123I-mIBG assessed cardiac sympathetic activity: standardizing towards clinical implementation
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Chapter 12

Tako-tsubo cardiomyopathy: how to understand possible pathophysiological mechanism and the role of $^{123}$I-mIBG imaging

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ABSTRACT

Tako-tsubo cardiomyopathy (TCM) is an increasingly recognized clinical syndrome characterized by acute reversible apical ventricular dysfunction, commonly preceded by exposure to severe physical or emotional stress. In this review we give a short overview on clinical presentation and treatment of TCM and discuss the possible pathophysiological mechanisms of TCM and the role of various non-invasive imaging modalities in TCM with a focus on the potential role of $^{123}$I-meta-iodobenzylguanidine (mIBG) scintigraphy.

Currently, the dominating hypothesis on the pathophysiology of TCM postulates that high levels of the neurotransmitter epinephrine may trigger a change in intracellular signaling in ventricular myocytes. More specific, epinephrine stimulates G-protein coupled $\beta_2$ adrenergic receptors ($\beta_2$AR) which are located on ventricular myocytes. Normal levels of this neurotransmitter predominantly stimulate the intra-cellular G-protein, and induce a positive inotropic effect. However, with significant increasing levels of epinephrine, the predominance of stimulation is shifted from G-stimulating to the G-inhibitor protein coupling, which leads to a negative inotropic effect. Interestingly, this negative inotropic effect is the largest in the apical myocardium where the $\beta_2$AR:$\beta_1$AR ratio is the highest within the heart. Echocardiography and ventriculography are essential to diagnose TCM, but new imaging tools are promising to diagnose TCM and to evaluate therapeutic efficacy. Cardiovascular magnetic resonance (CMR) can be used to differentiate TCM from other myocardial diseases, such as myocarditis. $^{123}$I-mIBG scintigraphy can be used to assess ventricular adrenergic activity and may guide optimization of individual (pharmacological) therapy.

These new insights into the possible pathophysiological mechanisms and novel diagnostic imaging modalities can be used as starting point for the development of international guidelines of TCM which may increase the awareness, and optimize the treatment of TCM.
INTRODUCTION

Tako-tsubo cardiomyopathy (TCM), also known as stress-induced cardiomyopathy, apical ballooning syndrome or broken heart syndrome was first described in Japan in 1990. It is characterized by transient systolic dysfunction of apical and/or mid segments accompanied with ballooning of the segments. The clinical presentation can mimic acute myocardial infarction, in the absence of obstructive coronary artery disease. The Japanese phrase ‘tako tsubo’ can be translated in English as ‘octopus pot’, a fishing jar with a narrow neck and wide base used to trap an octopus. This description reflects the visual appearance of the heart on left ventriculography. Although the first report was published in 1990 it lasted several years to recognize this phenomenon in Europe and the United States of America. In 2006, the American Heart Association incorporated TCM into its classification of cardiomyopathies as a primary acquired cardiomyopathy. Subsequently many publications have discussed on possible pathophysiological mechanisms of TCM, the diagnostic workup using multimodality imaging techniques, and therapeutic options. Currently, it can be anticipated that TCM is still under-diagnosed due to lack of awareness and knowledge of diagnostic possibilities. However, well established imaging techniques, such as cardiovascular magnetic resonance (CMR) and $^{123}$I-meta-iodobenzylguanidine ($^{123}$I-mIBG) scintigraphy are promising imaging modalities to diagnose TCM. To increase the awareness of TCM, this review will discuss new insights into possible pathophysiological mechanisms of TCM and the impact that these new insights may have on therapeutic and diagnostic strategies.

Diagnostic criteria

Although after the first publications TCM is increasingly recognized, there is no consensus or guideline on the diagnostic criteria for TCM. However, Prasad et al. proposed that the diagnosis of TCM requires all of the following criteria: 1. Transient hypokinesis, akinesis, or dyskinesis in the mid and apical segments of the left ventricle; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently but not always preceded by a stressful trigger; 2. The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; 3. New ECG abnormalities (ST elevation and/or T-wave inversion) or modest elevation in cardiac troponin levels; and 4. The absence of pheochromocytoma and myocarditis.

