The role of multimodality imaging in takotsubo cardiomyopathy

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Takotsubo cardiomyopathy (TC) is a syndrome of transient left ventricular (LV) dysfunction mimicking acute coronary syndrome. Although the mechanisms underlying the occurrence of TC are unknown, several imaging techniques contribute to its diagnosis. Here we review the current knowledge about TC, in particular, the pathophysiology and the role of imaging including nuclear cardiovascular medicine. (J Nucl Cardiol 2019;26:1602–16.)

Key Words: Takotsubo cardiomyopathy • ^{123}I-BMIPP • ^{123}I-MIBG • ^{18}F-FDG PET • cardiovascular magnetic resonance

Abbreviations

^{123}I-BMIPP	Iodine-123-labeled beta-methyl-P-iodophenylpentadecanoic acid
^{123}I-MIBG	Iodine-123-labeled metaiodobenzylguanidine
^{18}F-FDG	Fluorine-18-labeled fluorodeoxyglucose
ACS	Acute coronary syndrome
AR	Adrenergic receptor
CBF	Cerebral blood flow
CFR	Coronary flow reserve
CMR	Cardiovascular magnetic resonance
ECG	Electrocardiography
LV	Left ventricle/ventricular
EF	Ejection fraction
MBF	Myocardial blood flow
PET	Positron emission tomography
SPECT	Single-photon emission computed tomography
TC	Takotsubo cardiomyopathy

INTRODUCTION

Takotsubo cardiomyopathy (TC) was first described in 1990 in Japan by Sato et al.[1] TC is also known as broken heart syndrome,[2] apical ballooning syndrome,[3] and acute stress-induced cardiomyopathy. 'Takotsubo' is the Japanese term for an octopus (*tako*) trapping pot (*tsubo*), which is similar to the shape of the left ventricle (LV) at systole with a narrow neck and a round bottom (Figure 1).

TC is a transient cardiac syndrome, typically with LV apical akinesis and basal hyperkinesis mimicking LV aneurysm due to acute coronary syndrome (ACS).

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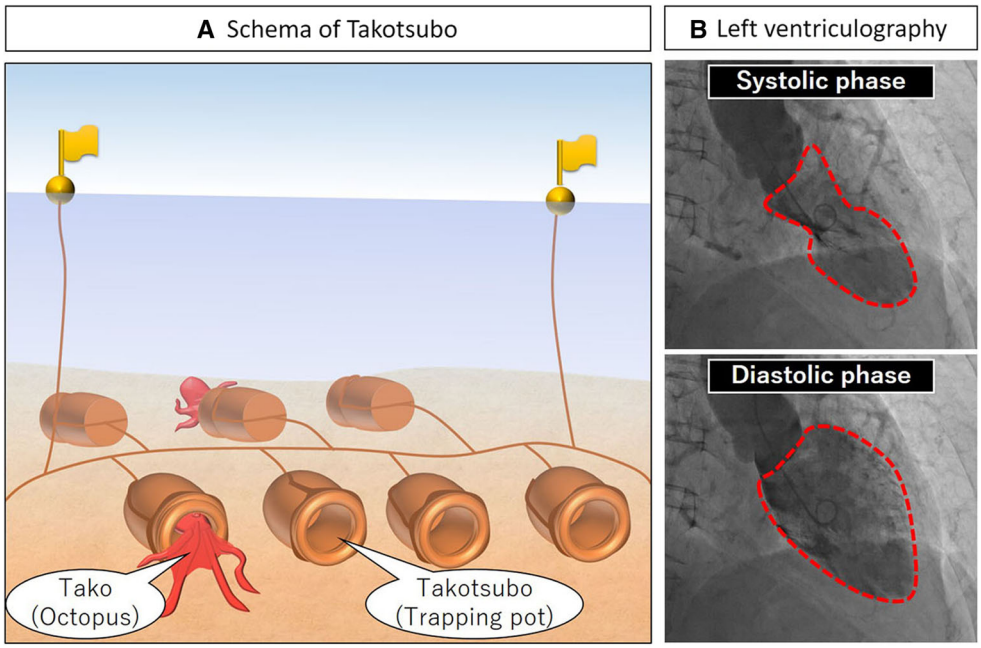

Figure 1. Schematic representation of takotsubo cardiomyopathy. A *takotsubo* is a pot used to catch an octopus. **A** A takotsubo is tied to a rope and submerged in the sea; it is retrieved after an octopus has entered the pot. **B** The shape of the takotsubo resembles the configuration of the left ventricle during systole on imaging, such as left ventriculography.

Patients with TC often present with chest pain, have ECG abnormalities (ST-segment elevation, T-wave negative conversion, and QT prolongation), and have mildly elevated cardiac enzyme levels. In the acute phase, various cardiac complications including lethal ventricular arrhythmia, pump failure, outflow tract obstruction, cardiac rupture, and systemic embolization may occur.

Although the mechanism(s) underlying the occurrence of TC are not yet known, several imaging techniques contribute to its diagnosis. Echocardiography and left ventriculography are used to the immediate assessment of the regional wall motion abnormalities. Nuclear cardiac imaging and cardiovascular magnetic resonance (CMR) imaging have been used for the diagnosis and understanding the pathogenesis of TC.

In this review, we discuss the current knowledge about TC, with a focus on its pathophysiology and the roles of multimodality imaging.

