

## Original Article



# Early Differentiation of Stress Cardiomyopathy from Acute Anterior Wall Myocardial Using Changing Cardiac Enzyme Patterns

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### Conflict of Interest

The authors have no financial conflicts of interest.

## ABSTRACT

**BACKGROUND:** Most patients with acute anterior wall ST elevation myocardial infarction (STEMI) or stress cardiomyopathy (SCMP) show elevations in cardiac enzymes that peak within 24 hours. The changing pattern of cardiac enzymes can be an early clue to the differentiation of anterior STEMI and SCMP.

**METHODS:** This study was a retrospective analysis (matching cases and respective control subjects) performed at a single center. We compared 27 patients with SCMP and 30 patients with anterior STEMI. We used laboratory data included cardiac marker, such as the initial creatine kinase MB (CK-MB) fraction and troponin T (Tn-T), at admission and peak CK-MB and Tn-T at follow up.

**RESULTS:** The mean age was  $69.3 \pm 14.1$  years, and 38.6% of patients were female. The SCMP patients were older, more often female, and had lower left ventricular ejection fractions than the anterior STEMI patients. The initial CK-MB was higher in the anterior STEMI group than in the SCMP group. In contrast, the initial Tn-T level was not significantly different between the 2 groups. Peak CK-MB and Tn-T levels and change from initial levels were significantly greater in the anterior STEMI group than they were in the SCMP group. SCMP could be differentiated from anterior STEMI based on peak CK-MB  $> 46.65$  ng/mL or Tn-T  $> 1.56$  ng/mL.

**CONCLUSIONS:** Follow-up changes in cardiac enzymes can be an effective early tool for differentiating SCMP from anterior STEMI.

**Keywords:** Stress cardiomyopathy; Acute anterior wall myocardial infarction; Creatine kinase, MB form; Troponin T

## INTRODUCTION

Stress cardiomyopathy (SCMP), originally described by Satoh et al.<sup>1)</sup> in 1990 and called takotsubo cardiomyopathy, is also called broken heart syndrome or apical ballooning syndrome. SCMP is most common in postmenopausal women, and is characterized by transient left ventricular (LV) dysfunction. SCMP is not correlated with the distribution of epicardial coronary arteries. The clinical presentation of SCMP overlaps significantly with

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acute coronary syndrome (ACS); it presents with increased cardiac biomarker profiles and an abnormal electrocardiogram (ECG) that suggest myocardial infarction. SCMP is estimated to occur in approximately 1%–2% of patients presenting with ACS.<sup>2)3)</sup> Echocardiography is the most useful imaging tool to assess changes in LV function such as symmetric regional wall motion abnormalities. However, on echocardiography, SCMP causes wall motion abnormalities that are similar to those seen in anterior ST segment elevation myocardial infarction (STEMI). Therefore, it can be difficult to distinguish SCMP from anterior STEMI, which requires immediate revascularization. Coronary angiography is needed, but not always available, to definitively differentiate SCMP from an anterior STEMI. Most patients with either STEMI or SCMP have a modest rise in cardiac enzymes that peaks within 24 hours of the event. Therefore, the changing pattern of cardiac enzymes can be a clue to differentiate SCMP from anterior STEMI in the early phase. In this study, we evaluated our noninvasive ability to distinguish between SCMP and acute anterior STEMI by using initial and follow-up cardiac biomarker levels (including creatine kinase-MB [CK-MB] fraction and troponin-T [Tn-T]).

**METHODS****Study design and patients**

This study was a retrospective analysis (matching for cases and respective control subjects) performed at a single center (Nowon Eulji Medical Center, Eulji University). SCMP was diagnosed based on the Mayo Clinic's criteria for Takotsubo cardiomyopathy.<sup>4)</sup> We studied 27 SCMP patients between January 2017 and December 2018 based on the following diagnostic criteria: acute presentation with ACS like symptoms, with acute ST-segment and T-wave changes on ECG and a rise in cardiac biomarkers (such as CK-MB and Tn-T); typical echocardiographic and angiographic finding (ballooning of the left ventricle); complete reversibility of the ejection fraction (EF) based on repeated transthoracic echocardiography (TTE). A total of 27 patients with SCMP were studied. A control group of patients who met the criteria for STEMI (based on the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction<sup>5)</sup>) was also assembled. The control group only included anterior STEMI patients with LAD territory wall motion abnormalities. The 30 patients in the control group were selected to evaluate their significant differences from the 27 patients in the SCMP group.

