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Different Characteristics between Patients with Apical and Non-Apical Subtypes of Stress-Induced Cardiomyopathy

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Background: Stress-induced cardiomyopathy (SCM) is characterized by apical ballooning on echocardiography, but some of SCM patients show non-apical involvement and their characteristics are not well defined.
Methods: We investigated 56 patients that were diagnosed as SCM and divided them into 2 groups: apical ballooning syndrome (ABS, n = 49, 87.5%) and non-apical ballooning syndrome (N-ABS, n = 7, 12.5%) groups. Patients with N-ABS were significantly younger than those of the ABS group (52 ± 11 vs. 73 ± 10 years, $p < 0.001$).
Results: Types of preceding stressors and clinical presentation including chest pain, pulmonary edema, cardiogenic shock and in-hospital mortality were comparable between the two groups. In the N-ABS group, wall motion score index was significantly lower than in the ABS group (1.61 ± 0.35 vs. 1.93 ± 0.31, $p = 0.016$). On electrocardiogram (ECG), T-wave inversion (57.1% vs. 95.8%, $p < 0.001$) were less frequent in the N-ABS than in the ABS group. Furthermore, maximum QT and corrected QT (QTc) intervals in the N-ABS patients were significantly shorter than the ABS patients (QT, 419.9 ± 66.1 vs. 487.3 ± 79.6 ms, $p = 0.038$; QTc, 479.0 ± 61.9 vs. 568.0 ± 50.5 ms, $p < 0.001$).
Conclusion: Patients with the N-ABS showed not only atypical echocardiographic findings, but also atypical clinical and ECG manifestations. Integrated consideration is needed to reach a diagnosis of the non-apical subtype of SCM.

KEY WORDS: Stress cardiomyopathy · Echocardiography.

Introduction

Since stress-induced cardiomyopathy (SCM) was first introduced in early 1990s,[1] it has been a widely known disease entity. Echocardiographic diagnosis of SCM can be made by demonstration of transient left ventricular (LV) apical ballooning with compensatory hyperkinesis of the basal portion (takotsubo cardiomyopathy). More recently, variant forms of SCM involving middle and/or basal segments with sparing of the apex have increasingly been recognized (inverted takotsubo cardiomyopathy).[2-6] However, it is not well known how great portion of patients with SCM present atypical distribution of regional wall motion abnormalities (RWMA) and whether there are different features between the apical and non-apical ballooning syndromes. We studied the composition of SCM patients and their presenting features in patients with the two subtypes of SCM regarding involving segments.

Methods

Subjects

We retrospectively reviewed digitally stored echocardiographic data and medical record of all patients who were diagnosed with SCM at Chonbuk National University Hospital from November 2004 to May 2011. The diagnosis of SCM was established by fulfillment of the following criteria: 1) presence of preceding stressors; 2) demonstration of apical or non-apical ballooning and compensatory hypercontractility of not involved segments by echocardiography; 3) new develop-

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ment of ST-T segment abnormalities or elevation of cardiac enzymes; 4) absence of significant flow-limiting stenosis of epicardial coronary arteries. The fourth element was proven by coronary imaging studies including conventional coronary angiography or computed tomographic coronary angiography. Patients with evidence of pheochromocytoma or myocarditis, or antecedent head trauma or intracranial bleeding as a stressor were excluded. The study protocol was approved by the local ethics committee of the institutional review board of Chonbuk National University Hospital.

Grouping into subtypes

All patients were arbitrarily divided into two subgroups according to akinetic segments: apical ballooning syndrome (ABS, classic takotsubo cardiomyopathy) and non-apical ballooning syndrome (N-ABS, inverted takotsubo cardiomyopathy) groups. Patients with apical or mid to apical ballooning were categorized into the ABS group and those with midventricular and/or basal involvement with sparing of the apex into the N-ABS subtype (Fig. 1).