ETIOLOGY

It was speculated that TC was seen in only a limited number of countries, because reports of TC in the 1990s (following the 1990 description by Sato et al) were mainly from Japan.[1] However, TC has been increasingly recognized around the world; the number of reports from countries other than Japan has rapidly increased since 2000.[4–6] Because the clinical condition presented by TC patients is similar to that presented by ACS, its accurate diagnosis is sometimes difficult. It had been estimated that approx. 1%-2% of patients with suspected ACS had TC.[6] The prognosis of patients with TC had been considered to be favorable due to the typically transient nature.[7,8] However, the International Takotsubo Registry, which is a prospective study including 1750 patients, reported that the rates of coexistence of CAD and mortality were higher than previously thought. In this study, 15.3% of TC patients (245/1597) showed the coexistence of CAD.[9] Follow-up results of TC revealed the rate of death from any cause of 5.6% per patient-year and a rate of major adverse cardiac and cerebrovascular events of 9.9% per patient-year.[9]

The rate of recurrence of TC was estimated to 1.8%-11% per patient-year.[8–10] The period from the first episode to the recurrence is reported 3 months to 13 years.[8,10] There was an interesting case whose initial occurrence was apical type and the recurrence was mid-ventricular type.[11]

PATHOPHYSIOLOGY

The pathophysiology of TC is not fully understood, but there are several postulated etiologies. TC typically

follows signs of physical and mental stress. The incidence of the experienced stress varies between reports, up to 85% of patients who were diagnosed as having TC had experienced either a significant emotional or physical stress.[3,12,13] Such stressors have varied widely among reports of TC cases, including natural disasters such as an earthquake, bereavement reaction, surprise party, a wedding, stress testing (such as dobutamine, ergonovine or treadmill), electric shock due to lightning, natural delivery, and more.[6,14–18] TC is reported more frequently in the summer season and during the morning hours.[19] In light of the characteristic pattern of TC onset, these findings suggest that an abnormal excitation of the sympathetic nervous system could be a major mechanism underlying TC. The reduction of estrogen due to menopause is also an important factor, as TC is more common in women, especially elderly women.[7] Although TC is commonly developed in elderly women, young patients can also be affected in the iatrogenic conditions such as anesthesia, surgical invasion, thyroid toxemia, sepsis, drug addiction, and in the postpartum period notably after Cesarean delivery.[20–22] When the patient receives the various types of the stressor, the nervous system is activated in order to preserve the homeostasis. Not only mental but also physical and environmental stresses are also related to the heart disease. Even with the same stress, reaction might be depending on individual risk factors that influence catecholamine production and/or myocyte and microvascular sensitivity to sympathetic stimulation. Even minor stressors can trigger the syndrome.[23]

Cardiac autonomic innervation is a complex system which contains the receptors, afferent/efferent nerves, and effector systems. Hyperactivity of the sympathetic nervous system is one of the major findings in TC. Activated post-ganglionic sympathetic nerve releases the norepinephrine into the synaptic cleft which binds to post-synaptic adrenergic receptor (AR) producing a wide range of cardiac effects to adjust the heart rate, blood pressure, and contractility. Autonomic cardiac effects may be determined by the relative extent and distribution of innervation in the heart. Disorders of the autonomic nervous system can lead to a manifestation of cardiovascular disorders.[24] High plasma catecholamine levels in patients with pheochromocytoma can induce reversible cardiomyopathy and cause a myocardial injury called contraction band necrosis.[25] Wittstein et al reported that the plasma catecholamine levels at presentation were approx. two- to threefold higher in TC patients compared to patients with acute myocardial infarction[16]; the elevation of the epinephrine concentration was especially remarkable. The myocardial histological changes in TC are similar to those seen in catecholamine cardiotoxicity.[17,26]

Results from animal studies have suggested that stunning of the myocardium was due to the acute catecholamine overload as a potential mechanism.[27,28] Changes in β AR signaling have an important role in the investigations of the pathophysiology of TC. Izumi et al make a new model of takotsubo-like cardiomyopathy with severe hypokinesis in apical regions and hyperkinesia in the basal region in monkeys and confirmed the effect of β1 AR blockers.[29] Paur et al demonstrated that apical ventricular cardiomyocytes have a higher β2 AR density and a greater β2 AR-induced sensitivity than basal cardiomyocytes in rats and that excessive epinephrine exposure led to a negative inotropic action and apical ballooning in rats.[27] An elevated epinephrine level leads to activation of the intracellular signal transport in myocardial cells with a change from Gs protein to Gi protein through β2 AR.[30] Apical stunning might be evoked by the epinephrine stimulation of β AR, causing a shift to the inhibitory signal.[30] On the other hand, excessive contraction due to sympathetic stimulation is seen at the basal myocardium that may lead to dynamic outflow tract obstruction. Mantravadi et al reported that autonomic nerve stimulation was found to bring about a reversal of the direction of repolarization along the apex to base axis of the rabbit heart,[31] which might be partially explain the clinical observations of the apical dysfunction in TC. Ueyama et al demonstrated that reversible LV apical ballooning in rat was normalized by pretreatment with α and β adrenergic receptor blockers.[32]

The physiological reaction to a stressful condition mediates the action of a stressor on its target organ.[33] Estrogen receptors are expressed in the blood vessels, heart, and the central nervous system.[34,35] Since TC is observed overwhelmingly in postmenopausal women, a lack of cardioprotective effect due to estrogen reduction is strongly expected. Estrogen plays crucial roles in protection against ischemic insults and the regulation of autonomic nervous function.[36]

The pathophysiology of TC also integrates neuroendocrine physiology, potentially involving the cognitive centers of the brain.[37] By using ^{99m}Tc ethyl cysteinate dimer (^{99m}Tc-ECD) SPECT in the acute and chronic phases, Suzuki et al measured the cerebral blood flow (CBF) in TC patients.[38] Their observations in the acute phase included increased CBF levels in the hippocampus, brainstem, and basal ganglia, paralleled by decreased CBF levels in the prefrontal cortex; the levels improved in the chronic phase. These results indicated the involvement of brain n the pathogenesis of TC.[38] Sudden, unexpected serious distress leads to the activation of estrogen receptors by neurons of the central self-controlled network, followed by a conspicuous increase in norepinephrine from the sympathetic nervous

system and epinephrine from the adrenal medulla.[36] The systemic blood pressure and cardiac afterload increase immediately after the contraction of the resistance vessels, which is due to the stimulated adrenoceptors in the blood vessels by the released epinephrine and norepinephrine.[39] On the other hand, the high circulation levels of epinephrine and norepinephrine cause catecholamine toxicity of myocardial cells by the occupation of adrenoceptors.

