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"Ballooning" patterns in takotsubo cardiomyopathy reflect different clinical backgrounds and outcomes: a BOREAS-TCM study

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Abstract Whether different patterns of ventricular ballooning in takotsubo cardiomyopathy (TCM) reflect differences in trigger mechanisms or clinical outcomes is unclear. Here we examined differences in the clinical characteristics of typical and atypical forms of TCM. TCM patients ($n = 251$) in the BOREAS Registry were enrolled for comparison of TCM with apical ballooning (type A, $n = 217$) and TCM with non-apical ballooning (type non-A, $n = 34$). The percentage of females was significantly lower in the type non-A group (58.8 vs. 75.6 %), while other demographic parameters and triggers of TCM were similar in the two groups. Rate of midventricular obstruction (MVO) was lower (2.9 vs. 14.3 %) in the type non-A group than in the type A group, though left ventricular ejection fractions in the two groups were comparable. During a follow-up period of 2.6 ± 2.8 years, TCM recurred in 2.9 % of the patients and cardiac death occurred in 4.0 %. Cox proportional hazard analysis indicated that body mass index (hazard ratio [HR]: 0.75, 95 % confidence interval [CI] 0.54–0.99) and MVO (HR: 14.71, CI 1.87–304.66) were determinants of TCM recurrence and that advanced age (HR: 1.09, CI 1.02–1.17) and cardiogenic shock (HR: 4.27, CI 1.07–18.93) were significantly associated with cardiac death. In conclusion, approximately 20 % of TCM patients show non-apical left ventricular ballooning, and female sex and MVO are less frequent in this type than in apical ballooning type TCM. Low body mass index and MVO are risk factors of recurrence, and advanced age and cardiogenic shock are risk factors of cardiac death in TCM.

On behalf of BOREAS-TCM investigators.

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Introduction

Takotsubo cardiomyopathy (TCM) is a cardiac syndrome characterized by chest symptoms mimicking acute coronary syndrome, transient left ventricular (LV) dysfunction and frequent episodes of mental or physical stress preceding the symptoms [1, 2]. TCM was first reported in 1991 by Japanese cardiologists [3] and so named for similarity of LV deformation (i.e., ballooning of the LV apex and narrowed LV base) to an octopus trap called "takotsubo" in Japanese. TCM has also been referred to as "transient LV apical ballooning syndrome" and "ampulla cardiomyopathy". However, recent studies [4–7] have shown that LV ballooning in TCM is not always in the apex and can occur in the mid-ventricular or basal region. In fact, up to 18–40 % of TCM cases were shown to be

such atypical forms of TCM in recent studies [6, 7]. Although long-term prognosis of typical TCM with apical ballooning was reported to be favorable [2, 8], it is unclear whether different patterns of LV ballooning in TCM reflect differences in trigger mechanisms or clinical outcomes.

The aim of this study was to examine whether clinical backgrounds and/or prognosis of TCM differ depending on patterns of LV ballooning. Patients with TCM enrolled in the BOREAS (Broad-range Organization for REnal, Arterial and cardiac studies by Sapporo Medical University Affiliates) Registry were divided into five groups with different LV ballooning patterns, and relationships between the pattern and comorbidities, complications and prognosis were examined. Prognosis was assessed by using recurrence of TCM and cardiac death as endpoints. Diagnostic criteria for TCM have not yet been established, and different criteria, including Mayo Clinic Criteria [9] and Gothenburg Criteria [10], have been proposed. To compare the results of this study with those of recent studies in which relatively large numbers of patients were enrolled [7, 11], we adopted Mayo Clinic Criteria.

Methods

Study subjects and inclusion criteria

The present study was conducted in accordance with the World Medical Association Declaration of Helsinki and with guidelines of the ethical committees of the institutes. We retrospectively enrolled 251 consecutive TCM patients from June 1999 to March 2012 in 15 hospitals that participate in the BOREAS Registry. In accordance with the Mayo Clinic Criteria [9], the following four criteria were required for diagnosis of TCM: (1) transient systolic dysfunction with marked LV contraction abnormality extending beyond a single epicardial arterial distribution, (2) absence of significant obstructive coronary artery disease explaining the LV contraction abnormality or angiographic evidence of acute plaque rupture, (3) new electrocardiographic (ECG) abnormalities (either ST elevation or T wave inversion) or modest elevation in cardiac troponin level, and (4) absence of pheochromocytoma or myocarditis. Although phenochromocytoma is an exclusion criterion, its cardiac complication is often indistinguishable from TCM by LV ballooning pattern [12–15]. In this study, patients showing LV ballooning at presentation underwent screening examinations for diagnosis of pheochromocytoma (**Screening of pheochromocytoma** below).