Prevalence

Some of the best available estimates on the prevalence of TCM come from small series of patients (7 to 16 patients per study) presenting with suspected acute coronary syndrome (ACS). The prevalence of TCM in these studies ranged between 1.9 – 2.2 percent. In line with these data a recent meta-analysis showed that TCM accounted for 1.7 – 2.2 percent of cases presenting with suspected ACS. In a large registry of 3265
patients with troponin-positive ACS the prevalence of TCM was 1.2 percent. TCM is diagnosed in about 0.02 percent of all general hospitalizations in the United States of America, mostly in elderly women. Since it can be assumed that TCM is under-diagnosed, the true prevalence is higher.

**Clinical features**

TCM affects predominantly post-menopausal women and is usually preceded by exposure to physical or emotional stress (e.g., unexpected death in the family, abuse, exhausting work). Major symptoms of TCM are chest pain at rest, mimicking acute myocardial infarction (AMI), and dyspnea. Syncope or out-of-hospital cardiac arrest are rare. Acute complications occur in approximately 20 percent of patients with TCM and include cardiogenic shock, left sided heart failure, pulmonary edema, torsades de pointes, left ventricular thrombus formation or free wall rupture. Cardiogenic shock can be due to left ventricular failure or obstruction of the outflow tract of the left ventricle.

**Electrocardiogram and biomarkers**

The ECG often reveals ST-elevation (predominately precordial) during the acute phase, followed by T-wave inversion, QT-prolongation and sometimes Q-wave formation during the subacute phase. Differentiation between TCM and AMI using ECG may be difficult. However, compared with anterior myocardial infarction, reciprocal ST-segment depression is less likely. In addition, occasionally ST-elevation in the inferior leads is present. Cardiac markers, especially high-sensitivity troponin, are slightly elevated and normalize earlier in TCM as compared to AMI. It has been shown that in patients with TCM high-sensitive troponin I is more elevated at presentation compared to patients with STEMI. However, the maximum high-sensitive troponin I during follow-up was higher in patients with STEMI than patients with TCM. However, these differences in high-sensitive troponin I on group level are very small and therefore not useful to differentiate between STEMI and TCM for each individual patient. Furthermore brain natriuretic peptide (BNP) or N-terminal pro-BNP are usually elevated as markers of ventricular dysfunction. However, these parameters are not specific for TCM and are not associated with a poor TCM prognosis.

**Echocardiography and ventriculography**

Transthoracic echocardiography or ventriculography during the acute phase may reveal left mid-ventricular dysfunction and apical akinesis or dyskinesis with apical ballooning. Importantly, most often wall motion abnormalities extent beyond the distribution of any single coronary artery. Mean left ventricular ejection fraction (LVEF) ranges from 20 to 49 percent. LV basal hyperkinesis with left ventricular outflow tract (LVOT) obstruction may occur and may cause severe mitral regurgitation as result of systolic anterior motion (SAM) of the anterior mitral valve leaflet. In the acute phase some patients with TCM are in shock. Urgent echocardiography is necessary to differentiate between LVOT obstruction and severe left ventricle dysfunction.
There is no accurate way to reliably discriminate between TCM and AMI using ECG and cardiac biomarkers. Coronary angiography is essential for the differentiation between TCM and AMI. In general significant coronary artery stenosis is absent in TCM.

