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Clinical Characteristics and Prognostic Factors of Stress-Induced Cardiomyopathy

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ABSTRACT

Background and Objectives: Stress-induced cardiomyopathy (SCM) is characterized by a transient left ventricular (LV) dysfunction due to emotional and physical stress. There are limited data about the clinical characteristics in Korean patients. We sought to clarify the clinical features and prognosis in patients with SCM. **Subjects and Methods**: We reviewed 39 cases diagnosed with SCM in a tertiary hospital. The SCM was diagnosed as: 1) no previous history of cardiac disease, 2) acute onset, 3) regional wall motion abnormality, typically in the takotsubo or inverted takotsubo shape by echocardiography, and 4) no significant stenosis in the coronary angiogram. We evaluated clinical characteristics, biomarkers, and prognosis. **Results**: Mean age was 61.3±16.1 years (female 69%). The triggering factors were physical stress in 32 patients (82%) and emotional stress in 5 patients (13%). The initial symptom was dyspnea (n=18, 46%) rather than chest pain (n=10, 26%). An initial electrocardiogram (EKG) presented T-wave inversion (n=18, 46%), ST-elevation (n=11, 28%), and ST-depression (n=2, 5%). Multivariate logistic regression analysis showed that initial high sensitive C-reactive protein (hs-CRP) {odds ratio (OR) 1.41, 95% confidence interval (CI); 1.02-1.97} and initial left ventricular ejection fraction (LVEF) (OR 0.89, 95% CI; 0.80-0.98) were significantly associated with death or cardiogenic shock, respectively. **Conclusion**: The major triggering factor of SCM is physical stress due to illness or surgical procedures, and the first manifestation is dyspnea rather than chest pain. Elevated hs-CRP and decreased LVEF at admission were independent risk factors for death or cardiogenic shock. **(Korean Circ J 2010;40:277-282)**

KEY WORDS: Takotsubo cardiomyopathy; Inflammatory response.

Introduction

The stress-induced cardiomyopathy (SCM) is characterized by acute, reversible, and transient left ventricular (LV) systolic dysfunction mimicking acute coronary syndrome without significant stenosis on coronary angiogram.[1)2)] This syndrome was first described by Satoh et al.[3)] and was named Takotsubo-cardiomyopathy because its shape resembles the tako-tsubo (Japanese octopus trap).[4)] The majority of patients are postmenopausal women who present with acute emotional or physical stress.[1)2)] Clinical features are acute onset chest pain or dyspnea, electrocardiographic ST changes with T-wave inversion, elevated cardiac biomarkers, elevated B-type natruretic peptide (BNP), apical or midventricular wall motion abnormality by echocardiography and favorable prognosis.[1)] The underlying etiology is unclear. There are limited data for clinical manifestations and prognostic factors of SCM in Korea.[5)6)] Therefore, we sought to clarify the clinical features and prognosis in SCM.

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Subjects and Methods

We retrospectively reviewed and analyzed 39 patients diagnosed with SCM from May, 2004, to January, 2009, in Wonju Christian Hospital. SCM was diagnosed as: 1) no previous history of cardiac disease, 2) acute onset,

3) a regional wall motion abnormality, typically in the takotsubo or inverted takotsubo shape by echocardiography, and 4) no significant stenosis in the coronary angiogram. We investigated baseline clinical characteristics, laboratory data, hospital course, complications, and clinical outcomes.

We defined ST-elevation as deviation >1 mm higher than the baseline in ≥2 contiguous leads. We defined T-wave inversion as a change from the previous electrocardiogram (EKG) in ≥2 contiguous leads. Echocardiography was performed at admission and rechecked at discharge or improved symptoms. Coronary angiography and left ventriculography were performed to evaluate coronary artery disease or LV systolic function. Significant stenosis was defined as >50% diameter stenosis by coronary angiography. Shock was defined as systolic blood pressure <90 mm Hg with signs of end-organ hypoperfusion requiring the use of vasopressor agents. Adverse clinical events were defined as death or cardiogenic shock.

