CLINICAL STUDY

The relationship of thyroid hormone status with myocardial function in stress cardiomyopathy

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Abstract

Objective: This study aimed to investigate thyroid hormone (TH) status and its relationship with myocardial function as well as clinical and biochemical parameters in stress cardiomyopathy (CMP). **Methods:** Forty-five patients with stress CMP (the patient group), 31 patients without stress CMP (the control II group), and 58 healthy subjects (the control I group) were included. Sick euthyroid syndrome (SES) was defined as low total triiodothyronine (T₃) with normal TSH levels.

Results: In the patient group at admission, prevalence of SES was 62.2%. Compared with the control I group, the patient group had a decrease in left ventricular ejection fraction (LVEF) and systolic blood pressure (BP) and an increase in troponin-I, CK-MB, and B-type natriuretic peptide (BNP) levels. Total T₃ levels were reduced, and anti-thyroid peroxidase antibody (anti-TPO Ab) positivity, C-reactive protein (CRP) and cortisol levels were elevated. Total T₃ levels were associated with acute physiology and chronic health evaluation II (APACHE II) score, LVEF, systolic BP, and cortisol levels in multivariate analysis. In the control II group, total T₃ levels were not associated with any variables. In the SES (*n*=28) and myocardial dysfunction (MDys, *n*=27) subgroups, increased APACHE II score and BNP levels as well as decreased LVEF and systolic BP were significant. Total T₃ levels were reduced, and CRP, cortisol and catecholamines levels were elevated. In the MDys subgroup, anti-TPO Ab positivity and titer were increased.

Conclusion: These results suggest that total T₃ levels may be associated with myocardial contractility, clinical severity, and cortisol levels. Thyroid autoimmunity may influence myocardial contractility in stress CMP.

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Introduction

The cardiovascular system is the main target organ of thyroid hormone (TH), and TH exerts multiple actions on cardiac function as well as peripheral vascular tone (1–10). Overt hypothyroidism decreases myocardial contractility, and diminished myocardial contractility reduces TH metabolism (11–13). Subclinical hypothyroidism also exhibits impairment of left ventricular (LV) diastolic function that returns to normal after TH replacement (14).

Sick euthyroid syndrome (SES) is the entity of changed peripheral TH profile in non-thyroidal illness (15–19). SES is characterized by decreased total T₃ levels and reciprocally increased reverse T₃ levels (20). For pathophysiology of SES, impaired peripheral deiodination of tetraiodothyronine (T₄), decreased TRH metabolism and reduced TH receptor expression have been suggested (20–22).

There is increasing evidence that altered TH status in SES may have an influence on clinical outcome and cardiac function (1, 23–26). It has been demonstrated that the degree of thyroid dysfunction was associated with severity of diseases, and low levels of biologically active TH predicted poor prognosis in several diseases (26–30). Previous studies have reported that low total T₃ levels were associated with increased mortality and impaired cardiac function and were strong prognostic predictors of death in heart disease (31–33).

Stress cardiomyopathy (CMP) described as apical ballooning syndrome, broken heart syndrome, ampulla or Takotsubo CMP presents angina-like chest pain, dyspnea or syncope (34–36). Although catecholamine is likely to play an important role in triggering stress CMP, pathophysiology of stress CMP is unknown (37, 38). Management of stress CMP mainly consists of supportive therapy because stress CMP has usually a good prognosis (34).

In heart failure, it has been shown that total triiodothyronine (T_3) levels were related to LV function and peak oxygen consumption, and i.v. T_3 administration increased cardiac output and decreased systemic vascular resistance (39–41). In SES accompanied by heart failure, previous studies have suggested that cardiac transplantation reversed changes of TH profile, and short-term synthetic T_3 replacement therapy improved ventricular performance as well as neuroendocrine parameters (42, 43). However, in stress CMP, alteration of TH status and myocardial function, and their relationship have not been elucidated.

This study aimed to investigate TH status and its relationship with myocardial function as well as clinical and biochemical parameters in stress CMP followed by acute physiological stress.

Subjects and methods

Subjects

Forty-five patients with stress CMP (the patient group) and 58 healthy subjects (the control I group) from ChunCheon Sacred Heart Hospital between January 2003 and December 2006 were included in the study.