Clinical data

Preceding events followed by SCM were defined as physical or emotional stressors; physical stressors were subcategorized into surgery/procedure-related and medical stressors. All kinds of surgery and medical procedures were considered as surgical/

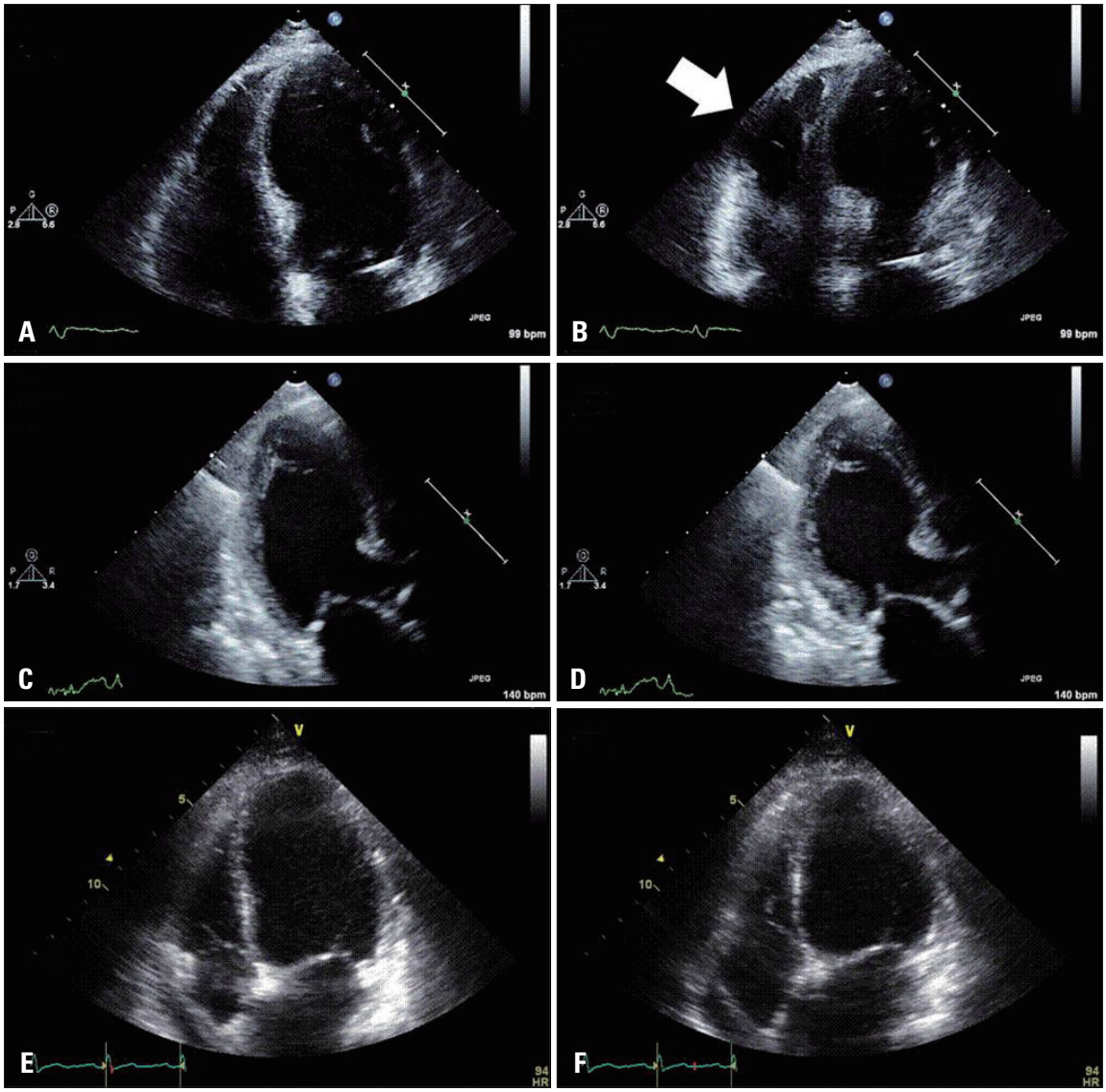

Fig. 1. Three cases of stress-induced cardiomyopathy (SCM). Apical four-chamber views in diastole (A) and in systole (B) of a 75-year-old woman with apical ballooning SCM subtype and right ventricular (RV) involvement. Note ballooning of the mid to apical segments and hyperkinesis of the base of the left ventricle (LV). The arrow indicates concomitant ballooning of the RV apex during systole. Apical long-axis views in diastole (C) and in systole (D) of an 82-year-old woman with non-apical ballooning subtype of SCM involving midventricle. Apical four-chamber views in diastole (E) and in systole (F) of a 54-year-old man with non-apical ballooning subtype of SCM involving basal segments. Note ballooning of the LV base during systole.

procedural stressors; the medical stressors included serious medical illnesses that were not related to any surgery or procedures. In patients with medical problems and combined surgery/procedures, causative stressors were determined according to the temporal sequences.

ECHOCARDIOGRAPHY

Left ventricular ejection fraction (LV EF) was measured by modified Simpson's method at the time of diagnosis and the first follow-up echocardiography. Wall motion score index (WMSI) of the LV was analyzed using a 16-segment model.[7][8] Segmental motion was scored from 1 (normal) to 4 (dyskinesia) and the WMSI was computed by the formula of total score/16. Right ventricular (RV) involvement was defined as accompanied wall motion abnormality of the RV segments equivalent to the involved segments of the LV. We also investigated concomitant LV mural thrombus or spontaneous echo contrast (SEC), LV outflow tract (LVOT) or midventricular obstruction, and pericardial effusion. Grade of mitral regurgitation (MR) was evaluated by distal jet area and effective regurgitant orifice area. Significant MR was defined as grade 3 to 4 MR. RV systolic pressure (RVSP) was calculated based on the peak velocity of tricuspid regurgitation. Significantly elevated RVSP was defined as ≥ 50 mmHg.

