

## The low serum T<sub>3</sub> level of the euthyroid sick syndrome is related to changes in stress cardiomyopathy

Lee SJ, Kang JG, Ryu OH, Kim CS, Ihm SH, Choi MG, Yoo HJ, Hong KS. The relationship of thyroid hormone status with myocardial function in stress cardiomyopathy. Eur J Endocrinol/ EJE-08-0808 [Pii] 10.1530/EJEJ 2009[doi]

### SUMMARY

**BACKGROUND** Thyroid hormone exerts many actions on cardiac function and peripheral vascular tone. Myocardial contractility is decreased by overt hypothyroidism, and in turn, impaired myocardial contractility reduces thyroid hormone metabolism. In addition, subclinical hypothyroidism also impairs left ventricular diastolic function, which returns to normal with thyroid hormone-replacement therapy. There also is information that the low T<sub>3</sub> serum levels in patients with the euthyroid sick syndrome (ESS) may have an influence on cardiac function. The aim of this study was to investigate thyroid hormone status and its relationship with myocardial function and the biochemical parameters in stress cardiomyopathy.

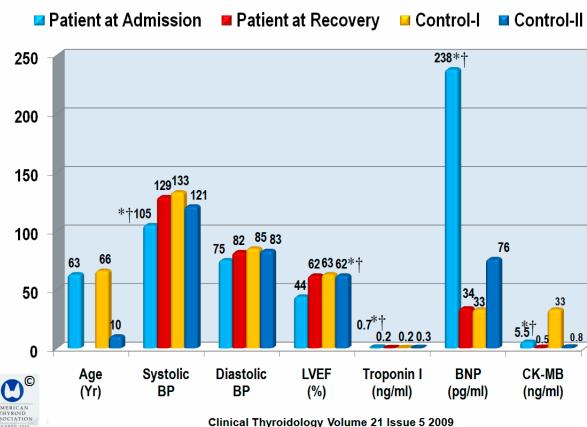
**METHODS** The study group comprised 45 patients with stress cardiomyopathy treated at the Hallym University Sacred Heart Hospital in Korea from January 2003 through December 2006. The two control groups were as follows: control group I consisted of 58 healthy subjects with no previous history of thyroid or cardiac disease, and group II consisted of 31 patients who had the same underlying diseases as the patient group without stress cardiomyopathy. The patient group had been hospitalized for at least 3 months prior to the study, and none were treated with drugs affecting thyroid function, such as amiodarone, dopamine, and glucocorticoids, at the time of admission and during hospitalization. The causes of stress cardiomyopathy were community-acquired pneumonia (in 24 patients), uncompensated hepatic disease (in 13), urinary tract infections (in 6), and sepsis

of unidentified origin (in 2). At the time of hospital admission, all the patients had coronary angiography showing no significant coronary artery stenosis or spasm. ESS was defined as normal serum thyrotropin (TSH) levels with serum triiodothyronine (T<sub>3</sub>) levels below the lower normal range (80 to 200 ng/dl). Myocardial dysfunction was defined as a left ventricular ejection fraction (LVEF) less than 50%. Within 24 hours of admission, the Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated. Echocardiographic examination and thyroid hormone measurements were performed at the time of hospital admission and were repeated after full recovery 6 months later. All patients were treated according to the underlying disease and were fully recovered without sequelae at the time of the study.

**RESULTS** The patient group comprised 45 patients, 14 men and 31 women with a mean ( $\pm$ SD) age of  $63 \pm 12$  years. The first APACHE II score was  $11 \pm 1.8$  and the mean hospital stay was  $23 \pm 14$  days. The LVEF and systolic but not diastolic blood pressure were significantly decreased at the time of admission, as compared with the tests in the control group I and the patient group after full recovery ( $P < 0.05$  for both observations). At the time of admission, troponin I, creatine kinase-myoglobin (CK-MB), and  $\beta$ -natriuretic peptide (BNP) were significantly increased as compared with the tests in control groups I and II ( $P < 0.05$  for both groups) (Figure 1).

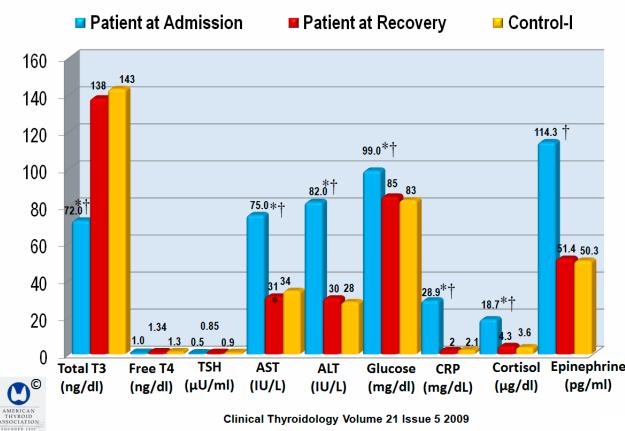
At the time of hospital admission, 62.2% of the patient group had ESS, with significantly decreased serum total T<sub>3</sub> levels but