Cardiac biomarkers {creatinine kinase MB (CK-MB) fraction and troponin-I}, high sensitive C-reactive protein (hs-CRP), and BNP were collected at admission and cardiac biomarkers were rechecked until normalization. EKG was performed daily. The trigger factor was categorized as emotional or physical stress. After discharge, all patients were followed in an out-patient clinic to re-evaluate symptoms, LV systolic function, and adverse events. SCM patients were grouped in 4 seasons to evaluate seasonal variation.

Continuous data were summarized as mean±SD and were compared by Student's t-test. Multivariate logistic regression analysis was performed to determine the independent variables associated with the occurrence of adverse events.

Table 1. Baseline characteristics and laboratory findings of stress induced cardiomyopathy

Variable	
Age (year)	61.3±16.1
Female (n, %)	27 (69)
Hypertension (%)	10 (26)
Diabetes mellitus (%)	3 (8)
Chronic obstructive pulmonary disease (%)	5 (13)
Smoking (%)	5 (13)
Clinical presentation	
Dyspnea	18 (46)
Chest pain	10 (26)
Mental change	8 (21)
Electrocardiographic changes (%)	
T-wave inversion	18 (46)
ST-segment elevation	11 (28)
ST-segment depression	2 (5)
Non-specific finding	6 (15)
Ejection fraction (%)	
At initial presentation	45±16
At discharge	61±13
Adverse clinical event (%)	
Cardiogenic shock	13 (33)
Death	3 (8)

Results

Clinical manifestations

The baseline characteristics of 39 SCM patients are presented in Table 1. Female patients were 69% (n=27) and the mean age was 61.3±16.1 years. Past medical history was 10 (26%) of hypertension, 3 (8%) of diabetes mellitus, 5 (13%) of chronic obstructive pulmonary dis-

Table 2. Trigger factors of stress induced cardiomyopathy

Trigger factor	Number of patient
Emotional stress	3
Acute illness	
Cardiogenic	
Bradyarrhythmia	2
PSVT	1
Neurogenic	
Seizure	2
CVA	2
Meningitis	1
Pulmonology	
COPD	1
Asthma	2
Pneumothorax	1
Pneumonia	2
ARF	1
AKA	2
DKA	1
Bucal cavity abscess	1
Cholecystitis	1
Stomach cancer	1
Tsutsugamushi fever	2
Accident	
Multiple contusion	1
Falling down	1
CO intoxication	1
Post-procedure or surgery	
BM biopsy	1
ERCP	1
TAH	1
Post-op HNP	1
Cholecystectomy	1
Anesthesia-related	1
Food or drug	2
Unknown	2
Total	39

PSVT: paroxysmal supraventricular tachycardia, CVA: cerebrovascular attack, COPD: chronic obstructive pulmonary disease, ARF: acute renal failure, AKA: alcoholic ketoacidosis DKA: diabetic ketoacidosis, BM: bone marrow, ERCP: endoscopic retrograde cholangiopancreatography, TAH: total abdominal hysterectomy, HNP: herniated nucleus pulposus

ease, and 5 (13%) current smokers. The initial symptom were dyspnea (n=18, 46%), chest pain (n=10, 26%), mental change (n=8, 21%), collapse (n=1, 3%), fever (n=1, 3%) and seizure (n=1, 3%). Mean symptom to arrival time in the emergency department was 426.9±431.9 minutes. The triggering factors of SCM were medical illness (n=23, 59%), emotional stress (n=6, 15%), procedure-related (n=3, 8%) , trauma (n=3, 8%), and food or drugs (n=2, 5%) (Table 2). Initial EKG presented T-wave inversion (n=18, 46%), ST-elevation (n=11, 28%), ST-depression (n=2, 5%), or non-specific findings (n=6, 15%). We observed an increasing trend of SCM in spring and winter but there was no statistical significance.

Laboratory and imaging findings

The peak CK-MB fraction and troponin I were 15.6±20.9 ng/mL (reference range: <5.0 ng/mL) and 6.8±12.3 ng/mL (reference range: <0.78 ng/mL), respectively. The BNP at admission was 745.4±905.6 pg/mL (reference range: <100 pg/mL). Initial hs-CRP was 44±61 mg/L (reference range: <5 mg/L) and 23 patients (59%) had elevated hs-CRP at admission. In echocardiography, the mean LV ejection fraction (EF) was 45±16% at admission and 61±13% at discharge. There were 3 cases of inverted takotsubo shape, 4 cases of transient LV outflow tract obstruction due to a hyperkinetic basal segment of LV, and 1 case of apical thrombus on the site of apical ballooning (Fig. 1). The patient who developed apical LV thrombus had a distal embolization in the right common iliac artery, right external iliac artery, and left femoral artery. She had anticoagulation therapy with warfarin and was discharged after 15 days without significant complications.