**Treatment**

Generally, in the acute phase of TCM the patient is treated with commonly used medication for systolic heart failure: beta-blockers (BB), ACE-inhibitors (ACE-I) and or angiotensine II receptor blockers (ARB) and diuretics. When a thrombus in the left or right ventricle is present, anticoagulation should be prescribed for 6 months to prevent systemic embolization. In the acute phase, TCM can be accompanied by cardiogenic shock. Inotropic agents are contra-indicated when shock is caused by LVOT obstruction as they may aggravate the clinical condition: inotropic agents may lead to catecholamine excess and can induce or worsen the degree of LVOT obstruction. In addition, intra-aortic balloon pump counter-pulsation can be used in these patients to improve hemodynamics. If shock is due to LV dysfunction without LVOT obstruction, inotropic agents are indicated. After the acute phase BB and ACE-I/ARB should be initiated and continued until left ventricular function is normalized. However, in light of preventing a possible recurrence of TCM, triggered by persisting increased myocardial adrenergic activity, it can be considered to continue BB and ACE-I/ARB treatment.

**Prognosis**

In general TCM has a favorable prognosis. However in the United States of America the in-hospital mortality is 4.2 percent. Interestingly male patients showed a higher mortality rate than females (8.4% vs. 3.6%). In general, after the acute phase left ventricular function normalizes in four weeks. Some studies have reported recurrence of apical ballooning. In one study with 100 patients followed for 4.4 years recurrence of TCM was found in 10% of patients whereas 31% had episodes of chest pain without significant coronary artery disease. Prognostic parameters of TCM are not known.

**Pathophysiology**

The precise pathophysiological mechanism of TCM has not been completely elucidated. Emotional, psychological or physical stress is frequently, but not always present prior to the onset of TCM, and may thus trigger the onset of disease. It has been suggested that epinephrine-mediated myocardial stunning in TCM is related to multiple coronary artery spasm and impaired coronary microcirculation. However, since various ballooning patterns extend beyond the distribution of any single coronary artery, ischaemia due to epicardial spasm seems unlikely and would not explain the various ballooning patterns. Considerable evidence points to epinephrine as an important factor in the pathophysiology. In the acute phase of TCM, plasma epinephrine levels are more elevated compared with the acute phase of a myocardial infarction. In general, these elevated epinephrine levels normalize within a few days. This is in keeping with the fact that TCM-like abnormalities, like apical wall motion abnormalities and ECG
changes are associated with epinephrine-secreting pheochromocytoma resulting in a “catecholamine storm”, but not with norepinephrine (NE)- and/or dopamine-secreting pheochromocytoma. However, it has been reported that accidental administration of epinephrine (including single intramuscular 1 mg dose from an epinephrine auto-injector) can result in TCM-like abnormalities.\textsuperscript{22}

NE predominately stimulates $\beta_1$AR on ventricular myocytes leading to a positive inotropic response. This is the result of $\beta_1$AR coupling to the G stimulating (Gs) protein. Epinephrine also binds to $\beta_2$AR and activates the same intracellular Gs-protein, but has a higher affinity for $\beta_2$AR ($K_d = 0.4$ nM) than NE ($K_d = 30$ nM).\textsuperscript{23} The mechanism of regional wall motion difference between apex and base is thought to be due to a greater proportion of $\beta_2$AR relative to $\beta_1$AR in the apex, since higher concentration of adrenergic innervations at the base of the heart is counterbalanced by increased apical BAR response/sensitivity to epinephrine.\textsuperscript{24,26,27} The human heart has a higher $\beta_2$AR:$\beta_1$AR ratio in apical than in basal cardiomyocytes.\textsuperscript{24,28} It was shown that this higher apical $\beta_2$AR:$\beta_1$AR ratio results in an enhanced $\beta_2$AR-specific inotropic response of the apical as compared to the basal cardiomyocytes.\textsuperscript{28} This higher $\beta_2$AR:$\beta_1$AR ratio in the apex makes this part of the myocardium probably more vulnerable/sensitive to excessive epinephrine stimulation, which may explain the decreased apical and preserved basal wall motion in the acute phase of TCM.