Another hypothesis of the pathophysiology of TC is microcirculatory disorder. Several studies have demonstrated the presence of impaired coronary microcirculation in patients with TC. Feola et al reported that the acute phase of TC is characterized by an inverse perfusion/metabolism mismatch with a reduction in the coronary flow reserve in the apical segments, which might be caused by the presence of a microcirculation disturbance limited to the apical LV segments.[40]

DIAGNOSTIC CRITERIA

The diagnostic criteria issued by the Takotsubo Cardiomyopathy Study Group (TCSG) are commonly used in Japan (Table 1),[41] and internationally, the Mayo Clinic Criteria are widely used as diagnostic criteria (Table 2).[42] In the TCSG criteria, non-contraction of the apex of the heart is essential. The Mayo Clinic criteria describe non-contraction in the middle part of the left ventricle as important, and non-contraction of the apex of the heart is not essential. In addition to this significant difference between the two sets of criteria, the TCSG and Mayo Clinic include differing patient exclusion criteria.

ECHOCARDIOGRAPHY AND LEFT VENTRICULOGRAPHY

Regional wall motion abnormalities (hypokinesis, akinesis, or dyskinesis) are revealed by echocardiography or left ventriculography. The classical finding is apical ballooning due to the akinesia, hypokinesia, or dyskinesia of the apical to middle segments of the LV and hyperkinesia of the basal segments. LVEF was reduced in 86.5% of patients with TC on admission and estimated left ventricular ejection fraction on the initial echocardiogram was about 40%.[9]

TC is classically described as apical ballooning, but other types such as mid-ventricular, basal, and focal type have been reported (Figure 2). Reversible right ventricle (RV) and biventricular dysfunction triggered by acute stress has also been reported in a manner similar to that seen in LV TC which provides a definitive clue to diagnose the TC.[43,44] RV involvement is seen about 18.6% in the TC.[45] RV involvement causes the higher rates of in-hospital morbidity and mortality as well as long-term events compared to the TC without RV involvement.[45]

RADIONUCLIDE MYOCARDIAL IMAGING

Non-invasive imaging by positron emission tomography (PET) and single-photon emission computed tomography (SPECT) enable the assessment of myocardial perfusion and myocardial tissue pathology. Fluorine-18-labeled fluorodeoxyglucose (^{18}F-FDG), iodine-123-labeled beta-methyl-P-iodophenylpentadecanoic acid (^{123}I-BMIPP), and iodine-123-labeled metaiodobenzylguanidine (^{123}I-MIBG) are frequently used to evaluate the pathological condition of TC. ^{18}F-FDG is an analogue of glucose and ^{123}I-BMIPP is an iodinated fatty acid analogue; both are used to assess myocardial metabolism.[46] ^{123}I-MIBG is an analogue of catecholamine used as a SPECT tracer to evaluate the presynaptic sympathetic innervation of the heart.[46]

We retrospectively searched the U.S. National Library of Medicine's MEDLINE database via PubMed for case reports and original articles involving TC, until December 2017 (Figure 3). Fourteen articles were excluded because the language used is not English. Review articles, editorial comments, and papers without a report of imaging findings in the acute/subacute phase were also excluded. We divided the articles into three subsets: those describing (1) imaging of metabolic changes using ^{18}F-FDG PET (Table 3), (2) the simultaneous assessment of ^{123}I-BMIPP SPECT and myocardial perfusion imaging (Table 4), and (3) a comparative estimate of sympathetic nerve function using ^{123}I-MIBG SPECT with perfusion imaging (Table 5).

Owa et al reported the first nuclear imaging findings of TC patients in 2001.[47] They studied four TC patients by obtaining serial cardiac SPECT images using ^{201}Tl, ^{123}I-BMIPP, and ^{123}I-MIBG in the acute (day 2 or 3), subacute (2 or 3 weeks later), and chronic phases (3 months later). The ^{123}I-MIBG and ^{123}I-BMIPP images showed a perfusion defect in the apical region, whereas the ^{201}Tl uptake was mildly decreased in the acute phase. In addition, the defect of ^{123}I-MIBG uptake persisted for several months, unlike the ^{123}I-BMIPP and ^{201}Tl uptake.

On the whole, myocardial perfusion at rest is preserved or relatively decreased in the apical region, which is concordant with the wall motion abnormality shown by echocardiography in the acute phase. The region with reduced perfusion is frequently smaller compared to the region with the wall motion abnormality. Reduced perfusion tracer uptake may be due to truly

Table 1. Guidelines for the diagnosis of takotsubo cardiomyopathy: the takotsubo cardiomyopathy study group