ELECTROCARDIOGRAM (ECG)

We reviewed all electrocardiograms (ECGs) during the SCM episode and determined whether there was ST-segment elevation or T-wave inversion. Heart rate at the time of diagnosis, and maximum QT and corrected QT (QTc) intervals were determined.

STATISTICAL ANALYSIS

Continuous variables were presented as mean ± standard deviation and discrete variables as absolute values and frequency (%). Chi-square test was used between-group comparison of discrete variables and independent-sample t-test was used for continuous variables. All statistical analyses were performed with Predictive Analytics Soft Ware Statistics 18.0 (formerly SPSS Statistics) for Microsoft Window® (SPSS Inc., Chicago, IL, USA). p values less than 0.05 were considered statistically significant.

RESULTS

CLINICAL DATA

Fifty-six SCM patients were enrolled. Patients with the ABS accounted for the majority of the SCM (n = 49, 87.5%), but the N-ABS formed a significant proportion (n = 7, 12.5%). Patients with the N-ABS were significantly younger than those with the ABS (52 ± 11 vs. 73 ± 10 years, $p < 0.001$). The two subgroups shared some common features in clinical presentations. Female patients were predominant in both groups (81.6% vs. 57.1%, $p = 0.140$). Types of preceding stressors were comparable: serious medical illnesses were the most frequent antecedent triggers of the SCM in both groups; the second frequent stressors were surgery or medical procedures; and emotional stressors were the least frequent one (Table 1).

Except for higher prevalence of hypertension in the ABS group (44.9% vs. 0%, $p = 0.023$), clinical presentations including underlying cardiovascular risk factors, chest pain, concomitant pulmonary edema, cardiogenic shock, use of inotropics, and subsequent in-hospital mortality were also similar in both groups (Table 1). Patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (79.6% vs. 28.6%, $p = 0.004$) and beta-blockers (85.7% vs. 57.1%, $p = 0.065$) were more frequent in the ABS group.

