



Importance of sympathetic nervous system activity during left ventricular functional recovery and its association with in-hospital complications in Takotsubo syndrome

Takero Matsuura¹ · Masafumi Ueno¹ · Yoshitaka Iwanaga¹ · Shunichi Miyazaki¹

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Abstract

The relationship between activation of the sympathetic nervous system (SNS) and improvement of left ventricular (LV) function and how this correlates with clinical outcomes are not fully explored in Takotsubo syndrome (TS). The purpose of this study is to evaluate the relationship between activation of the SNS and LV function improvement and how this correlates with clinical outcomes in TS. Patients with TS were retrospectively identified. Patients were divided into two groups according to the timing of LV function improvement: < 1 month (S group) and ≥ 1 month (L group). Activation of the SNS was assessed by plasma catecholamine measurement and Iodine-123 meta-iodobenzylguanidine (I¹²³-MIBG) scintigraphy. In-hospital complications included heart failure, cardiogenic shock, the use of invasive or noninvasive ventilation, life-threatening arrhythmia, cerebrovascular event and all-cause death. A total of 90 patients with TS were enrolled. Of these, 39 patients were in the S group and 51 in the L group. There were no significant differences between the two groups in clinical demographics. The L group was characterized by enhanced SNS activation, including higher levels of catecholamines and lower late heart–mediastinum ratio followed by higher washout rate in I¹²³-MIBG scintigraphy, compared with the S group. In-hospital complications were increased in the L group (56% vs. 33.3%, $p=0.03$), including higher rates of heart failure (45% vs. 23%, $p=0.03$) and in-hospital death (8.0% vs. 0%, $p=0.03$). In patients with TS, high activity of the SNS was observed in patients with delayed LV function recovery, which was associated with in-hospital adverse outcomes.

Keywords Activation of sympathetic nervous system · Timing of LV function improvement · Clinical outcomes · Takotsubo syndrome

Introduction

Takotsubo syndrome (TS) is characterized by chest pain, electrocardiographic changes and transient left ventricular (LV) dysfunction with apical and mid-ventricular segments akinesis or dyskinesis in the absence of obstructive coronary artery disease which mimics acute coronary syndromes [1–5]. Patients with TS show significant improvement of systolic function within a week and achieve complete recovery by a couple of months after onset [6]. Although the underlying pathophysiological mechanism of TS is not

well defined, several studies suggest that TS may be caused by an excess of catecholamines [7]. In the acute phase of TS, iodine-123 meta-iodobenzylguanidine (I¹²³-MIBG) scintigraphy shows impaired apical myocardial uptake of I¹²³-MIBG on planar images, which correlate with the impaired LV segments [8]. Interestingly, some parameters reflecting augmented sympathetic nervous system (SNS) activation, such as increased plasma catecholamine levels and decreased uptake of I¹²³-MIBG in affected LV segments, have been observed in the acute phase of TS, whereas improvement findings (reduced plasma catecholamine levels and heightened uptake of I¹²³-MIBG) have been found 3 months after the onset of TS [9].

TS generally has favorable outcomes, but some patients are prone to have severe in-hospital complications, including heart failure, cardiogenic shock, or life-threatening arrhythmias [10]. Recently, several studies have investigated the relationship between clinical factors

✉ Shunichi Miyazaki
smiyazak@med.kindai.ac.jp

¹ Division of Cardiology, Department of Medicine, Faculty of Medicine, Kindai University, 377-2 Ohnohigashi, Osakasayama, Osaka 589-8511, Japan

and clinical outcomes [11, 12]. Some studies have reported that male gender and physical stress were predictors of in-hospital complications and all-cause mortality in patients with TS [13]. However, the relationship between SNS and recovery of LV function and how this correlates with clinical outcomes have not been fully explored. Therefore, the aim of this study was to investigate the impact of SNS activity on LV function improvement and its association with clinical outcomes in patients with TS.