I. Definition
Takotsubo (ampulla) cardiomyopathy is a disease exhibiting an acute left ventricular apical ballooning of unknown cause. In this disease, the left ventricle takes on the shape of a "takotsubo" (Japanese octopus trap). There is nearly complete resolution of the apical akinesis in the majority of the patients within 1 month. The contraction abnormality occurs mainly in the left ventricle, but involvement of the right ventricle is observed in some cases. A dynamic obstruction of the left ventricular outflow tract (pressure gradient difference, acceleration of blood flow, or systolic cardiac murmurs) is also observed
Note There are patients, such as cerebrovascular patients, who have an apical systolic ballooning similar to that in takotsubo cardiomyopathy, but with a known cause. Such patients are diagnosed as having "cerebrovascular disease with takotsubo-like myocardial dysfunction" and are differentiated from idiopathic cases
II. Exclusion criteria
The following lesions and abnormalities from other diseases must be excluded in the diagnosis of takotsubo (ampulla) cardiomyopathy
A. Significant organic stenosis or spasm of a coronary artery. In particular, acute myocardial infarction due to a lesion of the anterior descending branch of the left coronary artery, which perfuses an extensive territory including the left ventricular apex. An urgent coronary angiogram is desirable for imaging during the acute stage, but coronary angiography is also necessary during the chronic stage to confirm the presence or absence of a significant stenotic lesion or a lesion involved in the abnormal pattern of ventricular contraction
B. Cerebrovascular disease
C. Pheochromocytoma
D. Viral or idiopathic myocarditis
Note For the exclusion of coronary artery lesions, coronary angiography is required. Takotsubo-like myocardial dysfunction could occur with diseases such as cerebrovascular disease and pheochromocytoma
III. References for diagnosis
A. *Symptoms* Chest pain and dyspnea similar to those in acute coronary syndrome. Takotsubo cardiomyopathy can occur without symptoms
B. *Triggers* Emotional or physical stress may trigger takotsubo cardiomyopathy, but it can also occur without any apparent trigger
C. *Age and gender difference* Known tendency to increase in the elderly, particularly females
D. *Ventricular morphology* Apical ballooning and its rapid improvement in the ventriculogram and echocardiogram
E. *Electrocardiogram* ST-segment elevations might be observed immediately after the onset. Thereafter, in a typical case, the T-wave becomes progressively more negative in multiple leads, and the QT interval prolongs. These changes improve gradually, but a negative T-wave may continue for several months. During the acute stage, abnormal Q-waves and changes in the QRS voltage might be observed
F. *Cardiac biomarkers* In a typical case, there are only modest elevations of the serum levels of cardiac enzymes and troponin
G. *Myocardial radionuclear study* Abnormal findings in myocardial scintigraphy are observed in some cases
H. *Prognosis* The majority of the cases recover rapidly, but some cases suffer pulmonary edema and other sequelae or death

reduced regional perfusion, relatively increased perfusion in the other region, and the partial volume effect.[48] The degree of perfusion abnormality may also depend on the time-interval between the onset of symptoms and the perfusion scan.[49] ^{123}I-BMIPP and ^{123}I-MIBG typically show a larger and more severe decrease than perfusion (Figure 4). The imaging pattern with each tracer tends to improve from the subacute phase to the chronic phase (Figure 5). Perfusion in most cases is normalized within 1 month, which is earlier compared to the improvement of the ^{123}I-BMIPP and ^{123}I-MIBG uptake.[50,51] Marfella et al reported interesting results about the effects of α-lipoic acid (ALA) therapy on sympathetic heart innervation in patients with TC.[52] They concluded that ALA treatment improved the adrenergic cardiac innervation compared to a placebo.

The cause of the metabolic abnormality of TC has not been fully known. The microvascular dysfunction led by the sympathetic changes due to the neurogenic stress might be one of the causes of the metabolic

Table 2. The clinical diagnosis of takotsubo cardiomyopathy: the mayo clinic criteria

1. Typical LV contraction pattern: transient hypokinesia, akinesis, or dyskinesia in the LV mid-segments with or without apical involvement accompanied by hypercontraction in the basal segments; RWMAs that extend beyond a single coronary artery vascular distribution; a stressful trigger is usually but not always present
2. Absence of obstructive CAD or angiographic evidence of acute plaque rupture
3. Newly developed ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin
4. Absence of recent head trauma, intracranial hemorrhage, pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy

LV, left ventricle; *RWMAs*, regional wall motion abnormalities; *CAD*, coronary artery disease; *ECG*, electrocardiography

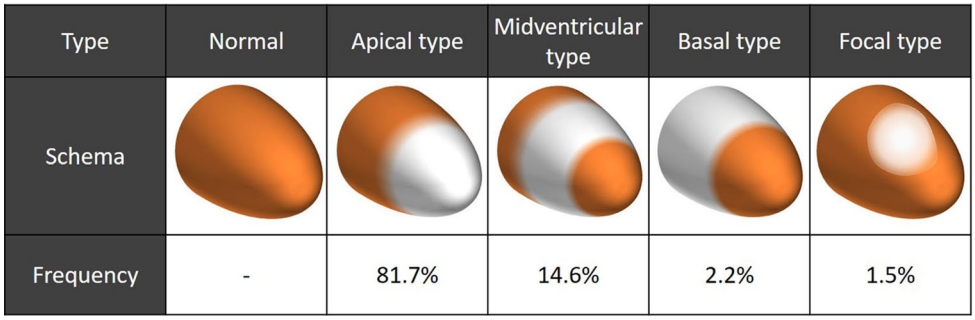

Figure 2. Variation of takotsubo cardiomyopathy (TC). Schema of TCs are displayed. White lesions are the territory of a transient abnormality in left ventricular wall motion. Apical type which is the so-called tako-tsubo is most frequent. Some of the other variations are reported such as mid-ventricular, basal, and focal type Modified from Templin.[9]

abnormality.[53,54] In the myocardial tissues of TC, the reversible intracellular accumulation of glycogen indicates a severe energy deprivation, and a disturbance in protein metabolism proved by the occurrence of multiple vacuoles and ubiquitin has been observed.[55] A direct myocardial toxicity due to the catecholamine excess is another pathophysiological mechanism related to myocardial changes.[55] Further studies suggesting an associated myocardial metabolic abnormality is warranted.