Prognosis

Three patients (8%) died due to pneumonia and 13 patients (33%) experienced cardiogenic shock. Inotropic agents were administered to 10 patients (26%), and 9 patients (23%) needed mechanical ventilation. Eleven patients (28%) received an emergency coronary angiogram to rule out acute ST-elevation myocardial infarction. The mean length of hospitalization was 14±14 days. Thirty-six patients were discharged after improvement of LV systolic function. During follow-up, there was no SCM recurrence or sudden death.

The SCM patients were divided into two groups according to the presence of cardiogenic shock or death: the adverse clinical event group (n=15) versus the no event group (n=24). These groups showed significantly different age (54.8±17.5 vs. 65.3±14.0 years; p=0.046), hospitalization (22.1±18.5 vs. 9.4±6.3 days; p=0.020), initial EF (34.9±15.5 vs. 50.6±13.8%; p=0.003), initial hs-CRP (76±80 vs. 23±35 mg/L; p=0.027), initial QTc (477.4±63.1 vs. 532.9±69.5 msec; p=0.018), peak CK-MB fraction (2.8±1.1 vs. 2.0±0.9 ng/mL; p=0.033) and peak troponin I (12.6±17.5 vs. 2.6±2.4 ng/mL; p=0.045) (Table 3). Multivariate logistic regression analysis (adjusted for age, sex, and risk factors) showed that hs-CRP at admission was associated with an odds ratio (OR) of 1.41 {95% confidence interval (CI) 1.02-1.97} for an adverse event. The initial LVEF was also signifi-

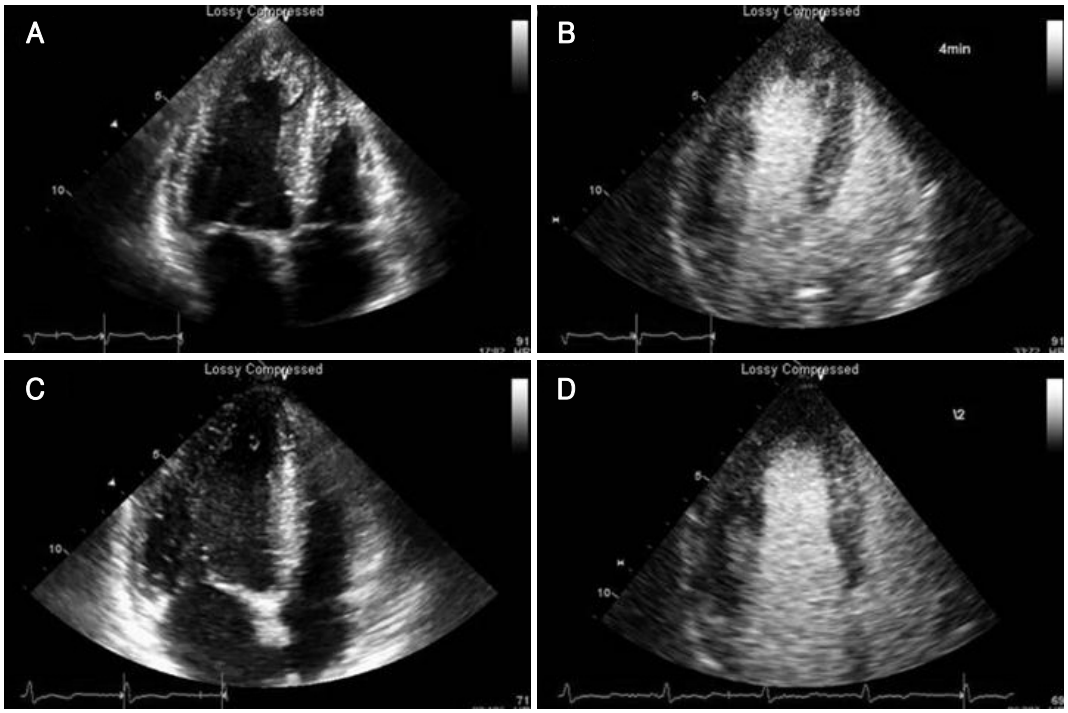

Fig. 1. An apical thrombus of the left ventricle due to stress-induced cardiomyopathy. Two dimensional echocardiography shows an apical LV thrombus (A and B) and disappeared apical thrombus (C and D) after anticoagulant therapy.