All patients were clinically stable. None of them were hospitalized at least three months prior to admission and had a history of thyroid or cardiac disease. In all patients, agents affecting thyroid function such as amiodarone, dopamine, and glucocorticoid were not taken at admission and during hospitalization. Stress CMP was diagnosed by the Mayo Clinic Criteria (34). Causes of stress CMP were community-acquired pneumonia ($n=24$), non-compensated liver disease ($n=13$), urinary tract infection ($n=6$), and sepsis of unidentified origin ($n=2$). In all patients at admission, coronary angiography was performed and showed no significant stenosis or spasm of coronary artery. SES was defined as low serum total T_3 levels less than the lower limit of normal with normal serum TSH levels. Myocardial dysfunction (MDys) was established by LV ejection fraction (LVEF) less than 50%. Acute physiology and chronic health evaluation (APACHE) II score was calculated within 24 h of admission (44). At the time of admission, full recovery and six months after full recovery, echocardiographic examination was carried out, and the levels of biochemical parameters including TH were measured. All patients were appropriately treated according to underlying diseases and were fully recovered without any sequela. The control I group had no previous history of thyroid or cardiac disease, and the control II group had the same underlying diseases as those of the patient group without stress CMP. Briefly, again the patient, control I and control II groups were as follows: the control I group, underlying disease (–) and stress CMP (–); the control II group, underlying disease (+) and stress CMP (–); the patient group, underlying

disease (+) and stress CMP (+). Study protocol was designed according to the declaration of Helsinki and approved by the ethical committee of the ChunCheon Sacred Heart Hospital, Hallym University.

Measurement of left ventricular ejection fraction

Transthoracic echocardiography was performed with Philips SONOS 7500 using a 4 MHz transducer. Echocardiographic images were obtained from parasternal long-axis, short axis and apical four-chamber views. LVEF was measured according to the criteria recommended by the American Society of Echocardiography (45).

Biochemical measurements

Fasting samples of venous blood were collected from the antecubital vein. Blood samples were centrifuged for 15 min at 4 °C. Serum AST, ALT, albumin, hematocrit (Hct), glucose, BUN, and creatinine were measured by automated analyzer.

Serum troponin-I was measured with Architect Stat Troponin-I kit (Abbott) by chemiluminescent microparticle immunoassay (CMIA), CK-MB using Architect Stat CK-MB kit (Abbott) by CMIA and B-type natriuretic peptide (BNP) using AxSYM BNP kit (Abbott) by microparticle enzyme immunoassay (MEIA). Serum total T_3 was measured with AxSYM Total T_3 Kit (Abbott) by fluorescence polarization immunoassay (FPIA), free thyroxine (T_4) using AxSYM free T_4 Kit (Abbott) by FPIA, TSH using AxSYM TSH Kit (Abbott) by MEIA and anti-TPO antibody using AxSYM Anti-TPO Kit (Abbott) by MEIA. Serum C-reactive protein (CRP) was measured with Cardio-Phase CRP kit (Dade Behring, Marburg, Germany) by nephelometry and cortisol using Cortisol RIA kit (Radim, Pomezia, Italy) by RIA. In supine position, plasma epinephrine (EP), norepinephrine (NEP), and dopamine (D) were measured by HPLC.

Reference ranges are as follows: troponin-I, 0–0.4 ng/ml; CK-MB, 0–5 ng/ml; BNP, 0–100 pg/ml; total T_3 , 80–200 ng/dl; free T_4 , 0.93–1.7 ng/dl; TSH, 0.4–4.7 mIU/l; anti-TPO antibody, 0–34 IU/ml; CRP, 0–8 mg/l; cortisol, 7–21 µg/dl; EP, 0–110 pg/ml; NEP, 70–750 pg/ml; D, 0–30 pg/ml.

Statistical analysis

Data are shown as mean $\pm$ s.d. Statistical analysis was carried out using SPSS version 10.0 program. Skewed data were logarithmically transformed before analysis. Comparisons of clinical and biochemical parameters between the patient and control groups and between the subgroups were done by unpaired Student's *t*-test or χ^2 test as appropriate. Relationships between clinical and biochemical parameters in the patient and control groups were analyzed by Pearson's analysis.