The methods for evaluating cardiac glucose metabolism using ^{18}F-FDG PET are divided into two groups: glucose loading preparation, and suppression of the physiological ^{18}F-FDG uptake. Studies of TC using ^{18}F-FDG PET with glucose loading revealed a discrepancy between normal or slightly decreased perfusion and more severely reduced ^{18}F-FDG uptake, which is called 'inverse metabolic-perfusion mismatch'[40,56] and suggests that TC represents a transient metabolic disorder at the myocardial cellular level. A ^{18}F-FDG PET with fasting study demonstrated that the uptake patterns can be divided into two major types: an intense apical ^{18}F-FDG accumulation, and decreased apical ^{18}F-FDG accumulation but preserved ^{18}F-FDG accumulation elsewhere, which may indicate a mixture of stunned or hibernated myocardium due to the ischemic microcirculatory dysfunction and disorder of glucose metabolism.[57] Myocardial blood flow (MBF)/coronary flow reserve (CFR) derived from ^{13}N-ammonia PET was compared with the FDG uptake by Feola et al[40] In their study, an inverse perfusion/metabolism mismatch with a reduction in CFR in the apical segments was seen in the acute phase of TC, and the mismatch was recovered after 3 months. Microcirculatory dysfunction might thus develop in the acute phase of TC.

OTHER TRACERS

Pessoa et al compared the ^{123}I-MIBG and ^{67}Ga citrate scans in the acute phase of five female TC patients.[4] They identified an apical defect of ^{123}I-MIBG, whereas there was no abnormal ^{67}Ga uptake, which indicated that TC was probably not associated with an inflammatory process. Ito et al confirmed the

Table 3. ^{18}F-FDG PET scan findings in takotsubo cardiomyopathy

	N	Female	Age, years	^{18}F-FDG protocol	Day	^{18}F-FDG finding	Perfusion	Follow-up ^{18}F-FDG finding
Kobylecka et al[57a]	18	17	74 (57-90)	Suppress	5.1 ± 4.6	8/18: Increase	7/8: Normal 1/8: Reduced	NA
						10/18: Relatively reduced	7/10: Reduced 3/10: Normal	NA
Crimizade et al[62]	1	1	84	NA	5	Reduced	Reduced	NA
Christensen et al[63a]	19	18	67 ± 1.9	Loading	5.7 ± 0.95	Reduced	Reduced	Improved
Ghadri et al[64]	1	1	80	NA	7	Reduced	Reduced	Improved
Ibrahim et al[65a]	1	1	70	Suppress	6	Increase	NA	NA
Miyachi et al[66a]	1	1	85	Suppress	6	Increase	Reduced	NA
Skovgaard et al[67]	1	1	72	Loading	Acute phase	Reduced	Reduced	Improved
Bonnemeier et al[68]	13	NA	NA	Loading	First week	Reduced	Normal	NA
Cimarelli et al[69a]	15	11	69.8 ± 20.5	Loading	8.9 (3-20)	Reduced	Normal	Improved (*n* = 6)
Morel et al[70]	5	5	NA	Loading	First week	Reduced	Normal	Improved (n = 3)
Feola et al[40a]	3	3	65, 74, 87	Loading	2	Reduced	Reduced	Improved
Burgdorf et al[71]	2	2	45	NA	4	Mildly reduced	Normal	NA
			41	NA	4	Reduced	Normal	NA
Cimarelli et al[72a]	2	2	83, 67	Loading	8	Reduced	Normal	NA
Yoshida et al[56]	8	NA	NA	Loading	8 ± 3	7/8: Reduced	Reduced (some of them)	NA
Rendl et al[5a]	1	1	67	Loading	5	Reduced	Reduced	Improved
Obunai et al[73a]	1	1	52	Loading	6	Reduced	Reduced	Improved
Total[a]	61	55 (90.2%)	70.5 (41-90)	Suppress: *n* = 20 (32.8%) Loading: *n* = 41 (67.2%)	6.2 (2-20)	Suppress (increase): *n* = 10 (16.4%) Suppress (decrease): *n* = 10 (16.4%) Loading (increase): *n* = 0 (9%) Loading (decrease): *n* = 41 (67.2%)	Normal: *n* = 30 (49.2%) Reduced: *n* = 30 (49.2%) NA: *n* = 1 (1.6%)	Improved: *n* = 30 (49.2%) NA: *n* = 31 (50.8%)

Day: after episode or hospital day, finding: uptake at the region of wall motion disturbance, loading: glucose loading prior to ^{18}F-FDG injection, suppress: the method to suppress the physiological ^{18}F-FDG uptake
NA, not available
[a]Total is calculated by the articles which data are full (without NA in the cell of the female, age, protocol, and exact day)

Table 4. ^{123}I-BMIPP and perfusion in takotsubo cardiomyopathy

	N	Female	Age, years	Day	^{123}I-BMIPP finding	Perfusion	Discrepancy to perfusion	Follow-up ^{123}I-BMIPP finding
Ito et al[74a]	1	1	62	3	Reduced	Normal	+	NA
Iida et al[75a]	1	1	70	5	Reduced	Normal	+	NA
Nagai et al[76]	1	1	74	NA	Reduced	Normal	+	NA
Shimizu et al[77]	20	NA	NA	Acute phase	Reduced	Reduced	+	NA
Matsuo et al[78a]	16	8	72 ± 3	11.1 ± 2.1	Reduced	Reduced (*n* = 13)	Some of them +	NA
Miyachi et al[66a]	1	1	85	6	Reduced	Reduced	+	NA
Ishibashi et al[79a]	1	0	66	15	Reduced	Reduced	+	NA
Uchida et al[80a]	9	7	73 ± 9.9	6.6 ± 3.3	Reduced	Normal (*n* = 5) Reduced (*n* = 4)	+	Improved (*n* = 8)
Sakuragi et al[81a]	1	1	59	10	Reduced	Reduced	+	NA
Fukui et al[82a]	1	1	84	25	Reduced	Normal	+	Improved
Ito et al[50]	7	5	63.1 ± 7.1	2–14	Reduced	Reduced	+	Improved
Ohwada et al[83a]	3	3	17	4	Reduced	Normal	+	NA
			25	7	Normal	Normal	−	
			33	1 month	Normal	Normal	−	
Suzuki et al[84a]	1	0	64	14	Reduced	Normal	+	NA
Owa et al[47]	4	4	64.3 ± 7.9	2–3	Reduced	Reduced	+	Improved
Total[a]	34	22 (64.7%)	69.1 [17–85]	10.3 [3–30]	Reduced: *n* = 33 (97.1%) Normal: *n* = 1 (2.9%)	Normal: *n* = 11 (32.4%) Reduced: *n* = 20 (58.8%) NA: *n* = 3 (8.8%)	+: *n* = 33 (97.1%) −: *n* = 1 (2.9%)	Improved: *n* = 10 (29.4%) NA: *n* = 24 (70.6%)