**Baseline Characteristics and Cardiac Parameters in Patient, Control-I and Control-II Groups**



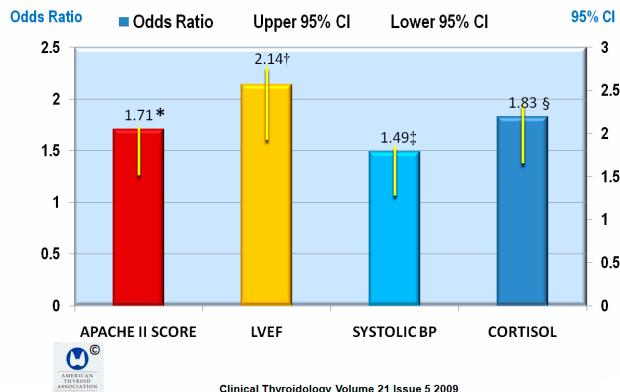
**Figure 1.** Troponin, serum CK-MB and BNP were significantly increased (\* $P < 0.05$ ) at the time of admission vs. control group I and vs. control group II; † $P < 0.05$ ). Systolic blood pressure (BP) levels were significantly suppressed in patients at the time of admission vs. patients at full recovery and subjected in both control groups (derived from data in Table 1 of Lee et al.).

**The Levels of Thyroid Hormones and Biochemical Markers in Patient, Control-I and Control-II Groups**



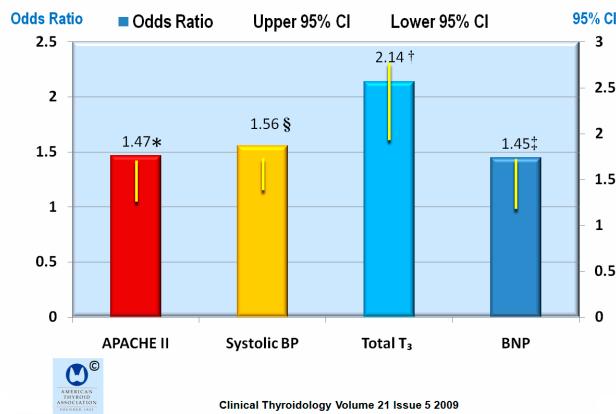
**Figure 2.** In addition to the levels shown, those of norepinephrine and dopamine were also significantly elevated at the time of admission as compared with the patient group at full recovery and control groups I and II. \* $P < 0.05$ . † $P < 0.05$ . (Derived from data in Table 2 of Lee et al.).

### Multivariate Analysis Results of Association of $T_3$ at Admission with Variables



**Figure 3.** Multivariate analysis findings are expressed as odds ratios for an association of serum  $T_3$  at the time of hospital admission as compared with APACHE scores. LVEF = left ventricular ejection fraction; BP = systolic blood pressure at the time of admission. \*P = 0.037. †P = 0.015. ‡P = 0.041. §P = 0.026. All P values are for significance of odds ratio.

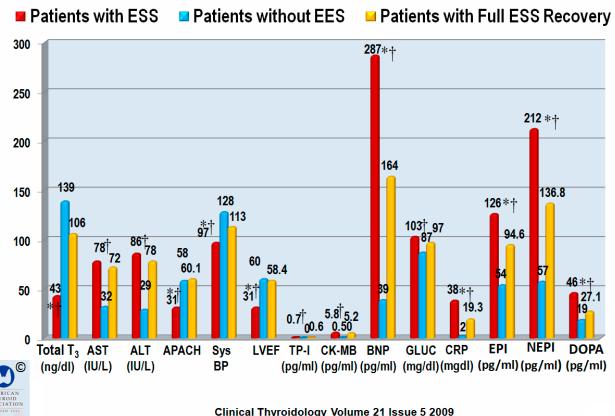
### Multivariate Analysis Results of Association of $T_3$ at Admission with Variables



**Figure 4.** Multivariate analysis findings for an association of LVEF at the time of admission as compared with other patient and laboratory variables at the time of admission. \*P = 0.032. †P = 0.028. ‡P = 0.015. §P = 0.04. BNP =  $\beta$ -natriuretic peptide.

normal  $T_4$  and TSH levels ( $P < 0.05$ ), as compared with those in control group I and the patient group at the time of full recovery. In addition, antithyroid peroxidase antibody (TPOAb) positivity but not titer was significantly elevated as compared with control group I ( $P < 0.05$ ). Also at the time of admission, the serum levels of alanine amino transferase (ALT) aspartate transaminase (AST), glucose, C-reactive protein (CRP), and cortisol, were all significantly higher as compared with those in control group I and the patient group at the time of full recovery ( $P < 0.05$  for all); in addition, plasma levels of epinephrine, norepinephrine, and dopamine were all significantly higher at admission as compared with the levels in patients at the time of full recovery (Figure 2).