Methods

Study population and study design

Patients with TS diagnosed using both echocardiography and coronary angiography at Kindai University Hospital were retrospectively identified from April 2001 to March 2018. Of these, patients who had serial echocardiographic follow-up were included in this study. The diagnosis of TS was based on the following Mayo Clinic criteria [14]:

1. transient hypokinesia, akinesia or dyskinesia of the LV midsegment with or without apical involvement; the regional wall motion abnormalities extending beyond a single epicardial vascular distribution; a stressful trigger often but not always present;
2. the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture;
3. new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and
4. the absence of pheochromocytoma or myocarditis.

All patients underwent echocardiography, electrocardiogram (ECG) and invasive/non-invasive coronary angiography, which were reviewed by two experienced independent cardiologists to evaluate the diagnosis of TS. The majority of patients underwent I^{123} -MIBG scintigraphy during the acute phase to assess adrenergic activity.

During the clinical course, LV function was assessed by echocardiography using the American Heart Association 17-segment model. In each segment, wall motion was classified into normokinesia, hypokinesia, akinesia and dyskinesia. Echocardiogram was performed at approximately 1-week interval until 4 weeks, and after that, it was performed at approximately 1-month interval until LV wall motion was completely normalized for each segment [15]. LV function improvement was defined when LV wall motion was completely normalized or back to the baseline for each segment. Patients were divided into two groups according to the timing of LV function improvement: < 1 month (S group) and \geq 1 month (L group).

This study was conducted in compliance with the Declaration of Helsinki with regard to investigations in human subjects, and the study protocol was approved by the institutional review board of the Kindai University Faculty of Medicine.

Blood sample collection

Blood samples were collected on admission for assessment of clinical hematology and biochemistry including brain natriuretic peptide (BNP), cardiac enzymes and plasma catecholamine levels. Cardiac enzymes including creatine kinase (CK), CK-MB, troponin I were measured at 3-h intervals until peak levels were reached. Plasma concentration of dopamine, epinephrine, and norepinephrine was measured under resting condition. The normal reference values for plasma epinephrine, norepinephrine, and dopamine were < 100 pg/ml, < 450 pg/ml and < 20 pg/ml.

I^{123} -MIBG scintigraphy

MIBG scintigraphy was carried out as soon as possible after admission. For each patient, heart–mediastinum ratio (H/M) and washout rate (WR) were calculated. Patients were given 50-mg potassium iodine after breakfast of the examination day to block thyroid iodine uptake. Planar anterior images of the chest were obtained 15 and 240 min after injection of 111 MBq of MIBG. The following systems were used; a Philips Bright View gamma camera; a Cardiac High Resolution collimator; a 256×256 matrix; and an acquisition time of 180 s. Image interpretation was done using the smart-MIBG (FUJIFILM RI Pharma Co, Ltd.) [16].

Clinical outcomes

In-hospital events including acute heart failure, use of invasive/non-invasive ventilation, cardiogenic shock, life-threatening arrhythmia, cerebrovascular event, and in-hospital death were assessed. An acute heart failure was defined by the presence of pulmonary edema in a patient requiring oxygen therapy, while cardiogenic shock was diagnosed in a patient with sustained systolic pressure < 90 mmHg. Life-threatening arrhythmia was defined as any ventricular arrhythmia that resulted in syncope or hypotension and required medical intervention. Long-term mortality was assessed based on chart review and/or telephone interview.

Statistical analysis

Continuous variables were analyzed for a normal distribution with the Kolmogorov–Smirnov test and presented as mean \pm standard deviation (SD) or as median and interquartile range (IQR) if a normal distribution was present or

not, respectively. Student's *t* test or Mann–Whitney's *U* test were used for comparisons of continuous variables where appropriate. Categorical variables are expressed as frequencies and percentages. Categorical variables were tested by means of the Chi-square test or Fisher's exact test. Control for potential confounders and analysis of independent correlates of LV function improvement ≥ 1 month and incidence of in-hospital complications were performed with a logistic regression model. Odds ratio (OR) and 95% confidence interval (CI) were calculated. All univariate variables $p < 0.1$ and those deemed of clinical interest were included in the statistical model.

