schneider B, Sechtem U (2016) Influence of age and gender in Takotsubo syndrome. Heart Fail Clin 12(4):521–530
14. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschope C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Bohm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Luscher TF (2015) Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med 373(10):929–938. https://doi.org/10.1056/NEJMoa1406761
15. Ghadri JR, Sarcon A, Diekmann J, Bataiosu DR, Cammann VL, Jurisic S, Napp LC, Jaguszewski M, Scherff F, Brugger P, Jancke L, Seifert B, Bax JJ, Ruschitzka F, Luscher TF, Templin C, Inter TAKC-i (2016) Happy heart syndrome: role of positive emotional stress in takotsubo syndrome. Eur Heart J 37(37):2823–2829. https://doi.org/10.1093/eurheartj/ehv757
16. Wittstein IS (2016) The sympathetic nervous system in the pathogenesis of Takotsubo syndrome. Heart Fail Clin 12(4):485–498
17. Wittstein IS (2012) Stress cardiomyopathy: a syndrome of catecholamine-mediated myocardial stunning? Cell Mol Neurobiol 32(5):847–857. https://doi.org/10.1007/s10571-012-9804-8
18. Nef HM, Mollmann H, Kostin S, Troidl C, Voss S, Weber M, Dill T, Rolf A, Brandt R, Hamm CW, Elsasser A (2007) Tako-Tsubo cardiomyopathy: intraindividual structural analysis in the acute phase and after functional recovery. Eur Heart J 28(20):2456–2464. https://doi.org/10.1093/eurheartj/ehl570
19. Aoki Y, Kodera S, Watanabe T, Miyauchi Y, Kanda J, Ooe K (2016) Autopsy findings in takotsubo cardiomyopathy with special reference to the autonomic nervous system. Int J Cardiol 203:236–237
20. Shams Y (2016) Clinical features and outcome of epinephrine-induced takotsubo syndrome: analysis of 33 published cases. Cardiovasc Revasc Med 17(7):450–455
21. Elikowski W, Małek-Elikowska M, Karoń J, Mrozińska M, Baszko A, Horbacka K (2017) Takotsubo cardiomyopathy after intravenous epinephrine administration following cardiac arrest provoked by pneumoperitoneum-a case report. Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiego 42(250):165–169
22. Nassif J, Nahouli H, Khali A, Mikhael E, Gharzeddine W, Ghaziri G (2017) Epinephrine-induced Takotsubo cardiomyopathy during laparoscopic myomectomy: case report and review of the literature. J Minim Invasive Gynecol 24:1037–1039
23. Kajander OA, Virtanen MP, Sclarovsky S, Nikus KC (2013) Iatrogenic inverted takotsubo syndrome following intravenous adrenaline injections for an allergic reaction. Int J Cardiol 165(1):e3–e5
24. Collen J, Bimson W, Devine P (2008) A variant of Takotsubo cardiomyopathy: a rare complication in the electrophysiology lab. J Invasive Cardiol 20(11):E310–E313
25. Winogradow J, Geppert G, Reinhard W, Resch M, Radke P, Hengstenberg C (2011) Tako-tsubo cardiomyopathy after administration of intravenous epinephrine during an anaphylactic reaction. Int J Cardiol 147(2):309–311
26. Ghanim D, Adler Z, Qarawani D, Kusniec F, Amir O, Carasso S (2015) Takotsubo cardiomyopathy caused by epinephrine-treated bee sting anaphylaxis: a case report. J Med Case Rep 9(1):247
27. Kido K, Guglin M (2017) Drug-induced Takotsubo cardiomyopathy. J Cardiovasc Pharmacol Ther 1074248417708618
28. Redfors B, Ali A, Shao Y, Lundgren J, Gan L-M, Omerovic E (2014) Different catecholamines induce different patterns of takotsubo-like cardiac dysfunction in an apparently afterload dependent manner. Int J Cardiol 174(2):330–336
29. Shao Y, Redfors B, Täng MS, Möllmann H, Troidl C, Szardien S, Hamm C, Nef H, Borén J, Omerovic E (2013) Novel rat model reveals important roles of β-adrenoreceptors in stress-induced cardiomyopathy. Int J Cardiol 168(3):1943–1950
30. Redfors B, Shao Y, Wikström J, Lyon AR, Oldfors A, Gan L-M, Omerovic E (2013) Contrast echocardiography reveals apparently normal coronary perfusion in a rat model of stress-induced (Takotsubo) cardiomyopathy. Eur Heart J Cardiovasc Imaging 15(2):152–157
31. Redfors B, Oras J, Shao Y, Seemann-Lodding H, Ricksten S-E, Omerovic E (2014) Cardioprotective effects of isoflurane in a rat model of stress-induced cardiomyopathy (takotsubo). Int J Cardiol 176(3):815–821