Multivariate analysis was conducted with multiple logistic regression in which only variables showing significant association in univariate analysis were introduced. Odds ratio (OR) and 95% confidence interval (95% CI) were also estimated. A *P*-value less than 0.05 was considered to be significant.

Results

The baseline characteristics of the patient and control I groups are summarized in Table 1. The mean APACHE II score at admission and the mean hospitalized day of the patient group were 11.0 ± 1.8 and 23 ± 14 days respectively. In the patient group, LVEF and systolic blood pressure (BP) but not diastolic BP at admission were significantly decreased compared with those of the control I group ($P < 0.05$) and of the patient group at full recovery ($P < 0.05$; Table 1). Troponin-I, CK-MB, and BNP levels at admission were significantly increased compared with those of the control I group ($P < 0.05$) and of the patient group at full recovery ($P < 0.05$).

In this study, prevalence of SES was 62.2% in the patient group. As shown in Table 2, in the patient group, total T_3 but not free T_4 and TSH levels at admission were significantly reduced compared with those of the control I group ($P < 0.05$) and of the patient group at full recovery ($P < 0.05$). Anti-TPO Ab positivity but not titer was significantly elevated compared with that of the control I group ($P < 0.05$). AST, ALT, glucose, CRP, and cortisol levels at admission were significantly higher compared with those of the control I group ($P < 0.05$) and of the patient group at full recovery ($P < 0.05$). EP, NEP, and D levels at admission were significantly more than those at full recovery ($P < 0.05$).

In the patient group at admission, total T_3 levels were associated with APACHE II score (OR, 1.71; 95% CI, 1.52–2.08; $P = 0.037$), LVEF (OR, 2.14; 95% CI, 1.93–2.78; $P = 0.015$), systolic BP (OR, 1.49; 95% CI,

1.28–1.86; $P = 0.041$), and cortisol (OR, 1.83; 95% CI, 1.66–2.34; $P = 0.026$) levels by multivariate analysis. LVEF was associated with APACHE II score (OR, 1.47; 95% CI, 1.26–1.71; $P = 0.032$), systolic BP (OR, 1.56; 95% CI, 1.39–1.74; $P = 0.028$), total T_3 (OR, 2.14; 95% CI, 1.93–2.78; $P = 0.015$) and BNP (OR, 1.45; 95% CI, 1.18–1.73; $P = 0.04$) levels by multivariate analysis. In the control II group, total T_3 levels were not associated with any variables by multivariate analysis. Free T_4 and TSH levels had no relation to the clinical or biochemical parameters in the patient, control I, and control II groups.

When the patient group was classified into SES ($n = 28$) and non-SES ($n = 17$) subgroups, the time of hospitalization was longer for the SES subgroup in respect to the non-SES subgroups (SES versus non-SES subgroup, 25 ± 12 vs 20 ± 8 days; Table 3). APACHE II score, LVEF, systolic BP, and BNP levels of the SES subgroup at admission were significantly different from those of the non-SES subgroups at admission ($P < 0.05$). In each subgroup, systolic BP, troponin-I, CK-MB, and BNP levels at admission significantly differed from those at full recovery ($P < 0.05$). In the SES subgroup, LVEF at admission was significantly lower compared with that at full recovery ($P < 0.05$).

Total T_3 levels at admission were significantly decreased in the SES subgroup compared with the non-SES subgroup ($P < 0.05$; Table 4). Total T_3 levels were significantly reduced at admission compared with at full recovery in each subgroup ($P < 0.05$). Anti-TPO Ab positivity and titer of the SES subgroup were similar to those of the non-SES subgroup. CRP, cortisol, EP, NEP, and D levels at admission were significantly increased in the SES subgroup compared with the non-SES subgroup ($P < 0.05$).

When the patient group was divided into two subgroups based on the presence of (MDys, $n = 27$) or absence of (non-MDys, $n = 18$) myocardial dysfunction, APACHE II score, systolic BP, and BNP levels of the MDys

Table 1 The baseline characteristics and cardiac parameters in the patient, control I, and control II groups at 6 months, at the time of 6 months after full recovery.