Demographic and clinical parameters, including psychological and physical stresses that possibly triggered TCM episodes, were determined on admission. Serum creatine kinase (CK) level was measured every 3 or 4 h for determining its peak value, and 12-lead ECG was recorded at hospital presentation and followed up during admission.

Evaluation of LV ballooning patterns

Left ventricular (LV) dimension and contractile functions were determined by left ventriculography (LVG) ($n = 185$) and/or transthoracic echocardiography (TTE) ($n = 228$) (Fig. 1). Echocardiographic examinations were repeated before modifying therapy for improvement or aggravation of heart failure and also before discharge. According to our previous study [16], systolic mid-ventricular narrowing with pressure gradient (PG) in the LV outflow tract being ≥ 15 mmHg was defined as mid-ventricular obstruction (MVO). Coronary artery stenosis was examined by coronary angiography in all the TCM patients.

Endpoints in assessment of prognosis after index episode of TCM

Cardiac death and recurrence of TCM were used for the assessment of prognosis during a follow-up period of 2.6 ± 2.8 years. Recurrence of TCM was defined as reappearance of LV contraction abnormality with significant ECG changes that had once been improved.

Screening of pheochromocytoma

Computed tomography scanning of the whole body was performed for screening of catecholamine-secreting tumors in all the patients during admission. When an adrenal mass was incidentally found, levels of epinephrine, norepinephrine and metanephrine in 24-h collected urine samples were determined after stabilization of heart failure. If any of the epinephrine, norepinephrine and metanephrine levels was above twofold of the upper limits of their normal values, ^{123}I-metaiodobenzylguanidine scintigraphy was performed to identify localization of the pheochromocytoma. Diagnosis of pheochromocytoma was finally confirmed by histological examination of surgically resected tumors.

Statistical analyzes

All numeric data are shown as mean $\pm$ SD. Mean values between two groups were compared using the unpaired t test. Categorical variables were analyzed using the χ^2 test, and Fisher's exact test was used when appropriate. Association of clinical parameters with recurrence or cardiac death was examined by the Cox proportional hazard model. Difference in event-free survival curves between groups was tested by the Kaplan–Meier method and the log-rank test. A P value of <0.05 was considered to be statistically significant.