**Data collection**

The demographic and clinical data included the age at diagnosis, sex, cardiovascular risk factors and echocardiographic data. The laboratory data included cardiac markers such as CK-MB and Tn-T at admission, and peak CK-MB and Tn-T at follow up.

**Statistical method**

Categorical variables are presented as frequencies and percentages. The  $\chi^2$  test or Fisher's exact test was performed to compare differences in the categorical variables between the 2 groups. Continuous variables are presented as means  $\pm$  standard deviations. The student's t-test was performed to test differences in the continuous variables between the 2 groups. The p-values  $< 0.05$  were considered significant. Receiver operating characteristics analyses of the absolute values of initial Tn-T and CK-MB and peak Tn-T and CK-MB were performed to assess their ability in differentiating SCMP case subjects from anterior STEMI control subjects. Data were analyzed using SPSS statistical software (version 19.0 for Windows; IBM Corp., Armonk, NY, USA).

## RESULTS

### Study population and baseline characteristics

There were 27 SCMP patients and 30 anterior STEMI patients enrolled between January 2017 and December 2018. The mean age was  $69.3 \pm 14.1$  years, and female patients accounted for 38.6% of the patients.

### Differences in SCMP group vs. anterior STEMI group

Those in the SCMP group were older, more often female, and had lower left ventricular ejection fractions (LVEFs) ( $75.4 \pm 10.8$  years vs.  $63.9 \pm 14.6$  years;  $p = 0.002$ , 66.7% vs. 13.3%;  $p < 0.01$ , 41.3%  $\pm$  8.4% vs. 46.9%  $\pm$  9.7%;  $p < 0.05$ ) than did those in the anterior STEMI group (Table 1).

The initial CK-MB was higher in the anterior STEMI group ( $23.3 \pm 43.5$  vs.  $5.9 \pm 5.1$  ng/mL;  $p < 0.05$ ) than it was in the SCMP group. In contrast, the initial Tn-T level was not significantly different between the 2 groups ( $0.9 \pm 1.8$  ng/mL vs.  $0.2 \pm 0.3$  ng/mL,  $p = \text{NS}$ ). The peak Tn-T and CK-MB levels were significantly higher in the anterior STEMI group than they were in the SCMP group ( $6.8 \pm 3.2$  ng/mL vs.  $0.4 \pm 0.4$  ng/mL;  $p < 0.001$ ,  $197.6 \pm 99.9$  ng/mL vs.  $9.7 \pm 10.7$  ng/mL;  $p < 0.001$ ). In addition, the changes in Tn-T and CK-MB levels from their initial to peak levels were significantly higher in the anterior STEMI group than they were in the SCMP group ( $5.1 \pm 3.4$  vs.  $0.2 \pm 0.4$  ng/mL;  $p < 0.001$ ,  $174.3 \pm 102.7$  vs.  $3.8 \pm 8.2$  ng/mL;  $p < 0.001$ ) (Table 2).

### Discriminating SCMP from anterior STEMI

The SCMP group could be distinguished from the anterior STEMI group using a peak Tn-T  $> 1.56$  ng/dL with a sensitivity of 90% and specificity of 100% (95% confidence interval [CI], 0–1; area under the curve [AUC], 0.990;  $p < 0.001$ ), and a peak CK-MB  $> 46.65$  ng/dL with a sensitivity of 90% and specificity of 100% (95% CI, 0–1, AUC, 0.974;  $p < 0.001$ ) (Figure 1).