### Baseline Characteristics and Cardiac Parameters of Patients with and without Euthyroid Sick Syndrome



**Figure 5.** Baseline characteristics for patients with ESS showing serum aspartate transaminase (AST), alanine transaminase (ALT), APACHE II (APACH) systolic blood pressure (Sys BP) LVEF left ventricular ejection time, troponin I (TPI),  $\beta$ -natriuretic peptide (BNP), C-reactive protein (CRP) epinephrine (EPI), norepinephrine (NEPI), and dopamine (DOPA) See Figure 1 legend for P values. (Derived from Tables 3 and 4 of Lee et al.)

Multivariate analysis found that total  $T_3$  levels at the time of admission were significantly associated with the APACHE II score (odds ratio [OR], 1.71; 95% confidence limits [CI], 1.52 to 2.08;  $P = 0.037$ ), LVEF (OR, 2.14; 95% CI, 1.93 to 2.78;  $P = 0.015$ ), systolic blood pressure (OR, 1.49; 95% CI, 1.28 to 1.86;  $P = 0.041$ ), and cortisol (OR, 1.83; 95% CI, 1.66 to 2.34;  $P = 0.026$ ) (Figure 3). In control group II, the total  $T_3$  levels were not associated with any variables by multivariate analysis, nor did the free thyroxine and TSH levels have any relation to the clinical or biochemical parameters in the patients or in control groups II and II. (Figure 4)

After the patient group was classified into two subgroups, the ESS group ( $n = 28$ ) and non-ESS group ( $n = 17$ ), the time of hospitalization was found to be longer in the ESS group ( $25 \pm 12$  vs.  $20 \pm 8$  days), and the APACHE II score, systolic BP, LVEF, troponin, CK-MB, and BNP were all significantly different in the ESS and non-ESS groups ( $P < 0.05$ ) (Figure 5).

When the patient group was subclassified into one with ( $n = 27$ ) and one without ( $n = 18$ ) myocardial dysfunction, the following were found to be significantly different in the two groups: APACHE II score, systolic blood pressure, troponin I, CK-MB, and BNP ( $P < 0.05$ ). In each subgroup, systolic blood pressure, troponin I, CK-MB, and BNP levels at the time of admission were also significantly different at the time of admission as compared with the same variables in the full-recovery group ( $P < 0.05$  for all). At the time of admission, serum total  $T_3$  levels were significantly decreased in the myocardial dysfunction group as compared with the subjects without myocardial dysfunction ( $P < 0.05$ ). After full recovery, there was no difference in cardiac and biochemical markers between the patients and control group I, the ESS subgroups, and the myocardial dysfunction groups.

**CONCLUSION** The low serum  $T_3$  level of ESS is related to changes in stress cardiomyopathy.

**COMMENTARY**

Endocrinologists are likely not to be familiar with stress cardiomyopathy, largely because it seems to be so far from our day-to-day activities. However, this article by Lee et al. brings this syndrome to our attention. In the early 1990s, Japanese physicians began reporting a unique, reversible cardiomyopathy that seemed to be precipitated by acute emotional stress (1). The stress cardiomyopathies as a group appear similar in that they seem to occur during times of enhanced sympathetic tone and may be precipitated by catecholamine stimulation of the myocardium. This syndrome was initially given the name Takotsubo cardiomyopathy (TC), but more recently has been referred to as apical ballooning syndrome or broken heart syndrome. The syndrome now has been reported worldwide and has been acknowledged by the American Heart Association as a unique form of reversible cardiomyopathy (2). In a systematic review, women 62 to 75 years of age accounted for 82% to 100% of patients with TC, but the syndrome has been described in individuals from 10 to 91 years of age (3). The presentation of TC is usually similar to an acute coronary syndrome with ischemia-like chest pain and abnormal ECG changes mimicking ischemia. Precipitants of stress cardiomyopathy include acute emotional stress, acute intracranial events, and acute medical illness, including sepsis, surgical procedures, and overproduction of catecholamines (pheochromocytoma). Apical and midventricular

left ventricular dysfunction is common but this may extend to global left ventricular hypokinesis. The formal diagnostic criteria have not yet been fully accepted, but include transient left ventricular motion abnormalities, absence of obstructive coronary artery disease, and new electrocardiographic abnormalities.

It has long been recognized that thyroid disease exerts serious effects on the heart and cardiovascular system (4), and the role of serum T<sub>3</sub> is becoming more prominent in this disorder. Iervasi and the cardiothoracic research group from Pisa have shown that low serum T<sub>3</sub> levels are the most significant predictor of cardiovascular and all-cause mortality in patients with heart disease. A recently published randomized, placebo-controlled study by the group (5) has shown that short-term levothyroxine-replacement therapy significantly improves the neuroendocrine profile and ventricular performance of patients with chronic heart failure.

The main findings in the study by Lee et al. are that low serum T<sub>3</sub> levels with normal free T<sub>4</sub> and TSH levels were associated with a decrease in the LVEF, which supports the notion that low total T<sub>3</sub> levels are correlated with myocardial contractility and dysfunction in patients with stress cardiomyopathy and reinforces the idea that ESS may play a major role in stress cardiomyopathy.

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**References**

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