Fig. 1 Left ventriculograms of five ballooning patterns in TCM. Right anterior oblique view in diastole (*left*) and systole (*right*) in each type of TCM. *TCM* takotsubo cardiomyopathy
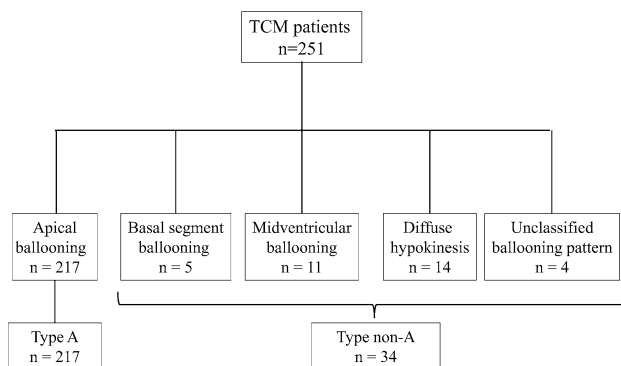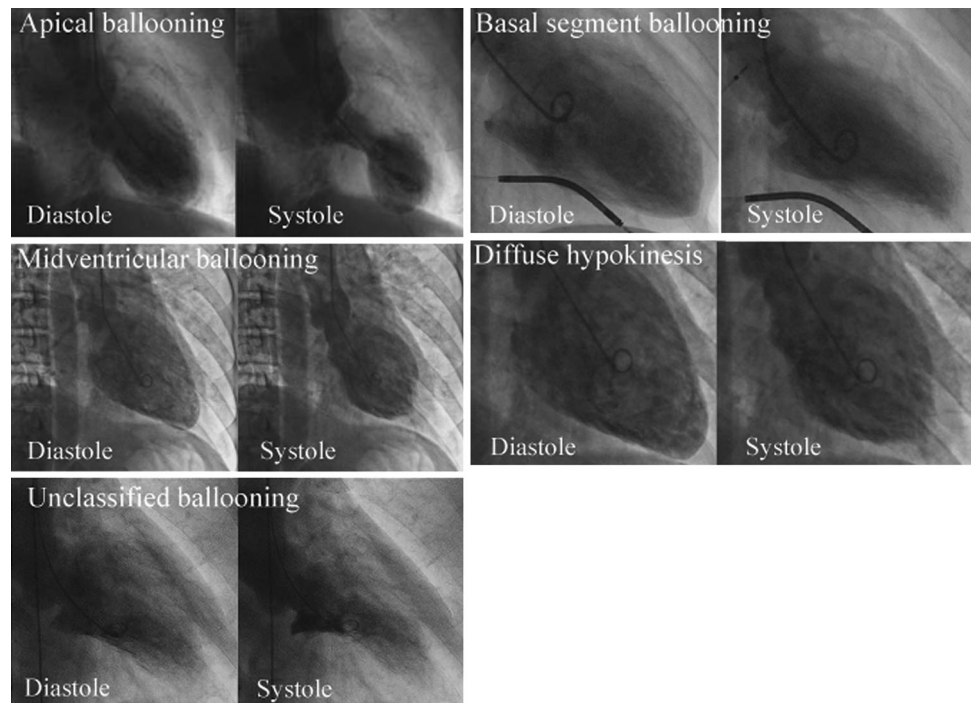
Fig. 2 Numbers of TCM patients with each pattern of ventricular ballooning. Patients were divided into a group with apical ballooning (type A) and a group with non-apical ballooning (type non-A). *TCM* takotsubo cardiomyopathy

Results

Patterns of LV ballooning

As shown in Fig. 1, different patterns of LV ballooning was observed in TCM patients: apical ballooning, basal segment ballooning, mid-ventricular segmental ballooning and diffuse LV hypokinesis. Cases with ballooning regions in a combination of apical, mid-ventricular or basal segments were defined as "unclassified ballooning pattern". 86 % of the 251 cases showed apical ballooning (typical TCM), and mid-ventricular ballooning and diffuse hypokinesis were observed in 4 and 6 % of the cases, respectively (Fig. 2). Basal segment ballooning was observed in only 2 % of the cases, and four cases showed "unclassified ballooning pattern". Since the number of cases in each pattern of non-apical ballooning was small, we pooled the cases of non-apical ballooning into one group (type non-A group) and compared their background characteristics and clinical variables with those of cases in a group with apical ballooning (type A group) (Table 1).

In the type non-A group, patients tended to be younger (66 ± 16 vs. 72 ± 14 years old, $p = 0.06$) and the percentage of females was significantly lower (58.8 vs. 75.6 %) than in the type A group (Table 1). There was no significant difference in prevalence of coronary risk factors (i.e., hypertension, dyslipidemia and diabetes mellitus), symptoms or signs at the onset of TCM between the two groups. ST elevation was a dominant ECG finding in both the type A group (72.4 %) and type non-A group (55.9 %), and peak CK levels were also comparable. However, incidence of MVO was significantly higher in the type A than in the type non-A group (14.3 vs. 2.9 %, $p = 0.01$), while LV ejection fraction (LVEF) was comparable between the two groups (40.0 ± 11.0 vs. 40.5 ± 13.7 %). Involvement of the right ventricle in the ventricular dysfunction was not significantly different in the type A and type non-A groups (3.7 vs. 11.8 %). Stressful events that preceded the onset of TCM symptoms could be identified in 75.6 % of type A patients and in 82.3 % of type non-A patients.