ECHOCARDIOGRAPHY

SCM was diagnosed by echocardiography 3.3 ± 2.7 days after clinical presentation. In the ABS group, 79.6% of patients showed RWMA of mid to apical portion of the LV and the SCM of the other 20.4% were only involved the apex. In the N-ABS group, 28.6% showed midventricular ballooning, and the other 71.4% demonstrated mid to basal involvement. Although LV EF of both groups were comparable at the initial presentation (46.7 ± 10.1% vs. 43.6 ± 8.8%, $p = 0.388$), WMSI were significantly lower in the N-ABS group (1.61 ± 0.35 vs. 1.93 ± 0.31, $p = 0.016$). RV involvement, LVOT or midventricular obstruction, and LV mural thrombus or SEC demonstrated only in the ABS group (Table 2). Despite more than two thirds of basal involvement in the N-ABS, significant MR was only developed in the ABS group (0% vs. 8.2%, $p = 0.433$). Mean RVSP and the development of significantly elevated RVSP were similar in both groups (Table 2).

Follow-up echocardiography was performed in 83.7% and 85.7% of patients in both groups ($p = 0.891$) 3.4 ± 6.5 and 1.9 ± 1.2 weeks after initial echocardiography ($p = 0.578$), respectively. Patients of the N-ABS group showed a trend of better recovery of follow-up LV EF and WMSI than the ABS group (LV EF, 59.0 ± 3.0% vs. 54.2 ± 5.0%, $p = 0.026$; WMSI, 1.08 ± 0.14 vs. 1.20 ± 0.28, $p = 0.304$).

ECG

All patients of the N-ABS group showed sinus rhythm, while 18.4% of the ABS patients demonstrated atrial fibrillation ($p = 0.216$). ST-segment elevation was demonstrated only in 28.6% of the N-ABS patients, whereas 59.2% in the ABS group ($p = 0.128$). T-wave inversion was less predominant in the N-ABS group (57.1% vs. 95.8%, $p < 0.001$) than in the ABS. Heart rate at the time of diagnosis was significantly higher in the ABS group than in the N-ABS group (101 ± 23 vs. 82 ± 15 bpm, $p = 0.041$), but prolongation of maximum QT and QTc intervals were less prominent in the N-ABS group (QT, 419.9 ± 66.1 vs. 487.3 ± 79.6 ms, $p = 0.038$; QTc, 479.0 ± 61.9 vs. 568.0 ± 50.5 ms, $p < 0.001$) (Table 3).

Table 1. Comparison of clinical features between the ABS and N-ABS groups

	ABS (n = 49)	N-ABS (n = 7)	*p*-value
Age (yr)	73 ± 10	52 ± 11	< 0.001*
Female, n (%)	40 (81.6)	4 (57.1)	0.140
Stressors, n (%)			0.983
Physical	41 (85.4)	6 (85.7)	
Surgical/procedural : medical	7 : 33 (14.9 : 70.2)	0 : 5 (0 : 71.4)	
Emotional	7 (14.6)	1 (14.3)	
Risk factors, n (%)			
Hypertension	22 (44.9)	0 (0)	0.023*
Diabetes mellitus	13 (26.5)	1 (14.3)	0.484
Dyslipidemia	20 (40.8)	1 (14.3)	0.175
Smoking	7 (14.3)	1 (14.3)	1.000
Prior history of stroke	7 (14.3)	0 (0)	0.285
Referral from, n (%)			0.464
ER	34 (69.4)	6 (85.7)	
ICU	6 (12.2)	1 (14.3)	
General ward	9 (18.4)	0 (0)	
Clinical features, n (%)			
Chest pain	12 (24.5)	1 (14.3)	0.550
Pulmonary edema	16 (32.7)	3 (42.9)	0.594
Shock	9 (18.4)	2 (28.6)	0.525
Cardiogenic shock	2 (4.1)	0 (0)	0.586
Use of inotropics	22 (44.9)	3 (42.9)	0.919
In-hospital mortality	0 (0)	0 (0)	-
Coronary artery imaging method, n (%)			0.130
CAG	35 (71.4)	3 (42.9)	
CTCA	14 (28.6)	4 (57.1)	
Medication, n (%)			
ACEI or ARBs	39 (79.6)	2 (28.6)	0.004*
Beta-blockers	42 (85.7)	4 (57.1)	0.065
Diuretics	33 (67.3)	5 (71.4)	0.829