	Patient group			Control I group	Control II group At admission
	At admission	At full recovery	At 6 months		
Number		45		58	31
Age (years)		63 ± 12		64 ± 7	66 ± 4
Gender (male/female)		14:31		19:39	9:22
BMI (kg/m^2)	22.6 ± 2.7	23.3 ± 1.7	23.3 ± 1.6	23.2 ± 1.6	22.8 ± 1.8
Diabetes, <i>n</i> (%)		6 (13.3)		7 (12.1)	4 (12.9)
Hypertension, <i>n</i> (%)		5 (11.1)		6 (10.3)	5 (16.1)
Systolic BP (mmHg)	$105 \pm 13^*, \dagger$	129 ± 12	127 ± 11	133 ± 12	121 ± 7
Diastolic BP (mmHg)	75 ± 8	82 ± 7	81 ± 5	85 ± 7	83 ± 4
LVEF (%)	$43.9 \pm 7.2^*, \dagger$	61.6 ± 8.4	60.7 ± 4.8	63.1 ± 4.3	62.4 ± 3.6
Troponin-I (ng/ml)	$0.7 \pm 0.3^*, \dagger$	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1
CK-MB (ng/ml)	$5.5 \pm 1.4^*, \dagger$	0.5 ± 0.2	0.3 ± 0.2	0.5 ± 0.1	0.8 ± 0.2
BNP (pg/ml)	$238 \pm 126^*, \dagger$	34 ± 9	35 ± 8	33 ± 17	76 ± 19

BMI, body mass index; BP, blood pressure; LVEF, left ventricular ejection fraction and BNP, B-type natriuretic peptide. * $P < 0.05$ versus the control I group.

$\dagger P < 0.05$ versus the patient group at recovery.

Table 2 The levels of thyroid hormones and biochemical markers among the patient, control I, and control II groups at 6 months, at the time of 6 months after full recovery.

	Patient group (n=45)			Control I group (n=58)	Control II group (n=31) At admission
	At admission	At full recovery	At 6 months		
Thyroid hormones					
Total T ₃ (ng/dl)	72±38*, [†]	138±15		143±17	75±16
Free T ₄ (ng/dl)	1.01±0.06	1.34±0.17		1.32±0.14	1.32±0.14
TSH (mIU/l)	0.51±0.09	0.85±0.18		0.91±0.13	0.91±0.13
Anti-TPO Ab (+), n (%)	22 (48.9)*	—	—	14 (24.1)	7 (22.6)
Anti-TPO Ab titer (IU/ml)	248±47	—	—	213±38	186±23
Biochemical markers					
AST (IU/l)	75±17*, [†]	31±8	—	34±6	31±8
ALT (IU/l)	82±16*, [†]	30±7	—	28±7	42±9
Albumin (mg/dl)	3.0±0.3	3.9±0.4	—	3.7±0.2	3.1±0.4
Hct (%)	37±5	42±6	—	42±4	43±3
Glucose (mg/dl)	99±12*, [†]	85±5	—	83±5	92±7
BUN (mg/dl)	24±6	18±4	—	21±3	25±4
Creatinine (mg/dl)	0.8±0.3	0.3±0.2	—	0.3±0.1	0.6±0.2
CRP (mg/l)	28.9±6.8*, [†]	2.1±1.4	2.0±0.7	2.1±1.4	22.4±5.3
Cortisol (ug/dl)	18.7±6.9*, [†]	4.3±2.0	4.2±0.8	3.6±1.7	16.1±4.5
Epinephrine (pg/ml)	114.3±45.2 [†]	51.4±13.1	50.3±7.4	—	93.5±32.6
Norepinephrine (pg/ml)	762.1±243.6 [†]	251.8±62.3	226.7±23.2	—	684.2±193.3
Dopamine (pg/ml)	39.2±15.7 [†]	17.9±5.1	15.1±2.9	—	31.4±12.1

Anti-TPO Ab, anti-thyroid peroxidase antibody; Hct, hematocrit and CRP, C-reactive protein. * $P < 0.05$ versus the control I group. [†] $P < 0.05$ versus the patient group at recovery.

subgroup at admission were significantly different from those of the non-MDys subgroup ($P < 0.05$; Table 5). In each subgroup, systolic BP, troponin-I, CK-MB, and BNP levels at admission significantly differed from those at full recovery ($P < 0.05$).