The log-rank test was used to compare the survival curves between the two patient groups classified the duration of LV function improvement: < 1 month (S group) and ≥ 1 month (L group). Factors with $p < 0.1$ on univariate analysis were entered into the Cox multivariate regression to define

independent risk factors for the outcome. A two-tailed *p* value of less than 0.05 was considered to indicate a statistically significant difference for all the analyses performed. Statistical analysis was performed using JMPv13.0 software (SAS Institute Inc., Cary, NC, USA).

Results

Study population

From April 2001 to March 2018, a total of 95 TS patients were admitted to our hospital. Of these, five patients were excluded due to lack of echocardiographic follow-up. Therefore, a total of 90 patients were included in this study. The baseline clinical characteristics are shown in Table 1. The average age was 76.5 ± 8.9 years and most patients were

Table 1 Characteristics of the patients at baseline

	All patients (<i>N</i> =90)	S group (<i>N</i> =39)	L group (<i>N</i> =51)	* <i>p</i> value
Age-years	76.5 \pm 8.9	75.3 \pm 8.6	77.3 \pm 9.1	0.29
Female	62 (68.8%)	28 (71.8%)	34 (66.7%)	0.60
BMI, kg/m ²	20.2 \pm 3.4	20.4 \pm 3.4	20.0 \pm 3.5	0.66
Coronary risk factors				
Hypertension	56 (62.2%)	24 (61.5%)	32 (62.8%)	0.91
Diabetes mellitus	27 (30.0%)	10 (25.6%)	17 (33.3%)	0.43
Hyperlipidemia	28 (31.1%)	12 (30.8%)	16 (31.4%)	0.95
Smoking	21 (24.4%)	9 (23.7%)	12 (25.0%)	0.89
The Presence of cancer	23 (25.6%)	8 (20.5%)	15 (29.4%)	0.33
Symptoms				0.63
Chest pain	41 (45.6%)	20 (51.3%)	21 (41.1%)	
Shortness of breath	26 (28.9%)	10 (25.6%)	16 (31.4%)	
Nonspecific symptoms	23 (25.5%)	9 (23.1%)	14 (27.5%)	
Type of trigger				0.88
Emotional stress	20 (22.2%)	8 (20.5%)	12 (24.0%)	
Physical stress	54 (60.0%)	23 (59.0%)	31 (62.0%)	
ECG features on admission				0.46
ST elevation	52 (57.8%)	20 (51.3%)	32 (62.8%)	
Inverted T wave	35 (38.9%)	17 (43.6%)	18 (35.3%)	
EF on admission, %	45.4 \pm 13.7	46.2 \pm 14.3	44.9 \pm 13.4	0.66
Laboratory findings				
HbA1c, %	6.1 \pm 1.1	5.9 \pm 1.1	6.3 \pm 1.0	0.25
CK, IU/l	357.9 \pm 642.1	282.7 \pm 310.8	415.5 \pm 807.9	0.33
CKMB, IU/l	25.2 \pm 23.9	24.1 \pm 29.4	26.1 \pm 18.9	0.70
Troponin I, ng/ml	4.2 \pm 6.6	2.5 \pm 3.9	5.4 \pm 7.9	0.04
BNP, pg/ml	670.2 \pm 884.9	559.8 \pm 597.0	751.2 \pm 1046.2	0.33
Timing of LV function improvement, weeks	4.2 \pm 3.8	2.1 \pm 0.9	7.4 \pm 4.3	0.01

All of the data are expressed as mean \pm standard deviation

BMI body mass index, *BNP* brain natriuretic peptide, *CK* creatine kinase, *ECG* electrocardiogram, *EF* ejection fraction, *LV* left ventricular

**p* values for the comparison between S group and L group

females. The most common symptom and trigger were chest pain and physical stress. I^{123} -MIBG scintigraphy was performed in 64 patients during the acute phase (7.3 ± 4.1 days after onset). The mean timing of LV function improvement was 4.2 ± 3.8 weeks.