The pathophysiological basis of TCM may be explained by a direct “toxic” effect of epinephrine on cardiomyocytes. This is supported by a recent study performed in rats, in which a high bolus of epinephrine, but not NE, resulted in a cardiomyopathy mimicking TCM.\textsuperscript{28} It has been demonstrated in animal studies that $\beta_2$AR, when exposed to high levels of epinephrine, shifts from positively inotropic Gs coupling to negative inotropic G-inhibitor (Gi) coupling.\textsuperscript{23,28} This process is described as ligand/stimulus directed-trafficking or biased agonism (Figure 1). This effect was not observed after equivalent high dose of NE. It is assumed that $\beta_2$AR has one binding site for NE and two binding sites for epinephrine.\textsuperscript{23} The affinity of epinephrine for these two different binding sites varies so that when the high binding sites are fully saturated with epinephrine then the low binding sites begin to form complexes with epinephrine. Binding of epinephrine to high-affinity sites triggers the Gs protein, whereas binding to the low-affinity site stimulates Gi protein (Figure 2).\textsuperscript{23} After the increased levels of epinephrine are cleared from the circulation, $\beta_2$AR shifts back from Gi to Gs protein coupling, enabling cardiomyocytes to recover their inotropic function. This would explain the reported recovery of ventricular function in TCM when epinephrine levels are normalized.

$\beta_2$AR coupling to Gi protein is reported to be cardioprotective and anti-apoptotic.\textsuperscript{29,30} Blocking $\beta_2$AR Gi signaling in animal models before exposure to increased epinephrine levels induced mortality due to cardiogenic shock and hypokinesia.\textsuperscript{28} This might be explained by the possible increased cardiotoxic effects of high epinephrine levels via uninhibited $\beta_1$AR-Gs and $\beta_2$AR-Gs signaling.
It was also reported that epinephrine-induced apical hypokinesis exacerbates after administration of βAR-blockers which activate two G proteins, Gs (stimulating) protein and Gi (inhibiting) protein, which have counteracting effects on adenylate cyclase. Adenylate cyclase generates cyclic AMP (cAMP), which activates protein kinase A (PKA), a kinase that regulates the activity of several cellular proteins including the L-type Ca\(^{2+}\) channel and the β\(_2\)AR.

Figure 1. Schematic representation of trans-cell-membrane signal transduction of G-protein-coupled receptors. Two signaling pathways are regulated by the type β\(_2\)-adrenergic receptor (β\(_2\)AR). Stimulation of the β\(_2\)AR (e.g., by epinephrine) can activate two G proteins, Gs (stimulating) protein and Gi (inhibiting) protein, which have counteracting effects on adenylate cyclase. Adenylate cyclase generates cyclic AMP (cAMP), which activates protein kinase A (PKA), a kinase that regulates the activity of several cellular proteins including the L-type Ca\(^{2+}\) channel and the β\(_2\)AR.

Figure 2. Model for reactions between norepinephrine and epinephrine with β\(_2\)AR. Norepinephrine (NE) binds to β\(_2\)AR (R) resulting in Gs (stimulating) protein coupling. β\(_2\)AR has 2 binding sites for epinephrine (E), a high-affinity site (R•E) and a low-affinity binding site (R•E•E). The high-affinity site results in Gs protein coupling. When R•E is fully saturated, E will bind to the low-affinity site which results in Gi protein coupling.