At admission, total T₃ levels were significantly decreased in the MDys subgroup compared with the non-MDys subgroup ($P < 0.05$; Table 6). In each subgroup, total T₃ levels were significantly reduced at admission compared with the levels at full recovery ($P < 0.05$). Anti-TPO Ab positivity and titer at admission were significantly higher in the MDys subgroup compared with the non-MDys subgroup ($P < 0.05$). At admission, CRP, cortisol, EP, NEP, and D levels were

significantly increased in the MDys subgroup compared with the non-MDys subgroup ($P < 0.05$).

There was no difference in cardiac and biochemical markers at 6 months after full recovery compared with those at full recovery between the patient and control I groups (Tables 1 and 2), between the SES and non-SES subgroups (Tables 3 and 4), and between the MDys and non-MDys subgroups (data are not shown).

Discussion

Stress CMP usually occurs in a situation of acute physiological or emotional stress, especially in

Table 3 The baseline characteristics and cardiac parameters of the subgroups with sick euthyroid syndrome (SES) and without SES (non-SES) in the patient group at 6 months, at the time of 6 months after full recovery.

	SES subgroup			Non-SES subgroup		
	At admission	At full recovery	At 6 months	At admission	At full recovery	At 6 months
Number		28			17	
Age (years)		62±11			64±8	
Gender (male/female)		9:19			5:12	
BMI (kg/m ²)	22.5±2.3	23.2±1.6	23.2±1.5	22.8±2.4	23.4±1.5	23.3±1.4
Diabetes, n (%)		4 (14.3)			2 (11.8)	
Hypertension, n (%)		3 (10.7)			2 (11.8)	
APACHE II score	11.7±1.3*	—	—	9.8±0.4	—	—
Systolic BP (mmHg)	97±8*, [†]	128±11	126±7	113±11 [†]	129±10	128±9
Diastolic BP (mmHg)	74±5	81±4	80±3	77±6	82±5	81±4
LVEF (%)	31.3±6.7*, [†]	60.1±7.7	60.4±4.1	58.4±7.1	63.0±8.2	61.2±4.3
Troponin-I (ng/ml)	0.7±0.2 [†]	0.2±0.1	0.2±0.1	0.6±0.2 [†]	0.2±0.1	0.2±0.1
CK-MB (ng/ml)	5.8±1.4*, [†]	0.5±0.1	0.3±0.1	5.2±1.2 [†]	0.4±0.1	0.3±0.1
BNP (pg/ml)	287±109*, [†]	38±8	36±5	164±73 [†]	29±6	32±3

SES, sick euthyroid syndrome; BMI, body mass index; BP, blood pressure; LVEF, left ventricular ejection fraction and BNP, B-type natriuretic peptide. * $P < 0.05$ versus the non-SES subgroup at admission. [†] $P < 0.05$ versus the SES subgroup at recovery. [‡] $P < 0.05$ versus the non-SES subgroup at recovery.

Table 4 The levels of thyroid hormones and biochemical markers between the subgroups with sick euthyroid syndrome (SES) and without SES (non-SES) in the patient group at 6 months, at the time of 6 months after full recovery.