32. Sachdeva J, Dai W, Kloner RA (2014) Functional and histological assessment of an experimental model of Takotsubo's cardiomyopathy. J Am Heart Assoc 3(3):e000921
33. Kołodzińska A, Czarzasta K, Szczepankiewicz B, Główczyńska R, Fojt A, Ilczuk T, Budnik M, Krasuski K, Folta M, Cudnoch-Jędrzejewska A (2018) Toll-like receptor expression and apoptosis morphological patterns in female rat hearts with takotsubo syndrome induced by isoprenaline. Life Sci 199:112–121

34. Abraham J, Mudd JO, Kapur N, Klein K, Champion HC, Wittstein IS (2009) Stress cardiomyopathy after intravenous administration of catecholamines and beta-receptor agonists. J Am Coll Cardiol 53(15):1320–1325
35. Randall WC, Szentivanyi M, Pace JB, Wechsler JS, Kaye MP (1968) Patterns of sympathetic nerve projections onto the canine heart. Circ Res 22(3):315–323
36. Kawano H, Okada R, Yano K (2003) Histological study on the distribution of autonomic nerves in the human heart. Heart Vessel 18(1):32–39
37. Kimura K, Ieda M, Fukuda K (2012) Development, maturation, and transdifferentiation of cardiac sympathetic nerves. Circ Res 110(2): 325–336
38. Vincentz JW, Rubart M, Firulli AB (2012) Ontogeny of cardiac sympathetic innervation and its implications for cardiac disease. Pediatr Cardiol 33(6):923–928
39. Zaroff JG, Rordorf GA, Ogilvy CS, Picard MH (2000) Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: evidence for neurally mediated cardiac injury. J Am Soc Echocardiogr 13(8):774–779
40. Vriz O, Minisini R, Citro R, Guerra V, Zito C, De Luca G, Pavan D, Pirisi M, Limongelli G, Bossone E (2011) Analysis of β1 and β2-adrenergic receptors polymorphism in patients with apical ballooning cardiomyopathy. Acta Cardiol 66(6):787–790
41. Mason DA, Moore JD, Green SA, Liggett SB (1999) A gain-of-function polymorphism in a G-protein coupling domain of the human β1-adrenergic receptor. J Biol Chem 274(18):12670–12674
42. Sandilands A, O'shaughnessy K, Brown M (2003) Greater inotropic and cyclic AMP responses evoked by noradrenaline through Arg389 β1-adrenoceptors versus Gly389 β1-adrenoceptors in isolated human atrial myocardium. Br J Pharmacol 138(2):386–392
43. Bruck H, Leineweber K, Temme T, Weber M, Heusch G, Philipp T, Brodde O-E (2005) The Arg389Gly beta1-adrenoceptor polymorphism and catecholamine effects on plasma-renin activity. J Am Coll Cardiol 46(11):2111–2115
44. Sharkey SW, Maron BJ, Nelson P, Parpart M, Maron MS, Bristow MR (2009) Adrenergic receptor polymorphisms in patients with stress (tako-tsubo) cardiomyopathy. J Cardiol 53(1):53–57
45. Spinelli L, Trimarco V, Di Marino S, Marino M, Iaccarino G, Trimarco B (2010) L41Q polymorphism of the G protein coupled receptor kinase 5 is associated with left ventricular apical ballooning syndrome. Eur J Heart Fail 12(1):13–16
46. Figtree GA, Bagnall RD, Abdulla I, Buchholz S, Galougahi KK, Yan W, Tan T, Neil C, Horowitz JD, Semsarian C, Ward MR (2013) No association of G-protein-coupled receptor kinase 5 or beta-adrenergic receptor polymorphisms with Takotsubo cardiomyopathy in a large Australian cohort. Eur J Heart Fail 15(7):730–733. https://doi.org/10.1093/eurjhf/hft040
47. Klein C, Hiestand T, Ghadri J-R, Templin C, Jäncke L, Hänggi J (2017) Takotsubo syndrome–predictable from brain imaging data. Sci Rep 7:5434
48. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC (2005) Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 352(6):539–548
49. Kume T, Kawamoto T, Okura H, Toyota E, Neishi Y, Watanabe N, Hayashida A, Okahashi N, Yoshimura Y, Saito K (2008) Local release of catecholamines from the hearts of patients with takotsubo-like left ventricular dysfunction. Circ J 72(1):106–108
50. Morel O, Sauer F, Imperiale A, Cimarelli S, Blondet C, Jesel L, Trinh A, De Poli F, Ohlmann P, Constantinesco A (2009) Importance of inflammation and neurohumoral activation in Takotsubo cardiomyopathy. J Card Fail 15(3):206–213