Table 1 Demographic and clinical characteristics

	Type A (n = 217)	Type non-A (n = 34)	P value
Age (years)	72 ± 14	66 ± 16	0.06
Female	164 (75.6 %)	20 (58.8 %)	0.048
Body mass index (kg/m²)	21.4 ± 4.6	22.0 ± 2.8	0.61
Comorbidities			
Hypertension	111 (51.0 %)	17 (50.0 %)	0.90
Diabetes	61 (28.1 %)	9 (26.5 %)	0.84
Dyslipidemia	51 (23.5 %)	9 (26.5 %)	0.71
Symptoms and signs			
Chest pain	90 (41.5 %)	11 (32.4 %)	0.31
Dyspnea	31 (14.3 %)	7 (20.6 %)	0.36
Hypotension	26 (12.0 %)	2 (5.8 %)	0.26
Cardiac arrest	8 (3.7 %)	4 (11.8 %)	0.10
Others	18 (8.3 %)	4 (11.8 %)	0.52
Heart rate (beats per min)	89 ± 24	95 ± 19	0.17
Systolic BP (mmHg)	126 ± 36	129 ± 33	0.75
Diastolic BP (mmHg)	74 ± 18	74 ± 21	0.84
ECG findings			
ST elevation	157 (72.4 %)	19 (55.9 %)	0.06
ST depression	50 (23.0 %)	12 (35.3 %)	0.14
T wave inversion	188 (86.6 %)	32 (94.1 %)	0.18
Q wave formation	48 (22.1 %)	5 (14.7 %)	0.31
Possible triggers			
Emotional stress	46 (21.2 %)	6 (17.7 %)	0.63
Medical procedure/ operation	32 (14.8 %)	8 (23.5 %)	0.21
Pulmonary disorders	29 (13.3 %)	4 (11.8 %)	0.79
Acute abdomen	14 (6.5 %)	2 (5.9 %)	0.90
Stroke	7 (3.2 %)	0 (0 %)	0.29
Catecholamine use	2 (0.9 %)	1 (2.9 %)	0.31
Other diseases	34 (15.7 %)	7 (20.1 %)	0.48
No apparent trigger	53 (24.4 %)	6 (17.7 %)	0.37
Peak CK (IU/l)	262 ± 221	310 ± 374	0.31
LVEF in acute phase (%)	40.0 ± 11.0	40.5 ± 13.7	0.79
Midventricular obstruction	31 (14.3 %)	1 (2.9 %)	0.03
Right ventricular involvement	8 (3.7 %)	4 (11.8 %)	0.04

Values are mean ± SD or n (%)

CK creatine kinase, *ECG* electrocardiogram, *LVEF* left ventricular ejection fraction

Complications in acute phase of heart failure caused by TCM

There was no significant difference between the type A and type non-A groups in incidences of complications,

including pulmonary edema and cardiogenic shock, or treatments in the acute phase of TCM as shown in Table 2. Peak CK level (262 ± 221 vs. 310 ± 374 IU/l), frequency of positive troponin T (26.7 vs. 29.4 %) and level of BNP (943 ± 1479 vs. 1513 ± 2565 pg/ml) on admission were also similar in the two groups. Within the type A group, occurrence of cardiogenic shock and right ventricular involvement were significantly more frequent in patients with MVO than in those without MVO (51.6 vs. 15.1 % and 12.9 vs. 2.2 %, respectively). Since MVO was observed in only one patient in the type non-A group, its impact on cardiogenic shock in this type of TCM remains unclear. The rate of right ventricular involvement was significantly higher in patients with MVO than in those without MVO (15.6 vs. 3.2 %, $p = 0.0021$), indicating an association between MVO and biventricular injury in TCM. Peak CK level was not significantly different between patients with and those without right ventricular involvement (181 ± 144 IU/l, $n = 12$, vs. 273 ± 251 IU/l, $n = 239$, $p = 0.21$). However, peak CK level was higher in patients with a Q wave in ECG than in those without a Q wave (356 ± 311 IU/l, $n = 52$, vs. 242 ± 219 IU/l, $n = 199$, $p = 0.003$).