*p < 0.05. ABS: apical ballooning syndrome, N-ABS: non-apical ballooning syndrome, ER: emergency room, ICU: intensive care unit, CAG: coronary angiography, CTCA: coronary computed tomographic angiography, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin-receptor blocker

Laboratory data

Peak cardiac troponin I (cTnI), peak N-terminal pro-natriuretic peptide (NT-proBNP), highly sensitive C-reactive protein (hs-CRP), hemoglobin, and serum creatinine levels were comparable between the two groups (Table 3). Mean serum sodium, potassium, and chloride concentrations of the two groups were within normal ranges, but sodium and chloride levels were significantly higher (sodium, 142.4 ± 4.7 vs. 138.5 ± 5.6 mmol/L, p = 0.081; chloride, 108.0 ± 5.7 vs. 103.2 ± 5.0 mmol/L, p = 0.025) and potassium level was lower (3.40 ± 0.27 vs. 3.85 ± 0.58 mmol/L, p = 0.048) with marginal significance in the N-ABS group than in the ABS group.

Discussion

This is one of the largest scale studies comparing apical ballooning with apex-sparing subtypes of SCM. A substantial portion (12.5%) of the SCM patients demonstrated midventricular or basal ballooning without involvement of the apex, and these patients showed atypical patterns of RWMA as well as atypical clinical presentations and electrocardiographic findings.

A classic SCM is known to typically affect postmenopausal women, while its extension in patients with overall ages. In this study, patients with N-ABS were significantly younger than those with ABS. However, women held a majority of both groups. The pathophysiology of elderly female preponderance of the classic SCM has been explained as the highest density of adrenoreceptor in the apex in this patient group.[9][10] Although the exact reason why the N-ABS develops in younger patients is not known, Ramaraj and Movahed[9] suggested that this might be due to rich distribution of adrenoreceptors at the base at a younger age.

Previous studies reported that chest pain is the most frequent (70-90%) and typical symptom of the SCM,[5][11] but chest pain was not a representative symptom in our study population.

Table 2. Comparison of initial and follow-up echocardiographic findings between the ABS and N-ABS groups

	ABS (n = 49)	N-ABS (n = 7)	*p*-value
Initial echocardiography			
Interval from clinical manifestation (days)	3.3 ± 2.9	2.9 ± 1.3	0.685
LV EF (%)	43.6 ± 8.8	46.7 ± 10.1	0.388
WMSI	1.93 ± 0.31	1.61 ± 0.35	0.016*
RV involvement, n (%)	3 (6.1)	0 (0)	0.501
LVOT or midventricular obstruction, n (%)	4 (8.2)	0 (0)	0.433
LV mural thrombus or SEC, n (%)	3 (6.1)	0 (0)	0.501
MR ≥ grade 3+, n (%)	4 (8.2)	0 (0)	0.433
TR Vmax (m/s)	2.74 ± 0.57	2.80 ± 0.46	0.820
RVSP (mmHg)	36.3 ± 12.9	37.1 ± 10.1	0.897
RVSP ≥ 50 mmHg, n (%)	6 (12.2)	0 (0)	0.327
E/E'	15.8 ± 6.6	12.6 ± 8.1	0.278
Pericardial effusion, n (%)	13 (26.5)	1 (14.3)	0.484
Follow-up echocardiography, n (%)	41 (83.7)	6 (85.7)	0.891
Interval from initial echocardiography (weeks)	3.4 ± 6.5	1.9 ± 1.2	0.578
LV EF (%)	54.2 ± 5.0	59.0 ± 3.0	0.026*
WMSI	1.20 ± 0.28	1.08 ± 0.14	0.304