Table 3. The comparison of clinical characteristics between event group and no event group

Variable	Event group*(n=15)	No event group (n=24)	p
Age (year)	54.8±17.5	65.3±14.0	0.046
Hospitalization (day)	22.1±18.5	9.4±6.3	0.020
Symptom to ER arrival time (minute)	507.6±488.1	393.7±418.1	0.569
Initial QTc (msec)	477.4±63.1	532.9±69.5	0.018
Initial BNP (pg/mL)	1103.3±1246.9	517.7±514.6	0.115
Initial CK-MB (ng/mL)	8.8±8.9	7.4±5.4	0.593
Peak CK-MB (ng/mL)	24.1±30.4	9.8±6.6	0.091
Initial TnI (ng/mL)	5.5±11.7	1.8±2.3	0.240
Peak TnI (ng/mL)	12.6±17.5	2.6±2.4	0.045
hs-CRP (mg/L)	76±80	23±35	0.027
Initial EF (%)	34.9±15.5	50.6±13.8	0.003

*Event was defined as combinations of any death or cardiogenic shock. QTc: Q-T interval correted for heart rate, BNP: B-type natriuretic peptide, CK-MB: creatinine kinase MB fraction, TnI: Troponin I, f/u: follow up, hs-CRP: highly sensitive C-reactive protein, EF: ejection fraction

Table 4. Clinical characteristics of published data with stress-induced cardiomyopathy

Study	Number of patients	Mean age	Female sex (%)	Chest pain (%)	ST elevation (%)	EF (%)
Tsuchihashi et al.[10]	88	67±13	86	67	90	41±11
Kurisu et al.[9]	30	70±8	93	63	100	49±12
Abe et al.[4]	17	74	82	53	82	-
Desmet et al.[11]	13	62±12	92	62	38	-
Bybee et al.[12]	16	71±12	100	69	81	39
Sharkey et al.[13]	22	65±13	100	91	59	29±9
Wittstein et al.[14]	19	63	95	95	11	20
Regnante et al.[15]	70	67±11	95	77	41	37±12
Lee[5]	18	63±18	83	66	39	39±9
Our data	39	61±16	69	26	28	45±16

EF: ejection fraction

cantly associated with an event (OR 0.89, 95% CI 0.80-0.98, p=0.024).

Discussion

Our study shows that elevated hs-CRP levels and initial impairment of LV systolic function relate to poor clinical outcome. Elevated CRP levels are found in SCM patients and related to impaired LV systolic function with BNP release.[7] Enhanced production of acute-phase proteins in the liver by catecholamines may result from direct stimulation or may be mediated by cytokines such as tumor necrosis factor-α or interleukin 6.[8] Pathologic findings of SCM revealed the infiltration of inflammatory cells, including activated macrophages.[9] Collectively, our findings and previous reports suggest that systemic or local inflammatory processes may affect myocardial dysfunction and clinical outcomes in SCM.

We had different gender-related differences, triggering factors, and initial symptoms than previous studies (Table 4). Postmenopausal females predominate in SCM due to estrogen deficiency after menopause. In animal models, postmenopausal females are more vulnerable to sympathetically mediated myocardial stunning.[16] Ovariectomised female rats with estradiol supplementation had significantly less stress-induced ventricular dysfunction, suggesting that estrogen possibly downregulates myocardial adrenoreceptors. New animal models propose that estrogen (via immunoreactive estrogen receptors in the central sympathetic neurons) directly attenuates the hypothalamo-sympathoadrenal axis, and also gives rise to cardioprotective substances such as atrial natruretic peptide, and heat shock protein 70.[17][18] We found a lower percentage of women (female 69%) with SCM, and physical stress was more common than emotional stress. Another SCM study has mostly male patients (65%) and LV apical ballooning developed in a considerable number of patients with severe physical stress who were admitted to the medical intensive care unit.[19] Hahn et al.[20] also showed that the triggering factors were physical stress (69%) rather than emotional stress. Thus, SCM also occurs in men after physical stress, and inflammation (high CRP), leading to the development and poor clinical outcome for SCM regardless of gender difference.