Use of mechanical circulatory supports (cardiopulmonary bypass and/or intra-aortic balloon pumping) tended to be more frequent in the type non-A group than in the type A group (17.7 vs. 7.8 %, $p = 0.09$). Intravenous injection of β-blockers was more frequently used in patients with MVO than in those without MVO (43.8 vs. 3.7 %).

Cardiac event rates

Recurrence rate was 2.8 % (7/251) during a follow-up period of 2.6 ± 2.8 years, and overall mortality after the onset of TCM was 4.0 % (10/251). There was no significant difference between the type A and type non-A groups in recurrence rate (2.8 vs. 2.9 %). Interestingly, acute recurrence (recurrence within 30 days after the initial episode of TCM) was observed only in type A TCM patients with MVO. In the univariate analysis, low BMI, MVO and right ventricular involvement were associated with recurrence of TCM (Table 3). Multivariate analysis (Table 4) confirmed that BMI and MVO are independent determinants of recurrence: hazard ratios (HRs) of recurrence for BMI (per increase by 1 kg/cm²) and MVO were 0.75 and 14.71, respectively. Ten patients died in the type A group during the follow-up period, whereas there was no case of cardiac death in the type non-A group (Fig. 3). Univariate and multivariate analyzes (Tables 3, 4) indicated that advanced age (HR: 1.09) and cardiogenic shock during the acute phase of heart failure (HR: 4.27) are risk factors of cardiac death in TCM patients.

Table 2 Complications and treatments during acute phase of heart failure (≤30 days)

	Type A (n = 217)		p value*	Type non-A (n = 34)	p value†
	MVO (+) (n = 31)	MVO (−) (n = 186)			
Complications					
Pulmonary edema	10 (32.2 %)	64 (34.4 %)	0.81	12 (35.3 %)	0.89
Cardiogenic shock	16 (51.6 %)	28 (15.1 %)	<0.01	7 (20.6 %)	0.97
VT/VF	4 (12.9 %)	19 (10.2 %)	0.66	7 (20.6 %)	0.12
Bradycardia	2 (6.4 %)	9 (4.8 %)	0.71	2 (5.9 %)	0.84
Pericardial effusion	0 (0 %)	14 (7.5 %)	0.11	0 (0 %)	0.13
Cardiac rupture	1 (3.2 %)	0 (0 %)	0.14	0 (0 %)	0.69
Mural thrombus	1 (3.2 %)	4 (2.2 %)	0.72	2 (5.8 %)	0.24
Right ventricular involvement	4 (12.9 %)	4 (2.2 %)	<0.01	4 (11.8 %)	0.04
Treatments					
Mechanical circulatory supports	4 (12.9 %)	13 (7.0 %)	0.29	6 (17.7 %)	0.09
Intravenous inotrops	7 (22.6 %)	42 (22.6 %)	1.00	10 (29.4 %)	0.39
Interavenous β-blockers	14 (45.2 %)	7 (3.8 %)	<0.01	1 (2.9 %)	0.15

Values are n (%)

MVO midventricular obstructions

* MVO (+) versus MVO (−) in type A TCM

† Type A TCM versus type non-A TCM

Table 3 Univariate analyses for risk factors of recurrence and cardiac death after index episode of TCM