Day: after episode or hospital day, ^{123}I-BMIPP finding: ^{123}I-BMIPP finding at the region of wall motion disturbance
NA, not available
[a]Total is calculated by the articles which data are full (without NA in the cell of the Female, Age, and exact Day)

Table 5. ^{123}I-MIBG and perfusion for takotsubo cardiomyopathy

	N	Female	Age, years	Day	^{123}I-MIBG finding	Perfusion	Discrepancy to perfusion	Follow-up ^{123}I-MIBG finding
Sestini et al[49]	22	21	70 ± 11	Acute	Reduced early 21/22 Late 22/22	Reduced (17/22)	+	Some of them
Crimizade et al[62a]	1	1	84	5	Reduced	Reduced	+	−
Marfella et al[52a]	48	48	63.8 ± 5.8	14 (median)	Reduced	Normal	+	Improved
Mesas et al[85a]	1	1	72	10	Reduced	Normal	+	−
Harris et al[86]	1	1	45	NA	Reduced	Reduced	+	Improved
Ikutomi et al[87]	1	1	64	Acute phase	Reduced	Normal	+	Improved
Chrapko et al[88]	1	1	46	Acute phase	Reduced	Normal	+	Improved
Skovgaard et al[67]	1	1	72	Acute phase	Normal	Reduced	+ (Inverse)	Normal
Carrero et al[89]	13	?	?	1st week	Reduced	Normal	+	−
Cimarelli et al[69]	8	7	64.9 ± 24.3	4-20	Reduced	Normal (*n* = 6)	+	Improved except for apex (*n* = 6)
Morel et al[70]	6	6	NA	1st week	Reduced	Normal	+	Improved (*n* = 3)
Izumi et al[90]	1	1	73	NA	Reduced	Reduced	+	NA
Burgdorf et al[71a]	2	2	45, 41	6	Reduced	Normal	+	NA
Uchida et al[80a]	9	7	73 ± 9.9	9.4 ± 2.5	Reduced	Normal (*n* = 5) Reduced (*n* = 4)	+	Improved
Cimarelli et al[72a]	2	2	83, 67	6	Reduced	Normal	+	NA
Burgdorf et al[91]	10	9	67 ± 4	3-9	Reduced	Normal-mildly reduced	+	NA
Sakuragi et al[81]	1	1	59	5 or 28	Reduced	Reduced	+	NA
Takeoka et al[92]	1	1	73	NA	Reduced	Normal	+	NA
Ito et al[50]	7	5	63.1 ± 7.1	2-14	Reduced	Reduced	+	Improved
Ohwada et al[83a]	3	3	17	6	Reduced	Normal	+	NA
			25	9	Normal	Normal	−	
			33	1 month	Normal	Normal	−	
Miyazaki et al[93a]	1	1	79	11	Reduced	Reduced	+	NA
Owa et al[47]	4	4	64.3 ± 7.9	2-3	Reduced	Reduced	+	Persistent for several months
Total[a]	67	64 (95.5%)	63.7 (17-84)	12.7 (5-14)	Reduced: *n* = 66 (98.5%) Normal: *n* = 1 (1.5%)	Normal: *n* = 61 (91.0%) Reduced: *n* = 6 (9.0%)	+: *n* = 66 (98.5%) −: *n* = 1 (1.5%)	Improved: *n* = 57 (85.1%) NA: *n* = 10 (14.9%)

Day: after episode or hospital day, ^{123}I-MIBG finding: ^{123}I-MIBG finding at the region of wall motion disturbance
NA, not available
[a]Total is calculated by the articles which data are full (without NA in the cell of the female, age, and exact day)

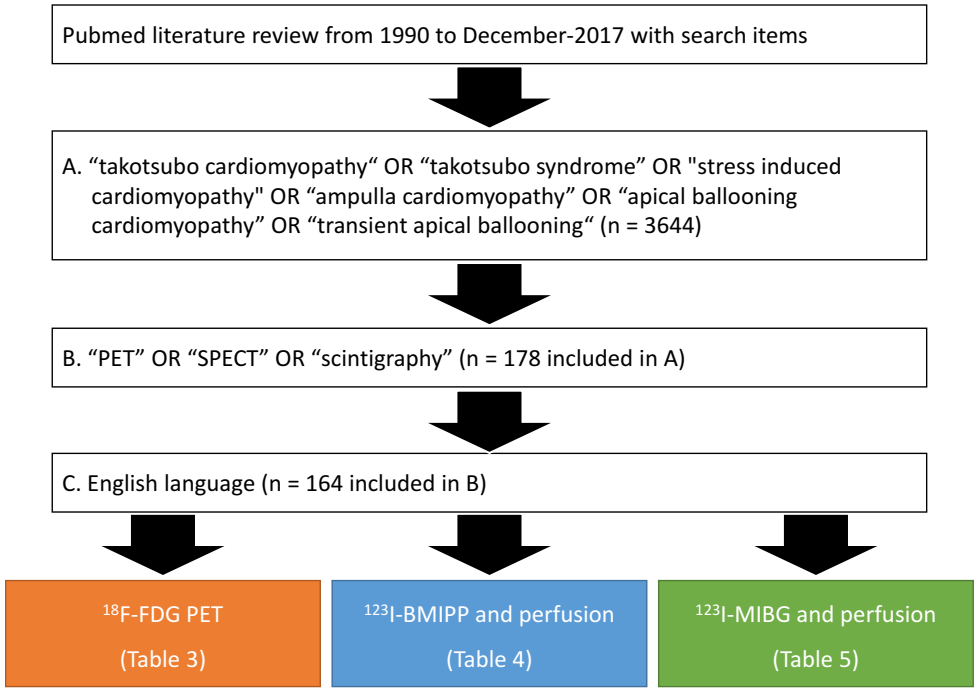

Figure 3. Flow chart describing our systematic search and report selection process.