Clinical characteristics and laboratory/scintigraphy findings related to the duration of LV function improvement

According to the timing of LV function improvement, 39 and 51 patients were in the S and L group, respectively. There were no significant differences in clinical demographics including age, gender, the presence of coronary risk factors, ECG feature, type of trigger, type of symptoms and ejection fraction (EF) on admission (Table 1). Figure 1 illustrates representative images of I^{123} -MIBG scintigrams of two patients according to timing of LV function improvement.

Regarding the laboratory findings, there were significantly higher levels of troponin I (5.4 ± 7.9 vs. 2.5 ± 3.9 ng/ml, $p=0.04$) and higher levels of catecholamines in the L group (epinephrine: 112.5 ± 112.2 vs. 80.3 ± 95.7 pg/ml, $p=0.25$, norepinephrine: 847.9 ± 590.2 vs. 576.4 ± 300.9 pg/ml, $p=0.03$ and dopamine: 35.7 ± 35.6 vs. 20.1 ± 12.7 pg/ml, $p=0.03$) (Fig. 2). In addition, I^{123} -MIBG scintigraphy findings revealed lower late H/M (2.09 ± 0.45 vs.

2.45 ± 0.44 , $p=0.01$) and higher washout rate (33.9 ± 13.8 vs. 26.4 ± 10.2 , $p=0.02$) in the L group compared with the S group (Fig. 2).

A multivariable logistic regression analysis including age, gender, EF on admission, norepinephrine, and troponin I as covariates showed that the levels of norepinephrine (OR 1.003, 95% CI 1.000–1.005, $p=0.01$) and troponin I (OR 1.540, 95% CI 1.079–2.197, $p=0.01$) were independent predictors of delayed LV function improvement.

Clinical outcomes

Table 2 shows the prevalence of in-hospital complications. The median duration of hospitalization was 18.5 days in the study population. It was comparable between the S and L groups (median days and IQR: 18 [12–26] vs. 19 [13–37], $p=0.25$). The incidence of in-hospital complications was significantly higher in the L group (56% vs. 33.3%, $p=0.03$), including heart failure (45% vs. 23%, $p=0.03$) and in-hospital death (8.0% vs. 0%, $p=0.03$). In a univariate analysis, the occurrence of in-hospital complications was associated with lower body mass index (BMI) (19.35 ± 3.65 vs. 20.84 ± 3.07 , $p=0.04$), lower EF ($39.86 \pm 13.07\%$ vs. $50.12 \pm 12.43\%$, $p=0.01$), higher levels of catecholamines (epinephrine: 167.9 ± 161.6 vs. 70.9 ± 53.7 pg/ml, $p=0.01$, norepinephrine: 1091.2 ± 694.4 vs. 587.8 ± 310.3 pg/ml, $p=0.01$,