Previous studies have reported that chest pain is a more frequent symptom than dyspnea.[1][2][20] But, our study showed that dyspnea was more frequent at initial presentation. The patients with dyspnea showed longer

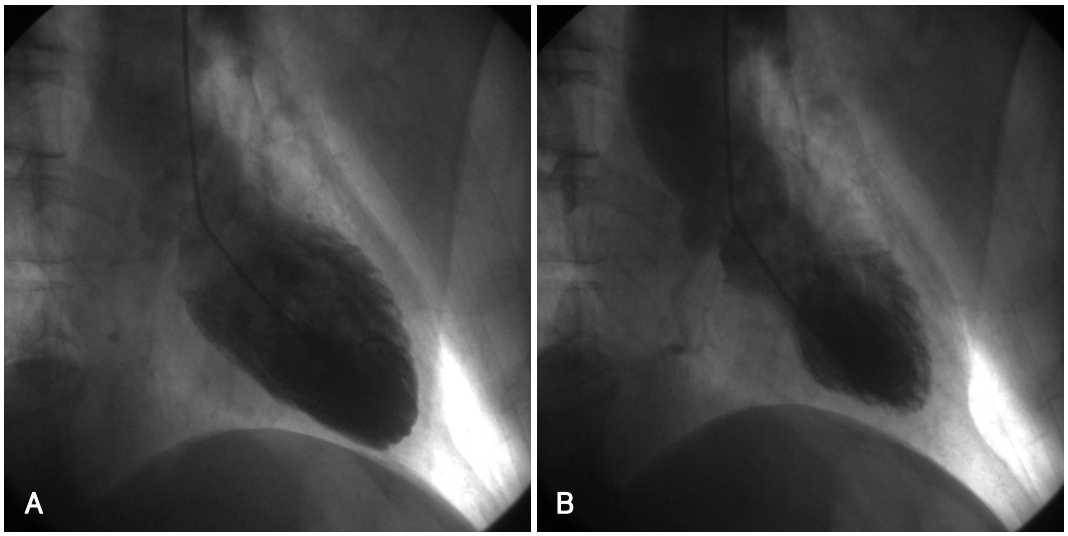

Fig. 2. A case of inverted stress-induced cardiomyopathy {systolic (A) and diastolic (B) phase}. Left ventriculogram (right anterior oblique view) shows hyper-contractility of the basal and apical segments and ballooning of the mid-segments.

hospitalization than patients with chest pain (18±18 vs. 10±8 days). And dyspnea group showed an elevated BNP level (966±1,118 vs. 779±773 pg/mL), higher hs-CRP level (53±77 vs. 22±29 mg/L) and decreased initial LVEF (42±17 vs. 50±15%), but none significant. The discrepancy between our data and previous reports is unclear, but could relate to the small sample size and wide range of standard deviation. A further large study is needed to reveal this phenomenon in the future.

We found atypical types of SCM. There are 3 cases of inverted takotsubo type, 4 cases of transient LV outflow obstruction type, and 1 case of apical thrombus (Fig. 2). Variations in regional wall motion in transient LV apical ballooning, transient mid-ventricular ballooning, and other entities involving excess catecholamines relate more to differences in the anatomic location of cardiac adrenergic receptors, the degree of excess sympathetic activity, or individual differences.[21] Transient severe LV dysfunction can cause serious complication such as cerebrovascular attack, renal infarct, and peripheral arterial obstruction that originates from an LV apical thrombus. Early evaluation of echocardiogram and anticoagulation therapy are important.

Our study is restricted to a single center experience and it cannot represent general characteristics of the Korea population. So, a multicenter prospective study needs to reveal the clinical characteristics and outcomes in Korean patients with SCM.

Conclusions

In our single center experience, the major triggering factor of SCM is physical stress due to medical illness or a procedure. The first manifestation is dyspnea rather than chest pain. Elevated hs-CRP and decreased LVEF at admission were independent risk factors for death or cardiogenic shock in patients with SCM.

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