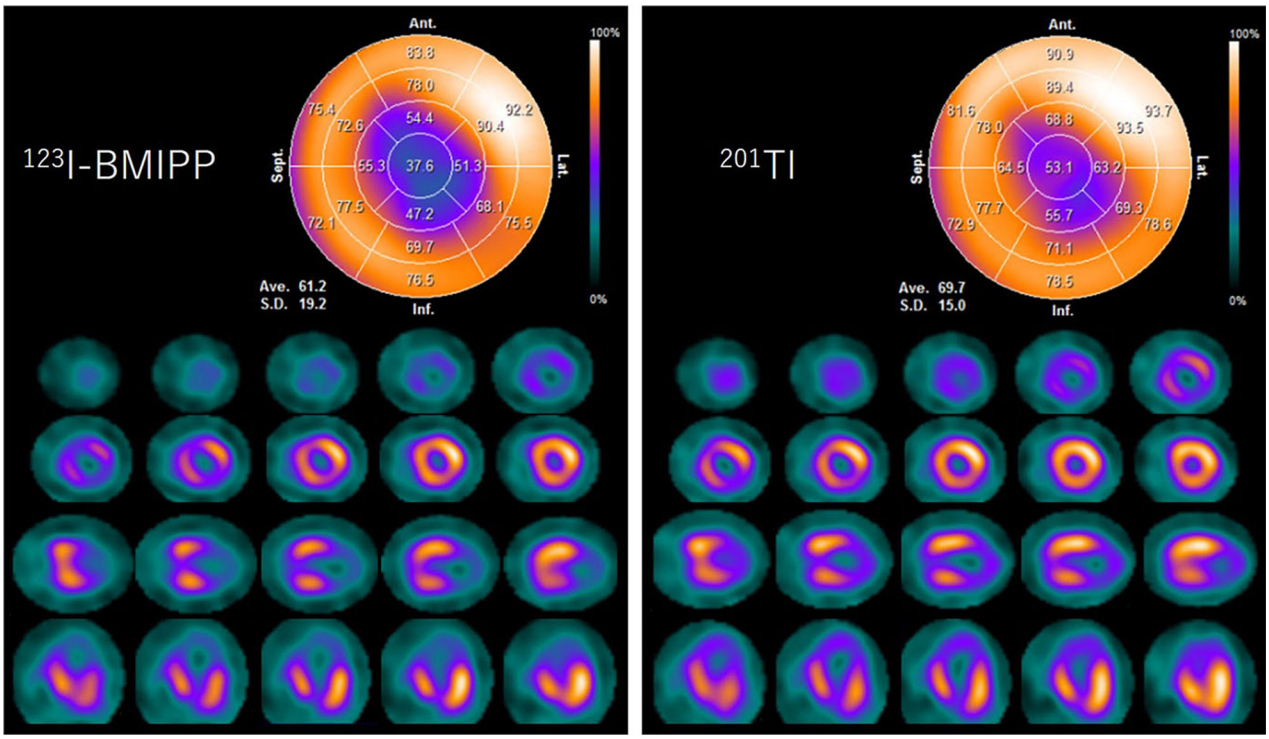

Figure 4. Representative case of takotsubo cardiomyopathy. ^{123}I-BMIPP and ^{201}Tl SPECT images were performed on day 3. A severely reduced uptake of ^{123}I-BMIPP and a slightly reduced uptake of ^{201}Tl in the apex are revealed, indicating severely impaired fatty acid metabolism rather than perfusion.

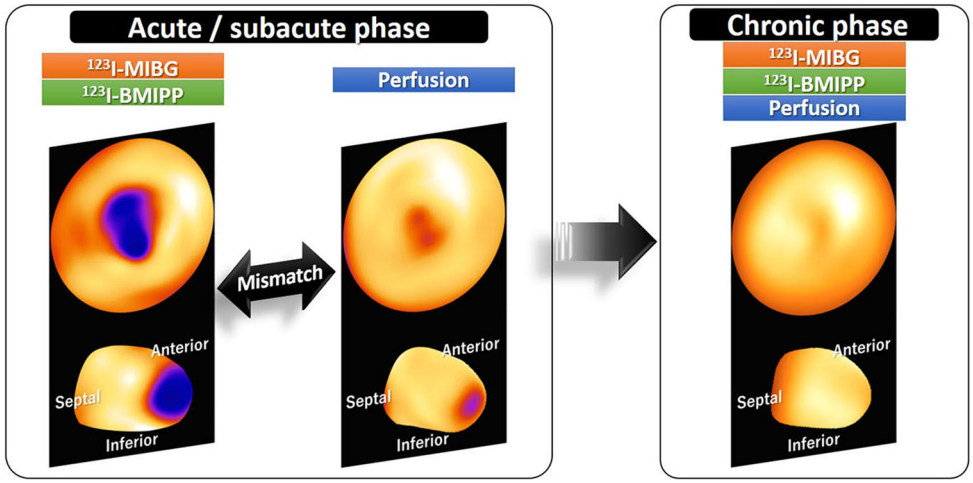

Figure 5. Schema of the polar maps of each tracer. In the acute or subacute phase, ^{123}I-BMIPP and ^{123}I-MIBG are typically decreased at the apical region, which is concordant with the wall motion abnormality shown by echocardiography. Myocardial perfusion at rest is relatively decreased (and smaller than that of ^{123}I-BMIPP and ^{123}I-MIBG) or preserved. The accumulation of each tracer tends to improve at the chronic phase.