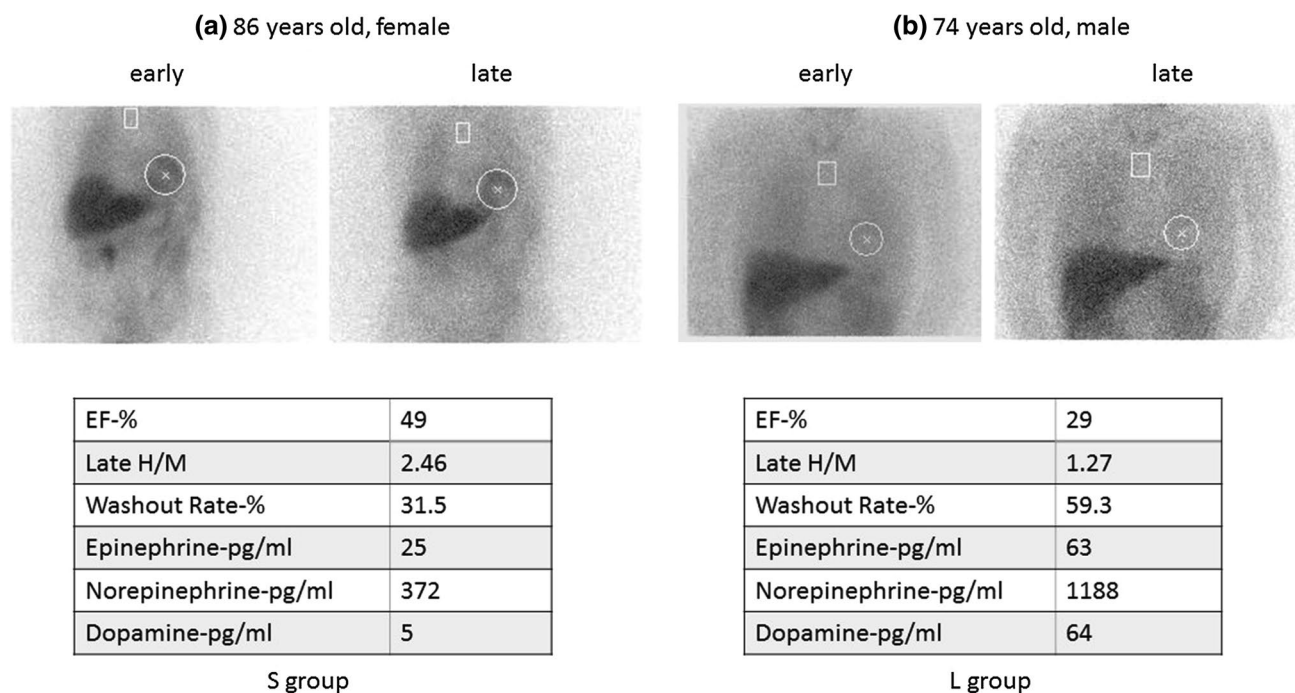


Fig. 1 Representative images of I^{123} -MIBG scintigrams according to the timing of left ventricular function improvement. Examples of a patient with Takotsubo syndrome (TS) according to the timing of LV function improvement: <1 month (S group) and ≥ 1 month (L

group) with images of the iodine-123 meta-iodobenzylguanidine (I^{123} -MIBG) scintigrams, as well as data for left ventricular ejection fraction (LVEF), late heart–mediastinum ratio (H/M late), washout rate, and plasma epinephrine, norepinephrine and dopamine levels