	SES subgroup (n=28)			Non-SES subgroup (n=17)		
	At admission	At full recovery	At 6 months	At admission	At full recovery	At 6 months
Thyroid hormones						
Total T ₃ (ng/dl)	42±9*, [†]	136±12	141±8	106±11 [‡]	143±14	142±7
Free T ₄ (ng/dl)	0.99±0.05	1.35±0.14	1.37±0.13	1.02±0.04	1.37±0.12	1.38±0.09
TSH (mIU/l)	0.49±0.08	0.87±0.10	0.96±0.12	0.54±0.07	0.88±0.09	0.94±0.11
Anti-TPO Ab (+), n (%)	14 (50.0)	—	—	8 (47.1)	—	—
Anti-TPO Ab titer (IU/ml)	263±37	—	—	229±23	—	—
Biochemical markers						
AST (IU/l)	78±15 [†]	32±6	—	72±13 [‡]	30±4	—
ALT (IU/l)	86±14 [†]	29±5	—	78±12 [‡]	31±5	—
Albumin (mg/dl)	3.0±0.2	3.8±0.2	—	3.1±0.2	3.9±0.2	—
Hct (%)	36±4	41±3	—	39±5	42±4	—
Glucose (mg/dl)	103±11 [†]	87±4	—	97±8 [‡]	81±3	—
BUN (mg/dl)	25±6	19±3	—	23±5	16±2	—
Creatinine (mg/dl)	0.8±0.2	0.3±0.1	—	0.7±0.2	0.2±0.1	—
CRP (mg/l)	38.3±6.4*, [†]	2.3±1.2	2.1±0.6	19.3±4.9 [‡]	1.8±0.5	1.7±0.3
Cortisol (ug/dl)	26.1±6.2*, [†]	4.5±1.8	4.6±0.7	11.2±2.1 [‡]	4.0±1.1	3.8±0.6
Epinephrine (pg/ml)	126.2±38.1*, [†]	53.9±12.6	52.8±6.9	94.6±23.2 [‡]	48.3±9.7	46.2±6.1
Norepinephrine (pg/ml)	813.7±212.4*, [†]	261.1±57.4	235.2±21.3	539.3±136.8 [‡]	226.4±47.2	213.3±19.7
Dopamine (pg/ml)	45.9±13.2*, [†]	18.7±4.3	15.9±2.5	27.1±7.4 [‡]	15.6±3.9	14.8±2.4

SES, sick euthyroid syndrome; Anti-TPO Ab, anti-thyroid peroxidase antibody; Hct, hematocrit and CRP, C-reactive protein. **P*<0.05 versus the non-SES subgroup at admission. [†]*P*<0.05 versus the SES subgroup at recovery. [‡]*P*<0.05 versus the non-SES subgroup at recovery.

post-menopausal women (34). In this study, the patient group at admission was in a physiologically stressful condition, the mean APACHE II score was 11.0, and the mean hospitalized period was 23 days. In the patient group, the mean age was 62 years, and female gender was 68.9% (31/45).

TH profile is often altered in several diseases, and the degree of altered TH profile correlates with the severity of underlying disease (20, 26–30). In the present study, we assessed TH status and its relation to clinical severity in stress CMP. Between the patient and control I groups, there was no difference in age, gender, BMI, and prevalence of diabetes and

hypertension. Although total T₃, free T₄, and TSH levels of the patient group at admission were decreased compared with those of the control I group, only total T₃ levels were significantly reduced and negatively correlated with APACHE II score. In the patient group at recovery, TH profile was normalized and was not different from that of the control I group. These results demonstrate that total T₃ levels are significantly decreased during the acute phase followed by normalization during recovery phase, and the magnitude of decreased total T₃ levels may be related to the severity of physiological stress in stress CMP.

Table 5 The baseline characteristics and cardiac parameters between the subgroups with myocardial dysfunction (MDys) and without MDys (non-MDys) in the patient group.

	MDys subgroup		Non-MDys subgroup	
	At admission	At full recovery	At admission	At full recovery
Number		27		18
Age (years)		64±10		62±9
Gender (male/female)		6:17		8:14
BMI (kg/m ²)	22.5±2.5	23.2±1.4	22.7±2.6	23.4±1.6
Diabetes, n (%)		2 (9.5)		4 (16.7)
Hypertension, n (%)		2 (9.5)		3 (12.5)
APACHE II score	11.8±1.4*	—	9.6±0.5	—
Systolic BP (mmHg)	79±7*, [†]	127±9	121±11 [‡]	130±11
Diastolic BP (mmHg)	72±4	81±5	78±6	83±6
Troponin-I (ng/ml)	0.8±0.2 [†]	0.2±0.1	0.6±0.2 [‡]	0.2±0.1
CK-MB (ng/ml)	5.7±1.3 [†]	0.6±0.2	5.3±1.2 [‡]	0.4±0.1
BNP (pg/ml)	295±118*, [†]	37±7	147±56 [‡]	31±6

MDys subgroup having left ventricular ejection fraction (LVEF) <50%. Non-MDys subgroup having LVEF ≥ 50%. BMI, body mass index; BP, blood pressure and BNP, B-type natriuretic peptide. **P*<0.05 versus the non-MDys subgroup at admission. [†]*P*<0.05 versus the MDys subgroup at recovery. [‡]*P*<0.05 versus the non-MDys subgroup at recovery.