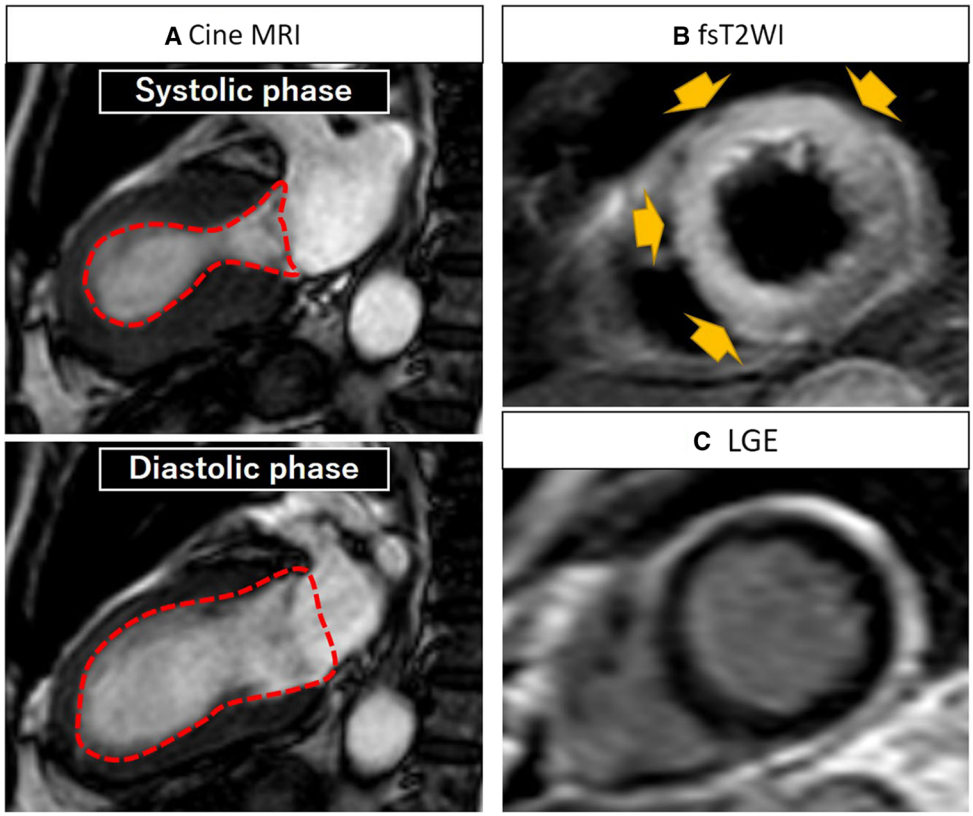

Figure 6. CMR imaging of takotsubo cardiomyopathy. **A** Wall motion abnormalities at the mid-ventricular to apical anterior segments with cine imaging as apical ballooning. High signal intensity with fat-saturated T2-weighted images (fsT2WI) (yellow arrows) due to the myocardial edema (**B**), but the absence of the late gadolinium enhancement (LGE) (**C**) are shown.

accumulation of the tracer ^{99m}Tc-pyrophosphate (PYP) during the acute phase of TC, the degree of which was significantly lower compared to that observed in acute myocardial infarction (AMI).[50] The accumulation of ^{99m}Tc-PYP is known to reflect the severity of myocardial ischemic injury due to Ca^{2+} overload.[58] Therefore, severe myocardial ischemia caused by a disturbance of the coronary microcirculation might be related to the causative mechanism of TC. Prasad et al confirmed the abnormal sympathetic activity in TC using ^{11}C-hydroxyephedrine PET.[59]

CARDIOVASCULAR MAGNETIC RESONANCE (CMR)

CMR imaging is helpful in the diagnosis and evaluation of TC.[60] Wall motion abnormalities at the mid-ventricular to apical anterior segments with cine imaging, abnormal high signal intensity due to myocardial edema derived on T2-weighted images, and the absence of both hypo-enhancement with first-pass perfusion imaging and late gadolinium enhancement (LGE) are useful to distinguish TC from AMI (Figure 6). AMI is typically diagnosed with hypo-enhancement with the first-pass perfusion and the extent of subendocardial or transmural LGE according to coronary territories.

LGE usually represents fibrosis indicating the extent of AMI. LGE is also useful in differentiating AMI from the other no-ischemic cardiomyopathies, which are characterized by an isolated mid-wall, or subepicardial distribution or patchy enhancements. TC has shown only slight LGE (under five standard deviations compared to the mean signal intensity of remote myocardium).[60] Not only LV but also RV wall motion abnormality can be detected by cine imaging. Patients with biventricular ballooning show a lower LV ejection fraction (LVEF) compared to patients with only LV ballooning, and they tend to have pleural effusions.[61]

CONCLUSION

We have briefly reviewed the role of the multimodality imaging in the assessment of TC. Echocardiography and left ventriculography are available to the immediate evaluation of the regional wall motion abnormalities. In the acute state of TC, a mismatch in distribution between the perfusion and metabolism/presynaptic sympathetic innervation is observed, and the metabolic abnormalities correspond to the akinetic region of the LV wall. The accumulation of each tracer used to date improves from the subacute phase to the chronic phase. Wall motion abnormalities, abnormal high signal intensity on T2-weighted images, and the absence of both hypo-enhancement with first-pass perfusion imaging and the LGE obtained from CMR imaging are helpful in the diagnosis and evaluation of TC.

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Disclosures

All authors have nothing to disclose.

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