51. Shams Y, Henareh L (2015) Plasma catecholamine levels in patients with takotsubo syndrome: implications for the pathogenesis of the disease. Int J Cardiol 181:35–38
52. Akashi Y, Barbaro G, Sakurai T, Nakazawa K, Miyake F (2007) Cardiac autonomic imbalance in patients with reversible ventricular dysfunction takotsubo cardiomyopathy. Journal of the Association of Physicians 100(6):335–343
53. Madhavan M, Borlaug BA, Lerman A, Rihal CS, Prasad A (2009) Stress hormone and circulating biomarker profile of apical ballooning syndrome (Takotsubo cardiomyopathy): insights into the clinical significance of B-type natriuretic peptide and troponin levels. Heart 95(17):1436–1441
54. Pinkham MI, Barrett CJ (2015) Estradiol alters the chemosensitive cardiac afferent reflex in female rats by augmenting sympathoinhibition and attenuating sympathoexcitation. Clin Exp Pharmacol Physiol 42(6):622–631
55. Saleh TM, Connell BJ (2000) 17β-Estradiol modulates baroreflex sensitivity and autonomic tone of female rats. J Auton Nerv Syst 80(3):148–161
56. Gautam S, Shankar N, Tandon OP, Goel N (2011) Comparison of cardiac autonomic functions among postmenopausal women with and without hormone replacement therapy, and premenopausal women
57. Hart EC, Charkoudian N, Joyner MJ, Barnes JN, Curry TB, Casey DP (2013) Relationship between sympathetic nerve activity and aortic wave reflection characteristics in postmenopausal women. Menopause (New York, NY) 20(9):967
58. Perseguini NM, de Medeiros Takahashi AC, Milan JC, Dos Santos PR, Neves VFC, Borghi-Silva A, Silva E, Montano N, Porta A, Catai AM (2014) Effect of hormone replacement therapy on cardiac autonomic modulation. Clin Auton Res 24(2):63–70
59. Lavi S, Nevo O, Thaler I, Rosenfeld R, Dayan L, Hirshoren N, Gepstein L, Jacob G (2007) Effect of aging on the cardiovascular regulatory systems in healthy women. Am J Phys Regul Integr Comp Phys 292(2):R788–R793
60. Giavarini A, Chedid A, Bobrie G, Plouin P-F, Hagège A, Amar L (2013) Acute catecholamine cardiomyopathy in patients with phaeochromocytoma or functional paraganglioma. Heart 99(19): 1438–1444
61. Brugts JJ, van Gent M, Caliskan K, Kofflard MJ (2014) Repetitive stress-induced cardiomyopathy due to inverted Takotsubo in exaggerated sympathetic stimulation by pheochromocytoma. Eur Heart J Cardiovasc Imaging 16(1):113–113
62. Gagnon N, Mansour S, Bitton Y, Bourdeau I (2017) Takotsubo-like cardiomyopathy in a large cohort of patients with pheochromocytoma and paraganglioma. Endocr Pract 23:1178–1192
63. Coupez E, Eschalier R, Pereira B, Pierrard R, Souteyrand G, Clerfond G, Citron B, Lusson J-R, Mansencal N, Motreff P (2014) A single pathophysiological pathway in Takotsubo cardiomyopathy: catecholaminergic stress. Arch Cardiovasc Dis 107(4): 245–252
64. Finsterer J, Wahbi K (2014) CNS disease triggering Takotsubo stress cardiomyopathy. Int J Cardiol 177(2):322–329
65. Porto I, Della Bona R, Leo A, Proietti R, Pieroni M, Caltagirone C, Spalletta G, Bolognese L, Cravello L (2013) Stress cardiomyopathy (tako-tsubo) triggered by nervous system diseases: a systematic review of the reported cases. Int J Cardiol 167(6):2441–2448
66. Khurana RK (2008) Takotsubo cardiomyopathy in a patient with postural tachycardia syndrome. Clin Auton Res 18(1):43–47
67. Harris ZM, Alonso A, Kennedy TP (2016) Adrenergic inhibition with dexmedetomidine to treat stress cardiomyopathy during alcohol withdrawal: a case report and literature review. Case reports in critical care 2016, 1, 9
68. Sarcon A, Ghadri J-R, Wong G, Lüscher TF, Templin C, Amsterdam E (2013) Takotsubo cardiomyopathy associated with opiate withdrawal. QJM: An International Journal of Medicine 107(4):301–302

69. Arora S, Alfayoumi F, Srinivasan V (2006) Transient left ventricular apical ballooning after cocaine use: is catecholamine cardiotoxicity the pathologic link? Mayo Clin Proc 81(6):829-32
70. Sharp RP, Welch EB (2011) Takotsubo cardiomyopathy as a complication of electroconvulsive therapy. Ann Pharmacother 45(12): 1559–1565