|	Recurrence			Cardiac death		
	HR	95 % CI	p value	HR	95 % CI	p value
Age (years)	1.07	0.99–1.18	0.05	1.08	1.01–1.16	0.02
Body mass index (kg/m²)	0.81	0.66–0.98	0.03	0.86	0.66–1.09	0.23
Comorbidities						
Hypertension	2.84	0.61–19.9	0.19	1.50	0.43–5.87	0.53
Diabetes	0.51	0.03–3.02	0.5	0.67	0.1–2.68	0.6
Dyslipidemia	1.38	0.2–6.43	0.71	1.45	0.31–5.22	0.6
ECG findings[a]						
T wave inversion	0.68	0.11–12.9	0.86	0.52	0.13–3.44	0.44
Q wave formation	4.47	0.98–22.8	0.05	0.43	0.02–2.27	0.37
Possible triggers						
Emotional stress	1.46	0.21–6.8	0.66	0.40	0.02–2.15	0.33
Medical procedure/operation	0.66	0.03–3.9	0.68	0.56	0.03–2.96	0.55
Pulmonary disorders	–	–		1.63	0.25–6.52	0.56
Acute abdomen	4.04	0.21–24.6	0.28	1.88	0.1–10.15	0.58
No apparent trigger	2.41	0.47–10.93	0.27	1.43	0.31–5.15	0.61
Peak CK (IU/l)	0.99	0.99–1.00	0.60	1.00	0.99–1.00	0.88
LVEF in acute phase (≤30 days) (%)	0.97	0.91–1.04	0.41	0.98	0.92–1.04	0.45
Midventricular obstruction	15.11	3.22–106.2	<0.01	1.69	0.26–6.77	0.53
Complications						
Pulmonary edema	0.71	0.1–3.32	0.68	1.97	0.55–7.07	0.29
Cardiogenic shock	3.05	0.6–13.88	0.16	6.11	1.75–23.91	<0.01
VT/VF	1.08	0.06–6.4	0.95	0.85	0.05–4.51	0.87
Right ventricular involvement	10.15	1.41–52.02	0.03	2.34	0.13–12.47	0.47
Treatments						
Mechanical circulatory supports	1.59	0.08–9.33	0.68	4.11	0.88–14.77	0.07
Intravenous inotrops	–	–		4.8	1.37–18.79	0.01
Intravenous β-blockers	3.16	0.44–15.05	0.22	–	–	–

HR hazard ratio, CI confidence interval

[a] ST-T changes are not included as variants since they are included in diagnostic criteria of TCM. HR and CI could not be calculated for some of the parameters in Table 1 because none or all of subjects in a group with that parameter developed recurrence or cardiac death

Table 4 Multivariate analyses for risk factors of recurrence and cardiac death after index episode of TCM

	HR	95 % CI	*p* value
Recurrence of TCM			
Body mass index[a]	0.75	0.54–0.99	*0.048*
Midventricular obstruction	14.71	1.87–304.66	*0.01*
Right ventricular involvement	7.51	0.90–55.48	*0.06*
Cardiac death			
Age	1.09	1.02–1.17	*<0.01*
Cardiogenic shock	4.27	1.07–18.93	*0.04*
Intravenous inotrops	3.24	0.81–1.24	*0.10*

HR hazard ratio, *CI* confidence interval

[a] Increase in body mass index by 1 kg/cm^2
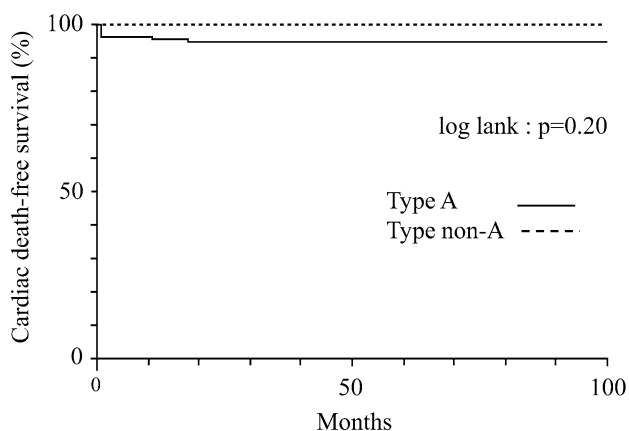
Fig. 3 The Kaplan–Meier curve of survival rates. There was no significant difference between Kaplan–Meier curves in the type A group (*dotted line*) and type non-A group (*solid line*)