**Table 1.** Baseline clinical and echocardiographic characteristics

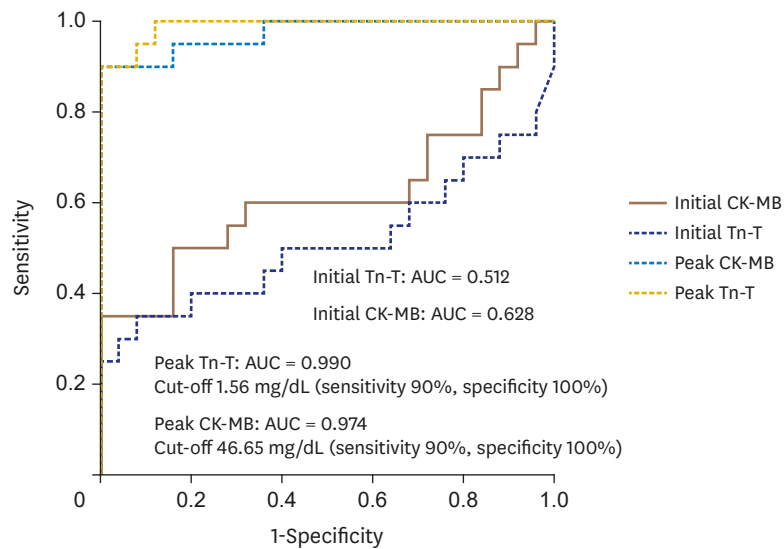
Clinical and echocardiographic data	Anterior STEMI (n = 30)	SCMP (n = 27)	p-value
Age (years)	$63.9 \pm 14.6$	$75.4 \pm 10.8$	0.002
Female sex (%)	13.3	66.7	$< 0.010$
Hypertension (%)	66.7	83.3	0.207
Diabetes (%)	27.3	44.4	0.212
Current smoking (%)	22.7	18.8	0.547
LVEF (%)	$46.9 \pm 9.7$	$41.3 \pm 8.4$	0.024
LV mass index (g/m <sup>2</sup> )	$111.1 \pm 23.7$	$122.1 \pm 32.6$	0.160
LA volume index (mL/m <sup>2</sup> )	$24.9 \pm 11.3$	$34.1 \pm 17.8$	0.031

STEMI: ST elevation myocardial infarction; SCMP: stress cardiomyopathy; LVEF: left ventricular ejection fraction; LV: left ventricular; LA: left atrium.

**Table 2.** Comparison of cardiac enzymes between anterior STEMI and SCMP

Biomarkers (ng/mL)	Anterior STEMI (n = 30)	SCMP (n = 27)	p-value
Initial CK-MB	$23.3 \pm 43.5$	$5.9 \pm 5.1$	0.038
Initial Tn-T	$0.91 \pm 1.80$	$0.24 \pm 0.26$	0.112
Peak CK-MB	$197.6 \pm 99.9$	$9.7 \pm 10.7$	$< 0.001$
Peak Tn-T	$6.76 \pm 3.16$	$0.44 \pm 0.37$	$< 0.001$
CK-MB changes	$174.3 \pm 102.7$	$3.8 \pm 8.2$	$< 0.001$
Tn-T changes	$5.13 \pm 3.39$	$0.23 \pm 0.37$	$< 0.001$

STEMI: ST elevation myocardial infarction; SCMP: stress-induced cardiomyopathy; CK-MB: creatinine kinase-MB; Tn-T: troponin-T.



**Figure 1.** The ROC curve of initial and peak CK-MB fraction and Tn-T level for differentiating anterior STEMI from SCMP. ROC: receiver operating characteristics; CK-MB: creatine kinase MB; Tn-T: troponin-T; STEMI: ST elevation myocardial infarction; SCMP: stress cardiomyopathy; AUC: area under the curve.

## DISCUSSION

SCMP presents with an acute onset of severe chest pain, dyspnea and ECG changes that are typical of anterior STEMI. The differential diagnosis of SCMP and anterior STEMI is essential for deciding whether reperfusion therapy is required. Coronary angiography is needed to definitively differentiate SCMP from an anterior STEMI. However, coronary angiography is not always possible in SCMP patients given their poor general condition and high risk of bleeding. In one study,<sup>6)</sup> 24.2% of total patients hospitalized in the intensive care unit were unable to undergo emergency coronary angiography. For this reason, many researchers have searched for simple tools to distinguish SCMP from anterior STEMI using ECG, echocardiography and cardiac biomarkers.