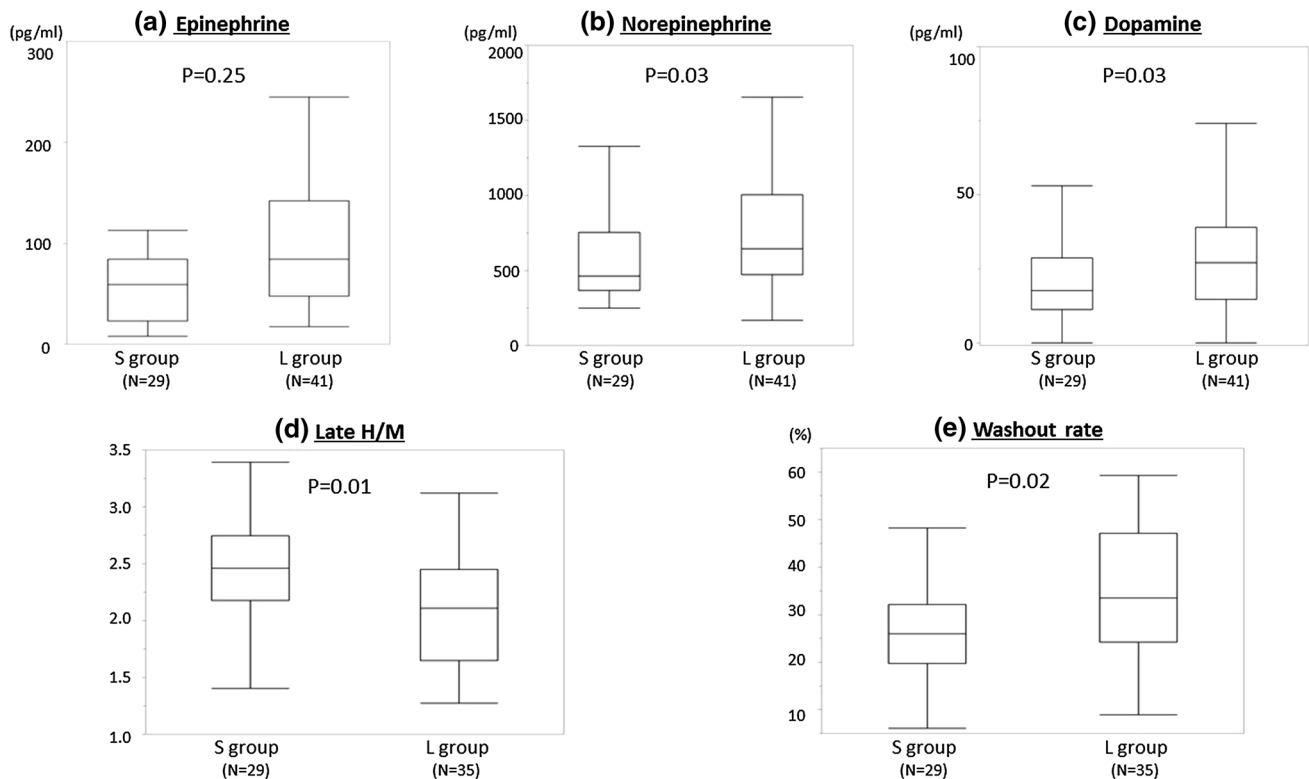


Fig. 2 Assessment of sympathetic nervous system activity. **a–c** The comparison of plasma catecholamine levels according to the timing of left ventricular function improvement. **d, e** The comparison of I^{123} -MIBG scintigraphy findings according to the timing of left ventricular function improvement. Lines within boxes represent median

values, the upper and lower boxes lines represent the 25th and 75th percentiles, respectively, and whiskers indicate minimal and maximal values. *L group* LV function improvement: ≥ 1 month, *S group* LV function improvement: < 1 month

Table 2 Comparison of in-hospital complications between the two groups (a) and multivariate logistics regression analysis for in-hospital complications (b)

(a)	S group (N=39)	L group (N=51)	p value
All in-hospital complications	13 (33.3%)	28 (54.9%)	0.04
Heart failure	9 (23.1%)	23 (45.1%)	0.03
Invasive or non-invasive ventilation	7 (17.9%)	13 (25.5%)	0.39
Cardiogenic shock	5 (12.8%)	6 (11.8%)	0.88
Life-threatening arrhythmia	2 (5.1%)	4 (7.8%)	0.60
Cerebrovascular event	0 (0%)	3 (5.9%)	0.06
All-cause mortality	0 (0%)	4 (7.8%)	0.03
(b)	Odds ratio	95% CI	p value
Age	0.937	0.850–1.033	0.19
Gender (male)	0.827	0.159–4.289	0.82
BMI	0.761	0.577–1.004	0.03
EF on admission	0.919	0.856–0.988	0.01
Epinephrine	1.011	1.001–1.021	0.01
LV functional recovery ≥ 1 month	9.304	1.089–79.50	0.01

BMI body mass index, *CI* confidence interval, *EF* ejection fraction, *LV* left ventricular, *L group* LV function improvement: ≥ 1 month, *S group* LV function improvement: < 1 month

dopamine: 44.8 ± 46.6 vs. 23.1 ± 15.6 pg/ml, $p=0.01$) and LV function recovery ≥ 1 month (54.9% vs 33.3%, $p=0.04$). A multivariable logistic regression analysis including age, gender, EF, epinephrine, and the timing of LV function improvement as covariates showed that the lower BMI, lower EF, higher levels of epinephrine and delayed LV functional recovery were independent predictors of incidence of in-hospital complications (Table 2).