Table 6 The levels of thyroid hormones and biochemical markers between the subgroups with myocardial dysfunction (MDys) and without MDys (non-MDys) in the patient group.

	MDys subgroup (n=27)		Non-MDys subgroup (n=18)	
	At admission	At full recovery	At admission	At full recovery
Thyroid hormones				
Total T ₃ (ng/dl)	64 ± 21*, [†]	139 ± 8	81 ± 26 [‡]	144 ± 13
Free T ₄ (ng/dl)	0.98 ± 0.04	1.35 ± 0.12	1.03 ± 0.06	1.38 ± 0.15
TSH (mIU/l)	0.51 ± 0.05	0.87 ± 0.09	0.54 ± 0.08	0.88 ± 0.11
Anti-TPO Ab (+), n (%)	15 (71.4)*	–	7 (29.2)	–
Anti-TPO Ab titer (IU/ml)	326 ± 41*	–	172 ± 29	–
Biochemical markers				
AST (IU/l)	79 ± 13 [†]	32 ± 6	71 ± 8 [‡]	30 ± 5
ALT (IU/l)	84 ± 14 [†]	31 ± 4	80 ± 12 [‡]	28 ± 3
Albumin (mg/dl)	3.0 ± 0.1	3.9 ± 0.3	3.1 ± 0.2	3.9 ± 0.2
Hct (%)	36 ± 3	41 ± 2	38 ± 4	42 ± 2
Glucose (mg/dl)	102 ± 9 [†]	86 ± 4	96 ± 7 [‡]	82 ± 3
BUN (mg/dl)	26 ± 4	18 ± 3	22 ± 5	17 ± 2
Creatinine (mg/dl)	0.8 ± 0.2	0.3 ± 0.2	0.7 ± 0.2	0.2 ± 0.1
CRP (mg/l)	35.7 ± 6.3*, [†]	2.2 ± 1.0	21.8 ± 6.1 [‡]	1.9 ± 0.7
Cortisol (ug/dl)	9.4 ± 2.3*, [†]	3.7 ± 1.4	27.1 ± 6.2 [‡]	4.8 ± 1.9
Epinephrine (pg/ml)	121.6 ± 35.2*, [†]	49.3 ± 10.4	101.3 ± 26.1 [‡]	52.2 ± 11.7
Norepinephrine (pg/ml)	845.2 ± 231.5*, [†]	273.4 ± 61.8	507.9 ± 128.2 [‡]	212.3 ± 43.6
Dopamine (pg/ml)	43.1 ± 12.3*, [†]	17.2 ± 4.1	28.4 ± 8.1 [‡]	15.8 ± 4.0

MDys subgroup having left ventricular ejection fraction (LVEF) <50%. Non-MDys subgroup having LVEF ≥ 50%. Anti-TPO Ab, anti-thyroid peroxidase antibody; Hct, hematocrit; CRP, C-reactive protein. **P* < 0.05 versus the non-MDys subgroup at admission. [†]*P* < 0.05 versus the MDys subgroup at recovery. [‡]*P* < 0.05 versus the non-MDys subgroup at recovery.

T₃, biologically active TH, influences expression of specific genes encoding structural and functional proteins of myocardium, thereby affecting myocardial architecture and contractility (7, 46, 47). Low total T₃ levels reduce myocardial contractility, and hypothyroidism leads to cardiac atrophy with the loss of cardiac arteriole, impaired myocardial blood flow and chamber dilation (13, 40, 48). It has been reported that total T₃ levels were correlated with cardiac index including LVEF and were independent predictors of peak oxygen consumption in heart failure (13, 39, 40). Furthermore, it has been suggested that total T₃ levels were associated with systolic and diastolic BP in heart failure (39, 49, 50).