It was also reported that epinephrine-induced apical hypokinesis exacerbates after administration of βAR-blockers which activate Gi protein coupling.\(^{26}\) A few β-blockers are pure neutral antagonists, while most act as partial or inverse agonists, or show biased agonism for βAR.\(^ {31}\) Propranolol has relatively high β\(_2\)AR-Gi protein inverse agonistic properties that enhance and prolong the negative inotropic effect of epinephrine at apex and base. Carvedilol has been shown to have less β\(_2\)AR-Gi protein inverse agonistic properties and consequently has little inotropic effects on the apex
but converts the initial positive inotropic response to epinephrine at the base to a significantly negative inotropic response. Therefore carvedilol, at least theoretically, may be useful in the treatment of TCM with severe LVOT obstruction secondary to basal hypercontractility. In contrast, the βAR-selective blocker bisoprolol reduced the positive inotropic effect at the base and had no effect on the apical myocytes. These findings suggest that treatment with βAR-blocker with more β2AR-blocking properties would be preferable. However, the above-described findings of βAR-blockers are mainly derived from animal experiments. Extrapolation of these findings to humans remains speculative. Although the possible mechanism of apical ballooning seems to be explained by the previously described effect of epinephrine, the question remains why not everyone who is exposed to emotional and physical stress develops TCM. We hypothesize two possibilities: patients with TCM have a higher release of epinephrine compared with persons without TCM and/or those with TCM are more sensitive to epinephrine due to higher density of β2AR and/or have another expression of Gs or Gi proteins.

TCM presents with typical apical ballooning, but there are reports that described reverse or inverted morphological patterns as a variant of this disease with involvement of the basal- and mid-ventricular segments and normal contractility of the apical segments.32,33 Since the use of CMR a few cases with right ventricle involvement have been reported.34 The mechanism of these different patterns is still unclear. It has been suggested that the variations in these regional wall motion abnormalities is mainly related to difference in the anatomic location of β2AR:β1AR ratio and/or polymorphism.

Sex Difference in TCM prevalence
There is a striking difference in the incidence of TCM in females as compared to males; about 90% of reported cases concern females.19 This could be explained by sex-related differences in adrenal medulla response to sudden high-intensity adrenergic stimulation and differences in the pharmacokinetics of epinephrine. In addition basal/resting epinephrine plasma levels are lower in women compared to men.36 This difference could reflect reduced basal release of epinephrine enabling the possibility for an increased sudden epinephrine response to stress. An increased sensitivity of the β2AR in women could favor the protective effects of β2AR-Gi protein signaling resulting in negative inotropism in the apical myocardium, the region with the highest density of β2AR. Perhaps men who lack this protective effect develop more acute cardiotoxicity mediated by β1AR-Gs protein signaling following high elevations in catecholamine levels, resulting in a fatal event rather than cardiomyopathy. This suggestion is supported by the increased in-hospital mortality of TCM in males compared with females (8.4% vs. 3.6%).19

TCM predominantly affects postmenopausal women assuming that estrogens play a role in the aetiology of TCM. It is known that estrogens have cardioprotective effects against acute myocardial injury through a variety of complex mechanisms.36 Yet, it is unclear how the lack of cardioprotective estrogens in postmenopausal women increases the risk of TCM. One of the possible mechanisms is upregulation of myocardial
β₁ARs. In line with this, myocardial β₁AR expression is upregulated in ovariectomized rats and this effect is reversed by estrogen replacement. These findings suggest that estrogen may affect cardiac responses to sympathetic stimulation by altering the expression of myocardial β₁ARs. However, TCM is mainly related to β₂ARs and therefore, changes in β₁AR expression by estrogens cannot fully explain the increased incidence of TCM in post-menopausal women. Changes in immediate early gene (IEG) expression could be an alternative explanation.

In rodent models it has been demonstrated that stress activates IEG expression in the central nervous system and myocardium. These myocardial changes in IEG expression are mediated by activation of both α- and βAR. It has been demonstrated that ovariectomized rats while subjected to immobilization stress have less IEG expression with estrogen supplementation compared to those without estrogen supplementation. This further underscores that estrogens have cardioprotective effects.