Discussion

Incidences and clinical outcomes of the atypical forms of TCM have not been characterized, since the number of cases with atypical LV ballooning was not large in most of the previous studies [4–7]. Recently, Eitel et al. [7] reported the rates of different patterns of LV ballooning in 239 consecutive patients determined by using cardiac magnetic resonance imaging (CMR). In their series of patients, atypical ventricular ballooning was observed in 18 % of TCM patients, 17 % of the patients showing mid-ventricular ballooning and 1 % showing basal ballooning. In the present series of 251 patients, the rates of atypical ventricular ballooning (14 %) and basal ballooning (2 %) were similar to those in the study by Eitel et al. [7], but mid-ventricular ballooning was observed in only 4 % of the patients and 6 % showed diffuse LV hypokinesis. The difference between the two studies in the rates of mid-ventricular ballooning and diffuse LV ballooning may be attributable to differences in timing of imaging and patient selection. Ventricular imaging was performed on the first day of hospital admission in all cases in the present study, but Eitel et al. [7] visualized LV dysfunction by use of CMR a median of 3 days after admission. Also, they excluded 17 patients with ventricular fibrillation or shock cases of in-hospital death from CMR imaging, though such cases were included in imaging by LVG and/or TTE in the present study. Recently, Murakami et al. [17] reported clinical characteristics of 107 TCM patients registered in Tokyo CCU Network. Only 8 % of the patients showed non-apical LV ballooning, including mid-ventricular ballooning and basal ballooning in 4 and 3 % of the patients, respectively. It is notable that patients in their study were older (75.2 vs. 71.2 years old) and had higher rates of preceding emotional stress (29 vs. 21 %) and chest pain on admission (54 vs. 40 %) compared with those in the present study. Collectively, the results of the present and earlier studies [4–7, 17] indicate that 10–20 % of TCM patients show ballooning in non-apical regions of the LV and that incidence of each non-apical type of LV ballooning depends on clinical backgrounds, possibly including time after the onset of TCM.

Mechanisms underlying different patterns of LV ballooning remain unclear as does the etiology of TCM itself. Increased catecholamine release, impaired microcirculation, coronary spasm and altered inflammatory responses have been proposed as mechanisms of TCM [18, 19]. However, coronary spasm has rarely been confirmed in TCM. There is no clear evidence indicating that catecholamine release or any insult to microvessels that occurs in a specific region is responsible for regional LV ballooning in TCM. On the other hand, regional difference in myocardial vulnerability to insult causing LV ballooning has been shown in cases of pheochromocytoma [12–15]. Increase in the plasma level of catecholamine derived from pheochromocytoma does not induce a uniform LV dysfunction but induces different patterns of LV ballooning [12–15], which mimics TCM. Although the mechanism underlying regional difference in susceptibility to catecholamine toxicity or microvascular injury is unclear, sex difference might be partly involved. Apical ballooning has been observed in 60–100 % of the female TCM patients with preceding episodes of psychological and/or physical stress [1, 20–22]. Although demographic features of TCM with non-apical ballooning were inconsistent in earlier studies because of the small numbers of such patients [6, 23, 24], we found that the percentage of females was significantly lower in the group with non-apical ballooning than in the group with apical ballooning (Table 1). The results suggest that susceptibility of the LV apex to TCM is closely associated with female sex.

Recurrence of TCM was examined in only a few earlier studies [8, 25]. In the present study, overall recurrent rate of TCM during a follow-up period of 2.6 ± 2.8 years was 3 % (7/251). Sharkey et al. [25] reported that recurrence rate was 5 % (7/133) over 2.3 ± 2 years in patients with TCM. In a study by Elesber et al. [8], TCM recurred in 11.4 % (10/100) of the patients during a follow-up period of 4.4 ± 4.6 years. Annual recurrence rate was higher within the first 4 years (2.9 %) and subsequently decreased to 1.3 % over the remaining period. Clinical characteristics of patients, including age, co-morbidities and LVEF at presentation, were similar in the earlier two studies and the present study, and the results of the studies collectively indicate that the recurrence rate of TCM during a period of 3–4 years after the initial episode of TCM is 3–5 %.

The present study showed, for the first time, that low BMI and MVO at presentation are risk factors for recurrence of TCM (Table 4). Although the recurrence rate of TCM is not high, TCM recurrence is as serious as the first episode and requires timely treatment. Hence, careful monitoring of hemodynamic parameters during acute phase of TCM is particularly important in cases with risk factors of recurrence. We do not have a clear explanation for the associations of low BMI and MVO with TCM recurrence. However, recent studies [26, 27] have suggested that hemodynamic response to mental stress is larger in subjects with smaller BMI, while baseline activity of the sympathetic nerve system in subjects with smaller BMI is lower than that in the subjects with larger BMI. Thus, higher sensitivity of the sympathetic nerve system to mental stress, a trigger of TCM, in subjects with smaller BMI might reduce the threshold for recurrence of TCM.