In the analysis of long-term mortality, 12 patients were excluded due to lost to follow-up. A total of 78 patients were included in the Kaplan–Meier analysis. Median follow-up time was 790.5 days (IQR 9–6046 days). A total of 22 patients died during follow-up period. No statistically significant differences were observed between the two groups (L group: 59.6% vs. S group: 40.4%, $p=0.14$) (Fig. 3). However, significantly more male patients died compared to female patients (52.0% vs 16.9%, $p=0.01$).

Using the multivariable cox regression analysis including age, gender, EF, the presence of cancer, the independent predictors of all-cause mortality were age (hazard ratio 1.05, 95% CI 1.01–1.08; $p=0.01$) and EF (hazard ratio 0.97, 95% CI 0.95–0.99; $p<0.01$) and the presence of cancer (hazard ratio 2.04, 95% CI 1.02–3.83; $p=0.03$).

Discussion

This is the first study, to the best of our knowledge, to evaluate clinical features and outcomes of TS focusing on the timing of LV function recovery. The key findings of our investigation were as follows: (a) patients with delayed improvement of LV function in TS had significantly higher levels of catecholamine and higher washout rate

in I^{123} -MIBG; (b) delayed improvement of LV function in patients with TS was associated with in-hospital complications, which did not affect long-term mortality. These findings indicate delayed LV functional recovery was associated with activation of the SNS in patients with TS, which may lead to poor clinical outcomes in the acute phase.

The causes of TS are not fully understood, although several mechanisms have been proposed. Stress has represented the main factor in TS, with more than 85% of cases precipitated by either a physically or emotionally stressful event that prefaces the start of symptoms [17]. Indeed, in our study population, approximately 80% of patients had physical or emotional stress. It has been hypothesized that catecholamine surges accompanied by cellular calcium overload result in regional microvascular dysfunction in susceptible patients [18]. The myocardial stunning supposedly caused by direct catecholamine-induced myocardial toxicity in TS patients has been attributed to the ensuing diffuse catecholamine-induced microvascular spasm or dysfunction [19]. Lyon et al. hypothesized that high levels of epinephrine trigger a switch in the intracellular signal trafficking from Gs (stimulated) to Gi (inhibited) protein signaling in β_2 adrenoceptor, which affects the apical myocardium, explaining the apical ballooning in TS [20]. While hyperactivation of SNS is thought to be pathogenic in TS, how this affects degree of LV dysfunction and the duration of LV function improvement is not fully explored [21, 22].

MIBG scintigraphy has been established as an important technique to evaluate cardiac SNS function [23]. The decrease of cardiac I^{123} -MIBG uptake is thought to reflect impaired adrenergic function or denervation in various cardiac diseases. The increase of the WR might imply some kind of myocardial damage that results in an increase of cardiac sympathetic activity to compensate for the dysfunction. Thomas et al. evaluated cardiac SNS activity with MIBG scintigraphy and plasma catecholamine samples in 32 patients with TS and 20 control subjects [9]. In particular, this study showed lower late H/M and higher WR in MIBG scintigraphy and concomitantly increased plasma levels of epinephrine in the subacute phase of TS compared with the control group in the subacute state. At follow-up, no differences in MIBG parameters were observed between the TS and control groups. The authors concluded that norepinephrine reuptake is blocked because of the high circulating levels of norepinephrine, which may account for the low H/M in late phase and high WR on MIBG imaging in the acute state of TS [9]. In comparison with previous investigations, our study evaluated not only the relationship between MIBG scintigraphy and plasma catecholamine, but also the effect on timing of LV function improvement and clinical outcomes. In our study population, the L group showed significantly lower late H/M and higher WR compared to the S group, which was