*p < 0.05. ABS: apical ballooning syndrome, N-ABS: non-apical ballooning syndrome, LV EF: left ventricular ejection fraction, WMSI: wall motion score index, RV: right ventricle, LVOT: left ventricular outflow tract, LV: left ventricle, SEC: spontaneous echo contrast, MR: mitral regurgitation, TR: tricuspid regurgitation, RVSP: right ventricular systolic pressure

Table 3. Comparison of electrocardiographic and laboratory findings between the ABS and N-ABS groups

	ABS (n = 49)	N-ABS (n = 7)	*p*-value
Electrocardiography			
Atrial fibrillation, n (%)	9 (18.4)	0 (0)	0.216
Heart rate (bpm)	101 ± 23	82 ± 15	0.041*
ST-segment elevation, n (%)	29 (59.2)	2 (28.6)	0.128
T-wave inversion, n (%)	46 (95.8)	4 (57.1)	< 0.001*
Maximum QT interval (ms)	487.3 ± 79.6	419.9 ± 66.1	0.038*
Maximum corrected QT interval (ms)	568.0 ± 50.5	479.0 ± 61.9	< 0.001*
Laboratory findings			
Hemoglobin (g/dL)	11.76 ± 2.20	11.53 ± 1.35	0.785
Hematocrit (%)	35.12 ± 6.58	34.19 ± 3.72	0.716
hs-CRP (mg/L)	48.75 ± 46.83	135.6 ± 0	0.116
Na (mmol/L)	138.5 ± 5.6	142.4 ± 4.7	0.081
K (mmol/L)	3.85 ± 0.58	3.40 ± 0.27	0.048*
Cl (mmol/L)	103.2 ± 5.0	108.0 ± 5.7	0.025*
Serum creatinine (mg/dL)	1.04 ± 0.80	1.72 ± 2.32	0.128
Peak troponin I (ng/mL)	2.74 ± 3.74	1.81 ± 2.39	0.526
Peak NT-proBNP (pg/mL)	12917 ± 12345	15089 ± 18185	0.729

*p < 0.05. ABS: non-apical ballooning syndrome, N-ABS: non-apical ballooning syndrome, hs-CRP: highly sensitive C-reactive protein, NT-proBNP: N-terminal pro-natriuretic peptide

Only 26.5% of overall patients experienced angina and only 14.3% in the N-ABS group. It might be partially contributed by that 32.7% of patients in this study were diagnosed with SCM during stay in the intensive care unit or ward due to their medical illnesses or after surgical or medical procedures. Most of them were referred for echocardiography to evaluate elevated cardiac biomarkers, ECG changes, heart failure, or shock rather than chest pain. Emotional stressors preceded SCM in only 16.3% of patients in the current study.

LV EF of patients in the two subgroups at the initial presentation were comparable (46.7 ± 10.1% vs. 43.6 ± 8.8%, p = 0.388), but the N-ABS patients showed significantly lower WMSI than patients in the ABS group (1.61 ± 0.35 vs. 1.94 ± 0.31, p = 0.016). We calculated WMSI using 16 segments because 17-segment method could aggravate WMSI in patients with apical involvement. The lower WMSI in the N-

ABS patients might mean more limited akinetic territory than in ABS, but it was associated with neither higher LV EF nor better clinical course including pulmonary edema, shock, or mortality.

ST-segment elevation and depression and T-wave inversion mimicking acute myocardial infarction are the characteristic ECG findings of the classic SCM. Prolongation of QTc interval is another representative feature. Zanobetti et al.[3] analyzed 22 previously reported cases with inverted takotsubo cardiomyopathy. Although ECGs of 9 patients (40.9%) demonstrated ST elevation, more than half of patients (59.1%) showed only subtle ECG changes such as mild ST depression or QTc prolongation. An interesting point of our study is that typical ECG changes including T-wave inversion, ST-segment elevation, and prolonged QTc were less prominent in the N-ABS patients. It suggests that ECG findings in patients with SCM could partially reflect the location of ballooning.