MVO was present in 12.7 % (32/251) of the TCM patients, and all of those patients except for one had apical ballooning TCM. This rate of MVO is comparable with previously reported rates (13–24 %) for TCM patients with apical ballooning [2, 16]. Given the fact that wall motion of unaffected LV segments becomes hyperkinetic for compensation, it is reasonable to assume that dyskinesis in the ventricular apex is prone to be accompanied by MVO. However, we previously showed that attenuation of MVO by intravenous β-blockers significantly increased LVEF and systolic blood pressure, while it did not have any effects in TCM patients without MVO [16, 28]. Moreover, change in PG in the LV outflow tract by β-blocker infusion was significantly correlated with changes in systolic blood pressure and LVEF [16]. These findings indicate that MVO itself contributes to heart failure in TCM.

TCM is primarily reversible myocardial damage and prognosis of TCM has been reported to be generally favorable. Thus, information regarding determinants of mortality by TCM has been very limited. Brinjikji et al. [29] used data for 24,702 patients admitted to hospital with code 42983 in the International Classification of Disease, 9th Revision in the National Inpatient Sample (NIS) hospital discharge database and reported that male sex, high Charlson comorbidity index and presence of underlying critical illnesses were indicated by multivariate analyzes to be independent risk factors of in-hospital mortality in TCM being 4.2 %. In their study, cardiogenic shock was selected by univariate analysis, but not by multivariate analysis, for in-hospital-death. Since their study was a database search, type of LV ballooning, level of LV dysfunction and severity of co-existing cardiac disease in the study subjects are unknown, and their data cannot be directly compared with those in the present study.

Pheochromocytoma is one of the exclusion criteria in the Mayo Clinic Criteria for diagnosis of TCM [9]. However, it is not easy to exclude pheochromocytoma at the time of hospital presentation of cases with TCM phenotypes [12–15, 30–35]. Plasma levels of epinephrine and norepinephrine are markedly elevated in patients with acute phase of TCM [33], and histological changes in the myocardium are similar in TCM and catecholamine-mediated cardiomyopathy [34, 35]. In the present study, 282 patients with TCM-like LV ballooning were initially registered, and 8 patients (2.9 %) were found to have occult pheochromocytoma. In contrast to TCM showing apical ballooning in ∼80 % cases, only 2 of the pheochromocytoma patients showed apical ballooning at presentation, and the other 6 patients presented with basal ballooning ($n = 1$), mid-ventricular ballooning ($n = 3$) or diffuse ventricular hypokinesis ($n = 2$). Patients with pheochromocytoma were younger (61 ± 13 years old) than those with TCM, but other demographic or clinical parameters were not significantly different from the other cases. Hence, occult pheochromocytoma should be seriously considered in apparent TCM cases with non-apical ballooning, particularly when the patient is relatively young.

There are limitations in the present study. First, for retrospective design, treatment protocol of TCM was not standardized. Thus, data on rates of complications, recurrence and cardiac death may suffer from some bias. Second, the possibility that cases with acute myocarditis were erroneously enrolled, particularly in the group of diffuse ventricular hypokinesis, could not be completely excluded. However, the rate of emotional and/or physical stress preceding TCM (75 %) and peak CK level (269 ± 279 IU/l) in TCM patients with diffuse LV hypokinesis were similar to those in patients with other types of LV ballooning. Third, whether the time intervals from onset of TCM to full recovery of LV function are similar in patients with apical and non-apical LV ballooning is an important question, but we could not critically determine that time interval since the protocol of serial assessment of LV function was not standardized in this study.

In conclusion, approximately 20 % of TCM patients show LV ballooning in non-apical regions, and female sex and MVO are less frequent in this atypical type of TCM than in typical TCM with apical ballooning. There was no significant difference between patients with non-apical and apical ballooning TCMs in rates of mental stress and physical stress (medical procedures/operations) before the onset of TCM. Rate of recurrence of TCM over a 3-year period is approximately 3 %, and low BMI and MVO are independent risk factors of recurrence. Advanced age and cardiogenic shock at presentation are risk factor of cardiac death in TCM, though both typical and atypical forms of TCM have favorable long-term prognosis.

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