Stress CMP may present heart failure, hypotension or cardiogenic shock by decreased stroke volume and LV outflow tract obstruction (34). In our study, we evaluated the relationship of TH status to myocardial contractility and BP in stress CMP. Total T₃ but not free T₄ and TSH levels of the patient group at admission were associated with LVEF and systolic BP, and LVEF was associated with APACHE II score. In the control II group, total T₃, free T₄, and TSH levels were not associated with any variable including BP and LVEF. These findings displaying interaction between TH and heart indicate that total T₃ levels as well as clinical severity may be correlated with myocardial contractility in the patients with stress CMP.

BNP is a strong predictor of morbidity and mortality in heart failure (51). It has been shown that BNP as well as troponin I and CK-MB levels were elevated in stress CMP as in heart failure or acute myocardial infarction, and increased BNP levels were related to clinical

severity, hemodynamic stress, and myocardial contractility (37, 38). In this study, troponin-I, CK-MB, and BNP levels of the patient group at admission were elevated compared with those of the control I group, and BNP levels were correlated with LVEF but not with total T₃ levels. Although relationship between BNP levels and TH is still controversial, these data probably ascertain that BNP levels are increased and correlated with LVEF in stress CMP.

In the present study, prevalence of SES was 62.2% (28/45). To our knowledge, this is the first report about the prevalence of SES in stress CMP, and illustrates that SES may be common in stress CMP. In the patient group at admission, APACHE II score, total T₃ levels, LVEF, systolic BP, troponin-I, CK-MB, and BNP levels significantly differed between the SES and non-SES subgroups. These results reinforce that SES may be related to changes of cardiac indices in stress CMP. In the MDys subgroup, systolic BP and total T₃ levels were significantly reduced, and APACHE II score and BNP levels were significantly elevated. These findings also demonstrate that myocardial dysfunction may be correlated with decreased total T₃ levels in stress CMP.

Since anti-TPO Ab positivity but not titer was significantly increased in the patient group compared with the control I group, we compared anti-TPO Ab positivity and titer between the SES and non-SES as well as between the MDys and non-MDys subgroups. Interestingly, although anti-TPO Ab positivity and titer had no difference between the SES and non-SES subgroups, these were significantly elevated in the MDys subgroup compared with the non-MDys subgroup. Considering that physiological stress causes

reduced myocardial contractility (stress CMP) and total T₃ levels (SES), and altered TH levels are related to the presence and titer of thyroid autoantibodies, it may be suggested that induction of anti-TPO Ab in stress CMP is associated with physiological stress leading to activation of cortisol, catecholamines and cytokine, and thyroid autoimmunity affects myocardial contractility. However, the suggestion needs to be clarified in further studies.

Cortisol has been implicated in the etiology of SES (15, 20, 28). In our study, cortisol levels of the patient group, the SES subgroup, and the MDys subgroup at admission were significantly increased compared with those of the control group, the non-SES subgroup, and the non-MDys subgroup. Total T₃ levels of the patient group at admission were negatively correlated with cortisol levels. These data indicate that cortisol levels may be involved in pathophysiology of SES in stress CMP.

Adrenergic system seems to play a crucial role in stress CMP, and epicardial coronary spasm, microvascular spasm and direct myocyte injury may be the possible mechanism (37, 38). Neuroendocrine activation is also probably related to SES (15, 20). It has been reported that short-term synthetic T₃ administration induced deactivation of neuroendocrine system and improvement of cardiac performance in heart failure with low free T₄ levels (43). Recent experimental evidences have shown that adrenergic system interacted with TH signaling, and increased adrenergic activity with low T₃ levels influenced on fetal phenotype of cardiac cells (52, 53). In this study, catecholamines levels were significantly elevated in the patient group compared with the control I group, and in the SES subgroup and the MDys subgroup compared with the non-SES subgroup and the non-MDys subgroup.

In the present study, none of the patient group died or was rehospitalized during follow-up, and no association between total T₃ levels or LVEF and prognosis was observed probably due to good outcome. The mean hospitalized day of the SES subgroup was not different from that of the non-SES subgroup.

In conclusion, this study demonstrates that SES may be prevalent, and clinical severity may be related to myocardial contractility in stress CMP. Furthermore, total T₃ levels and anti-TPO Ab may be associated with myocardial contractility as well as clinical severity and cortisol levels in stress CMP.

Declaration of interest

There is no conflict of interest.

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