Non-invasive imaging techniques
For the diagnosis of TCM echocardiography is the imaging modality of first choice. It’s widely available, easy to perform at the bedside and it is non-ionizing. However with developments in CMR and nuclear imaging by mean of ¹²³I-mIBG scintigraphy, it’s possible to distinguish TCM from other cardiac diseases and to evaluate the cardiac adrenergic activity. (Figure 3)
Cardiovascular magnetic resonance

CMR is suited for evaluation of patients with TCM and can help differentiating TCM from myocarditis or myocardial infarction. In addition to the accurate visualization of regional wall motion abnormalities it enables quantification of right and left ventricular function and assessment of additional abnormalities like pericardial effusion, and ventricular thrombus. Compared to echocardiography CMR is an excellent non-invasive imaging technique to visualize right ventricle involvement or inverted TCM. CMR also provides markers for reversible injury such as edema, inflammation and irreversible injury, like necrosis and fibrosis. In contrast to myocardial infarction late gadolinium enhancement (LGE) as a marker for fibrosis has only been seen in 0 to 8% in case of TCM.34,39,40 This finding may help differentiate TCM from entities with similar clinical presentations such as myocarditis and myocardial infarction, i.e. myocardial infarction typically exhibits a subendocardial pattern of LGE while myocarditis usually displays a patchy subepicardial pattern.34 T2 weighted images can help to visualize edema.41

Global edema with high signal intensity (SI ratio of myocardium to skeletal muscle of 1.9 or higher) in the mid and apical myocardium confirms the diagnosis TCM, whereas a patchy signal is more compatible with myocarditis.34 Recently, a novel CMR method using T1 weighted mapping has been reported to assess acute myocardial edema.42 This non-contrast method seems promising as it has high diagnostic performance compared to T2 weighted CMR and is highly reproducible.

123I-mIBG scintigraphy

Meta-iodobenzylguanidine (mIBG) is a NE analog that has the same presynaptic uptake, storage and release mechanism as NE. Radiolabeling of mIBG with 123I or 131I allows for imaging with gamma cameras. In 1980 the potential use of 131I-mIBG for cardiac imaging was suggested.43,44 The last decades, 123I-mIBG scintigraphy has been developed to evaluate cardiac adrenergic function and the usefulness of 123I-mIBG scintigraphy has been demonstrated in many cardiac diseases.45-47

In TCM 123I-mIBG scintigraphy reveals impaired apical myocardial uptake of 123I-mIBG on planar images (Figure 4).48,49 This is thought to be induced by increased adrenergic stimulation and consequently increased NE levels. Interestingly, the trigger of TCM is high release of epinephrine, but not NE. The impaired uptake of 123I-mIBG may be explained as follows: NE and epinephrine are both taken up from the synaptic cleft by the uptake-1 (i.e. NE transporter: NET) and uptake-2 (i.e. extraneuronal monoamine transporter: EMT) (Figure 5). It has been demonstrated that uptake of NE is inhibited in the presence of high levels of epinephrine.50 Therefore, in TCM decreased uptake of NE (i.e. 123I-mIBG) via uptake-1 could be explained as an indirect effect to high circulating levels of epinephrine.