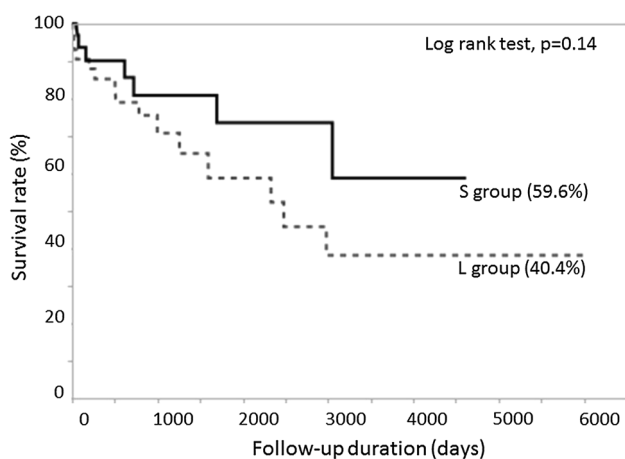


Fig. 3 Kaplan–Meier estimates for long-term mortality according to the timing of left ventricular function improvement. *L* group LV function improvement: ≥ 1 month, *S* group LV function improvement: < 1 month

also associated with poor clinical outcomes. Based on our findings, some of these mechanisms might be explained by the fact that patients with hyperactivation of local cardiac SNS and higher levels of norepinephrine had longer exposure to these surges, leading to delayed improvement of LV function.

TS generally has a favorable outcome. However, a variety of complications occur in the acute phase [24–27]. Indeed, the results of our study showed high rates of in-hospital complications (45.6% of all patients), while they were observed in 52% of the patients in a similar sample size TS registry [28]. Previous studies have shown that several factors may be associated with clinical outcomes in patients with TS. Ansari et al. demonstrated that TS patients receiving catecholamine therapy have poor in-hospital outcomes in comparison to patients not receiving any form of catecholamine support [29]. Giannakopoulos et al. reported that the in-hospital morbidity rate was significantly higher in TS patients with physical stressors [30]. Interestingly, TS patients suffering from physical stress had significant higher level of catecholamine and higher incidence of in-hospital complications as compared to patients with emotional stress in our study population (data not shown). Increased SNS activity could affect in-hospital clinical outcomes in two ways: (1) a direct effect mediated by the augmented concentrations of catecholamines (e.g., provoking acute LV outflow obstruction and increased ventricular afterload, as well as inducing ventricular arrhythmias and subsequent sudden cardiac death); and (2) an indirect effect through a delayed LV function recovery, which might be associated with complications due to heart failure or ventricular arrhythmias. However, further studies are warranted to determine the underlying mechanisms behind the association of augmented activation of SNS and impaired in-hospital outcomes in TS.

Long-term mortality has been reported in several investigations. Weidner et al. reported that males suffering from TS revealed a higher risk for all-cause mortality than females over a 5-year follow-up period [31]. A similar trend was observed in our study. 16 of 28 males (57.1%) had in-hospital complications and 13 (46.4%) had died during long-term follow-up, while 25 patients of 62 females (40.3%) had in-hospital complications and 9 (14.5%) had died. Most of the previous studies reported that higher age, male, and lower EF were independent predictors of long-term mortality in TS patients [32, 33]. In the multivariate Cox regression analysis of our study population, similar findings were observed. There was a trend towards increased long-term mortality in the group with delayed LV function recovery, without reaching statistical significance, which could be due to the small sample size of the present investigation. These hypotheses must be validated in larger cohort studies.

Study limitations

Several limitations of our study should be mentioned. First, this is a retrospective study from a single center. Second, some data were unavailable such as plasma catecholamine levels and MIBG scintigraphy. Third, we did not compare plasma catecholamine levels between TS and the other acute medical illness as a control group. In addition, 12 patients were lost to follow-up. Finally, since long-term clinical outcome was assessed based on telephone interview in some cases, the cause of death was uncertain.

Conclusions

In patients with TS, high activity of the SNS was observed in patients with delayed LV function recovery, which was associated with in-hospital adverse outcomes.

Compliance with ethical standards

Conflict of interest Takero Matsuura: has no conflict of interest to report. Masafumi Ueno: has no conflict of interest to report. Yoshitaka Iwanaga: has no conflict of interest to report. Shunichi Miyazaki: has no conflict of interest to report.

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