71. Madias JE (2016) Low prevalence of diabetes mellitus in patients with Takotsubo syndrome: a plausible 'protective' effect with pathophysiologic connotations. Eur Heart J Acute Cardiovasc Care 5(2):164–170
72. Madias JE (2016) Details about diabetes mellitus in reported patients with Takotsubo syndrome, and its importance in unraveling the pathophysiology of the disease. Int J Cardiol 209:70–71
73. Madias JE (2016) An animal model of diabetic peripheral neuropathy and the pathophysiology of takotsubo syndrome: a proposal of an experiment. Int J Cardiol 222:882–884
74. Burgdorf C, Richardt D, Kurz T, Adler S, Nötzold A, Kraatz E, Sievers H, Richardt G (2003) Norepinephrine release is reduced in cardiac tissue of type 2 diabetic patients. Diabetologia 46(4):520–523
75. Stiermaier T, Moeller C, Oehler K, Desch S, Graf T, Eitel C, Vonthein R, Schuler G, Thiele H, Eitel I (2016) Long-term excess mortality in Takotsubo cardiomyopathy: predictors, causes and clinical consequences. Eur J Heart Fail 18(6):650–656
76. Shams Y (2015) The pathogenesis of reversible T-wave inversions or large upright peaked T-waves: sympathetic T-waves. Int J Cardiol 191:237–243
77. Shams Y (2015) RESPONSE: the electrocardiographic changes in mid-basal (inverted) Takotsubo syndrome. Ann Noninvasive Electrocardiol 6(20):614–614
78. Duran-Cambra A, Sutil-Vega M, Fiol M, Núñez-Gil I, Vila M, Sans-Roselló J, Cinca J, Sionis A (2015) Systematic review of the electrocardiographic changes in the takotsubo syndrome. Ann Noninvasive Electrocardiol 20(1):1–6
79. Abildskov J (1976) Adrenergic effects on the QT interval of the electrocardiogram. Am Heart J 92(2):210–216
80. Magnano AR, Talathoti N, Hallur R, Bloomfield DM, Garan H (2006) Sympathomimetic infusion and cardiac repolarization: the normative effects of epinephrine and isoproterenol in healthy subjects. J Cardiovasc Electrophysiol 17(9):983–989
81. Marra MP, Zorzi A, Corbetti F, De Lazzari M, Migliore F, Tona F, Tarantini G, Iliceto S, Corrado D (2013) Apicobasal gradient of left ventricular myocardial edema underlies transient T-wave inversion and QT interval prolongation (Wellens' ECG pattern) in Tako-Tsubo cardiomyopathy. Heart Rhythm 10(1):70–77
82. Lee J-H, Uhm J-S, Shin DG, Joung B, Pak H-N, Ko Y-G, Hong G-R, Lee M-H (2016) Clinical significance of changes in the corrected QT interval in stress-induced cardiomyopathy. Korean J Intern Med 31(3):507–516
83. Santoro F, Brunetti ND, Tarantino N, Romero J, Guastafierro F, Ferraretti A, Di Martino LF, Ieva R, Pellegrino PL, Di Biase M (2017) Dynamic changes of QTc interval and prognostic significance in takotsubo (stress) cardiomyopathy. Clin Cardiol 40: 1116–1122
84. Waldenborg M, Soholat M, Kähäri A, Emilsson K, Fröbert O (2011) Multidisciplinary assessment of tako tsubo cardiomyopathy: a prospective case study. BMC Cardiovasc Disord 11(1):14
85. Ortak J, Khattab K, Barantke M, Wiegand UK, Baensch D, Ince H, Nienaber CA, Bonnemeier H (2009) Evolution of cardiac autonomic nervous activity indices in patients presenting with transient left ventricular apical ballooning. Pacing Clin Electrophysiol 32(s1): S21–S25
86. Madias JE (2016) Do we need MIBG in the evaluation of patients with suspected Takotsubo syndrome? Diagnostic, prognostic, and pathophysiologic connotations. Int J Cardiol 203:783–784
87. Sverrisdóttir YB, Schultz T, Omerovic E, Elam M (2012) Sympathetic nerve activity in stress-induced cardiomyopathy. Clin Auton Res 22(6):259–264
88. Vaccaro A, Despas F, Delmas C, Lairez O, Lambert E, Lambert G, Labrunee M, Guiraud T, Esler M, Galinier M (2014) Direct evidences for sympathetic hyperactivity and baroreflex impairment in Tako Tsubo cardiopathy. PLoS One 9(3):e93278
89. Norcliffe-Kaufmann L, Kaufmann H, Martinez J, Katz SD, Tully L, Reynolds HR (2016) Autonomic findings in Takotsubo cardiomyopathy. Am J Cardiol 117(2):206–213
90. Ali A, Redfors B, Omerovic E (2015) How baroreceptor dysfunction could predispose to the takotsubo syndrome. Int J Cardiol 182: 105–106