Mortality in patients with SCM has been variously reported from 1-2% to as high as 25.9%.[11-15] SCM might also be complicated with cardiogenic shock,[14)15)] pulmonary edema,[14)] LV mural thrombus,[12)] and dynamic midventricular or LVOT obstruction[12)16)] and rarely with cardiac rupture.[15)17)] Prognostic factors of SCM have not been clearly established. However, severely decreased LV EF at the time of diagnosis and high hs-CRP,[13)] RV involvement,[18)] old age,[19)] higher Acute Physiology And Chronic Health Evaluation II score,[20)] and delayed recovery of LV function[12)] have been described as poor prognostic factors associated with death, cardiogenic shock, or heart failure. No in-hospital death developed in this study. It might be partially affected by selection bias that patients with critical medical condition resulted in mortality were excluded because they could not undergo coronary imaging studies. Older age, higher WMSI, and slightly higher NT-proBNP and cTnI levels in patients in the ABS group were not related to mortality. These inconsistent findings with previous studies might be resulted from a small study population.

Several recent studies described the different characteristics between typical and variant types of SCM.[9)14)21-23)] The proportion of the atypical SCM has been reported 20 to 40% of overall SCM, although the authors of these studies did not use the same criteria to group the patients into the typical and atypical subgroups. Two of the studies[9)21)] used the same classification as we did. They divided SCM patients into 'reverse' and 'other' groups: the 'other' group included patients with apical and/or midventricular involvement. The other three studies[14)22)23)] categorized SCM into 'apical' and 'non-apical' subtypes: isolated midventricular ballooning belonged to the 'non-apical' group in these studies. This heterogeneity in grouping might lead to different features between the subgroups among the studies.

Three studies[9)14)21)] reported that N-ABS involved younger patients than ABS, which was consistent with the current study whereas others showed no age differences between the two groups.[22)23)]

There are no standardized diagnostic criteria of SCM. We used the classic concept of SCM and defined a foregoing stressor as a mandatory component of diagnostic criteria, but all of the other studies applied the proposed Mayo criteria.[24)] Four studies[9)14)21)23)] delineated the differences between two groups whether stressors preceded the SCM or not. Two of them[9)21)] showed that all patients with the reverse subtype experienced antecedent stressors in which was significantly higher frequency than in the typical SCM group. Our study and three[14)21)23)] of the previous ones showed compatible findings that the types of preceding stressors were comparable between the two subgroups.

ECG in the SCM patients showed diverse patterns in the previous reports. In our study, ST-segment elevation, T-wave inversion and QT prolongation were prominent in the apical SCM group and non-apical SCM patients showed more vague ECG changes. Three of the previous studies[14)21)22)] reported that ST elevation or T-wave inversion were more prevalent in the typical SCM group in which were consistent with the present study. However, there were variable findings regarding QT or QTc prolongation: Jabara et al.[22)] showed that patient with non-apical SCM demonstrated more frequent QT prolongation; two studies[9)14)] revealed no difference in QT or QTc intervals between two subgroups.

In the present study, patients in the two subgroups did not differ in in-hospital clinical course including shock, pulmonary edema, and mortality. Two previous studies[14)21)] demonstrated that pulmonary edema, cardiogenic shock, and use of inotropics were more frequent in the apical group although death, recurrence, and hospital stay were comparable. They also showed that NT-proBNP level was higher in the apical group. Jabara et al.[22)] described that serious complications following the SCM such as ventricular tachycardia, shock, pulmonary edema, and death, only occurred in the apical SCM group, even though no statistically significant meaning. However, the initial LV EF was significantly lower and troponin T was significantly higher in the apical group in their study and these findings suggest that there were more extensive myocardial involvement and it might contribute to the occurrence of the complications. Although LV EF at the time of presentation and peak cTnI and NT-proBNP levels were not different, our study is unique showing that WMSI was significantly higher in the ABS group than in the N-ABS subgroup suggesting more extensively involved segments.

The major limitation of our study is that this is a retrospective and single-center study. Scheduled serial measurement of echocardiography, ECG, and cardiac enzymes, and clinical follow-up were not performed. It is statistically underpowered due to the small number of the non-ABS group.

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