Single Photon Emission Computed Tomography (SPECT) 123I-mIBG is important for regional evaluation of myocardial innervation in TCM. SPECT 123I-mIBG imaging demonstrated mainly decreased NE uptake of the myocardial apex.48 Interestingly, this pattern follows the increasing β2AR:β1AR ratio from the base to the apex. Apical
cardiomyocytes have been shown to express a higher density of β2ARs and therefore a higher sensitivity to epinephrine compared to the basal cardiomyocytes, resulting in epinephrine-induced regional stunning.\textsuperscript{28} We assume that the hyperadrenergic state by high levels of epinephrine causes downregulation of β2ARs. Alterations in the pre-synaptic signal transduction result in an impaired uptake-1 function in order to maintain high levels of catecholamines with effect of stimulating those β2ARs that are still functional. This hypothesis is supported by studies showing that the presynaptic trace amine-associated receptor 1 (TAAR 1) in the brain is activated by monoaminergic neurotransmitters like NE, dopamine and serotonin. TAAR1 activation by these common biogenic amines can modulate monoaminergic transporters, including the dopamine, NE and serotonin transporter.\textsuperscript{51,52} It can be assumed that this not only occurs in the brain, but also in other organs such as the heart (Figure 5). This phenomenon may explain the impaired apical uptake of $^{123}$I-mIBG on SPECT images in patients with TCM. Although left ventricular function and epinephrine levels are normalized after a few weeks, several case reports show persisting decreased $^{123}$I-mIBG uptake on SPECT images in the apical myocardium.\textsuperscript{48,49} The mechanism of this persisting regional impaired uptake of $^{123}$I-mIBG uptake is yet unclear. We assume that the increased apical density and sensitivity of the β2AR to epinephrine causes a prolonged effect of downregulation of β2AR and impaired uptake-1 function. This would maintain relatively higher levels of epinephrine and NE in the synaptic cleft and would in turn cause these receptors and transporters to recover more slowly compared to more basal located β2ARs. In addition, the phenomenon of persisting decreased myocardial $^{123}$I-mIBG uptake may in part be explained by preexisting myocardial sympathetic denervation. Of interest is whether especially the slow recovery of apical $^{123}$I-mIBG uptake may identify those patients who are at a higher risk for the recurrence of TCM. Therefore SPECT $^{123}$I-mIBG may guide optimization of individual (pharmacological) therapy to prevent recurrent TCM.
Figure 5. Schematic representation of the sympathetic synapse. Norepinephrine (NE) is synthesized within neurons by an enzymatic cascade. Dihydroxyphenylalanine (DOPA) is generated from tyrosine and subsequently converted to dopamine by DOPA decarboxylase. Dopamine is transported into storage vesicles by the energy-requiring vesicular monoamine transporter (VMAT). NE is synthesized by dopamine β-hydroxylase within these vesicles. Neuronal stimulation leads to NE release through fusion of vesicles with the neuronal membrane (exocytosis). Most NE undergoes reuptake into nerve terminals by the presynaptic NE transporter (uptake-1) and is re-stored in vesicles (following uptake by vesicular amine transporter 2 (VMAT2)) or is metabolized in cytosol dihydroxyphenylglycol (DHPG) by monoamine oxidase (MAO). Postsynaptic NE undergoes reuptake into the myocytes by the extraneuronal monoamine transporter (uptake-2). Presynaptic trace amine-associated receptor 1 (TAAR 1) can be activated by monoaminergic neurotransmitters like NE and epinephrine. TAAR1 activation can modulate uptake-1 resulting in decrease uptake of NE.
CONCLUSION

TCM is increasingly recognized as a separate clinical diagnosis. The diagnosis should particularly especially be considered in female patients with chest pain and/or unexplained heart failure. It is essential to exclude significant coronary artery stenosis by coronary angiography. Typical apical left ventricular ballooning is present on ventriculography and echocardiography. High levels of epinephrine and the subsequent bias agonism of β2ARs may play a pivotal role in the development of TCM. As predominantly postmenopausal women are mainly affected, estrogens may play a role. However, the exact mechanism is yet unclear and needs to be investigated. Another unanswered question is why not everyone with stress develops TCM. New imaging techniques such as CMR may help in differentiating TCM from myocarditis and myocardial infarction. In addition CMR can also visualize right ventricle involvement or inverted TCM. 123I-mIBG myocardial scintigraphy may assess the adrenergic state and may be useful for estimating prognosis and guiding (pharmacological) therapy. Animal studies suggest that treatment with a neutral antagonist like carvedilol would be preferable than an inverse agonist like propanolol, but this hypothesis has not been tested in humans. The prognosis after the acute phase of TCM is good, although recurrent TCM has been described.

Finally, there is a need to establish a registry for TCM patients to better understand its natural history and its true occurrence. This would help to better define the disease process and would in turn enable a better understanding of possible risk factors associated with the start of the disease but also helps in identifying risk factors associated with prognosis and recurrence of TCM. In addition randomized trials should be performed to evaluate therapeutic strategies to promote swift recovery of left ventricular function and prevent recurrence of TCM.
REFERENCES


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