TTE with color and tissue Doppler is the preferred noninvasive imaging test for patients with suspected SCMP.<sup>7)</sup> TTE plays an important role not only in identifying patterns of myocardial wall motor disorders, but also in diagnosing complications that can occur in SCMP. Echocardiography can detect early complications, such as a left ventricle cardiovascular thrombus, mitral regurgitation, or pericardial effusion, and aid in treatment. For example, if a patient with SCMP has consistently low blood pressure, echocardiography can be used to evaluate dynamic LV outflow obstruction and/or LV function. The role of echocardiography is particularly important in patients presenting with elevated cardiac enzymes. However, it remains very challenging to differentiate apical ballooning in the acute phase from antero-apical stunning due to myocardial ischemia from left anterior descending artery occlusion (especially if the artery is large and wraps around the apex). In addition, it may take a week or more for apical ballooning to recover on echocardiography. A recent study<sup>8)</sup> found that longitudinal strain improves before LVEF improves. However, improvement in longitudinal strain also requires 2–3 days, and is expensive.

Several studies have attempted to differentiate between anterior STEMI and SCMP using cardiac biomarkers, since cardiac biomarkers are known to reach a peak level 24 hours after

both anterior STEMI and SCMP occur. Among cardiac biomarkers, B-type natriuretic peptide (BNP) is produced and released in association with ventricular distension. The BNP level is significantly higher in SCMP than it is in acute myocardial infarction (AMI). In addition, the troponin and CK-MB levels are usually higher in AMI than they are in SCMP. Patients with SCMP have lesser elevations in the cardiac myonecrosis markers (such as myoglobin, CK-MB and troponins) compared to those of AMI patients because of a lack of significant myocardial necrosis in SCMP.<sup>9)</sup> Ramaraj et al.<sup>10)</sup> found that a Tn-T level > 6 ng/mL is unlikely in SCMP. In addition, Templin et al.<sup>11)</sup> reported that peak Tn-T levels in patients with SCMP are generally < 10 ng/mL, which is substantially lower than those of patients with AMI.

Among troponins, we studied Tn-T for several reasons. Ramaraj et al.<sup>10)</sup> showed that there was no significant association between the initial LVEF and some cardiac marker such as creatinine kinase, CK-MB and troponin I (Tn-I). However, Tn-T alone showed a significant inverse correlation with initial LVEF. The cause of this association between LVEF and Tn-T is not known. However, there is a similar correlation between Tn-T and decreased LVEF in nonischemic cardiomyopathy, which is more prominent than that in ischemic cardiomyopathy.<sup>12)</sup>

Our results are similar to those of prior studies. The peak CK-MB and peak Tn-T were significantly lower in SCMP patients than they were in anterior STEMI patients ( $9.7 \pm 10.7$  ng/mL vs.  $197.6 \pm 99.9$  ng/mL;  $p < 0.001$ ,  $0.44 \pm 0.37$  ng/mL vs.  $6.76 \pm 3.16$  ng/mL;  $p < 0.001$ ). Both the peak levels and changes in CK-MB and Tn-T from their initial levels were significantly lower in SCMP than they were in anterior STEMI ( $0.23 \pm 0.37$  ng/mL vs.  $5.13 \pm 3.39$  ng/mL;  $p < 0.001$ ,  $3.8 \pm 8.2$  ng/mL vs.  $174.3 \pm 102.7$  ng/mL;  $p < 0.001$ ). Peak Tn-T and CK-MB levels of > 1.56 ng/mL and > 46.65 ng/mL, respectively, exclude SCMP with 90% sensitivity and 100% specificity (AUC, 0.990;  $p < 0.001$ :0.974;  $p < 0.001$ ). In another study,<sup>10)</sup> Tn-I was positive on admission for 98.4% of SCMP patients, with a peak occurring earlier than that in ACS patients ( $6.0$  [0.0–12.0] vs.  $12.0$  [6.0–18.0] hours,  $p < 0.001$ ). Therefore, we can distinguish SCMP from anterior STEMI based on a peak Tn-T > 1.56 ng/mL or CK-MB > 46.65 ng/mL reached within 12 hours of hospital admission.

This study has several limitations. In addition to its retrospective nature and those associated limitations, our sample size of SCMP patients was small given that this was a single center study. In addition, 66.7% of the SCMP group was female, while 86.7% of the anterior STEMI group was male. The SCMP group was also significantly older than was the anterior STEMI group. Nonetheless, it should be recognized that SCMP predominantly occurs in postmenopausal women.

Our study suggests that the peak levels of Tn-T and/or CK-MB within 12 hours of admission can be used to distinguish SCMP from anterior STEMI. A peak level of Tn-T < 1.56 ng/mL and/or a peak level of CK-MB < 46.65 ng/mL suggests SCMP over anterior STEMI.

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