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BRIEF REPORT

Effects of Thyroxine Therapy on Right Ventricular Systolic and Diastolic Function in Patients with Subclinical Hypothyroidism: A Study by Pulsed Wave Tissue Doppler Imaging

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Introduction: The effects of L-thyroxine (L-T_4) replacement for subclinical hypothyroidism (SH) on right ventricle (RV) functions has not been previously studied by means of pulsed wave tissue Doppler imaging (PWTDI). We investigated the effects of L-T_4 therapy on RV function in patients with SH using PWTDI.

Patients and Methods: Fifty-three patients with newly diagnosed SH and 25 controls were evaluated by standard echocardiography and PWTDI. After euthyroidism was restored by L-T_4, measurements were repeated. Myocardial systolic wave (S_m) velocity, isovolumic acceleration (IVA), myocardial precontraction time (PCT_m), and PCT_m to contraction time (CT_m) ratio were calculated as systolic indices. Early (E_m) velocity, late (A_m) velocity, E_m to A_m ratio, and myocardial relaxation time (RT_m) were determined as diastolic measurements.

Results: S_m was similar in patients and controls, whereas IVA was significantly lower in patients with SH ($P < 0.001$). SH patients had significantly decreased E_m velocity, whereas A_m velocity and E_m to A_m ratio did not differ. PCT_m and RT_m were significantly longer, and PCT_m to CT_m ratio was significantly higher in patients ($P = 0.002$, $P = 0.002$, $P < 0.001$, respectively). S_m velocities were similar before and after L-T_4 replacement, whereas IVA significantly increased after therapy ($P < 0.001$). E_m tended to increase ($P = 0.05$), whereas A_m and E_m to A_m ratio were not changed. PCT_m, PCT_m to CT_m ratio, and RT_m decreased significantly ($P < 0.001$ for all).

Conclusions: SH is associated with RV systolic and diastolic dysfunction, and L-T_4 treatment improves these abnormalities. PWTDI, especially IVA, may be a suitable tool for the early detection of RV systolic dysfunction. **(*J Clin Endocrinol Metab* 91: 3490–3493, 2006)**

SUBCLINICAL HYPOTHYROIDISM (SH) is a common disorder with a prevalence ranging from 1 to 10% of the adult population, characterized by an elevated level of TSH but normal free T_3 and free T_4 concentrations, usually in the absence of clinical symptoms (1). SH-associated cardiovascular dysfunction has been increasingly recognized in recent years (2–4). Decreased thyroid hormone level is associated with poor left ventricular (LV) contractility and relaxation, and most of these alterations reverse by L-thyroxine (L-T_4) therapy (3–5).

Recently, there has been considerable interest in the assessment of right ventricle (RV) function. Because of the complex geometric shape, standard echocardiography might fail in reliable assessment of RV function. Myocardial velocity measurement by pulsed wave tissue Doppler imaging (PWTDI) is virtually independent of ventricular shape and thus might be a valid marker of RV functions (6, 7). Although several reports documented the association of SH and LV function by PWTDI, only two studies investigated the RV function in patients with SH (2, 8–11). To our knowledge, the effect of L-T_4 replacement therapy on RV function in patients with SH has not been studied yet. In this study, we assessed RV functions using PWTDI in patients with SH before and after L-T_4 replacement therapy.

Patients and Methods

This prospective study was conducted at a thyroid outpatient clinic. The study protocol was approved by the local ethics committee, and informed consent was obtained from all participants.

Fifty-three patients with newly diagnosed SH due to Hashimoto's thyroiditis were enrolled. The control group (n = 25) consisted of healthy individuals with normal TSH, serum antithyroglobulin (anti-Tg), and antithyroid peroxidase (anti-TPO) antibody levels matched for age, sex, and body mass index (BMI). The exclusion criteria were pregnancy, hepatic or renal dysfunction, hypertension, heart failure, ischemic or valvular heart disease, atrial fibrillation, respiratory disease, pulmonary hypertension, diabetes mellitus; significant neurological or psychological disease, and malignancy. None of the subjects received medications that can alter heart rate and serum thyroid hormone concentrations.

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Abbreviations: A, Late; A_m, late myocardial; anti-Tg, antithyroglobulin; anti-TPO, antithyroid peroxidase; BMI, body mass index; CT_m, myocardial contraction time; DT, deceleration time; E, early; E_m, early myocardial; IVA, isovolumic acceleration; L-T_4, L-thyroxine; LV, left ventricular; PAP, pulmonary artery pressure; PCT_m, myocardial precontraction time; PWTDI, pulsed wave tissue Doppler imaging; RT_m, myocardial relaxation time; RV, right ventricle; SH, subclinical hypothyroidism; S_m, myocardial systolic wave.

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Medical history, physical examination, electrocardiogram, and chest radiogram were normal for all participants. Fasting venous blood samples were drawn between 0800 and 0900 h. Free T_3, free T_4, and TSH levels were determined by immunometric assays (Diagnostic Products Corp., Los Angeles, CA). Anti-Tg and anti-TPO levels were measured with RIAs (Dynotest; Brahms, Berlin, Germany). The normal ranges for free T_3, free T_4, TSH, anti-TPO, and anti-Tg are 3–6.5 pmol/liter, 10–22 pmol/liter, 0.3–4.5 mIU/ml, 5–34 IU/ml, and 10–115 IU/ml, respectively.

SH was diagnosed on the basis of elevated serum TSH and normal free T_3 and T_4 levels in two different measurements 4 wk apart. All patients were positive for both anti-Tg and anti-TPO autoantibodies.

After baseline assessment, patients with SH were assigned to receive L-T_4 replacement starting with 25 μg/d. TSH was measured every 8 wk for dose adjustment. Euthyroid state was achieved with a mean dose of 68 μg/d in 16.8 ± 4.4 wk. Six months after restoration of euthyroidism, patients were reevaluated.

Two blinded sonographers performed the echocardiographic examinations using Vingmed System 7 (Vivid 7; GE, Horten, Norway), according to the recommendations of the American Society of Echocardiography (12). Tricuspid inflow velocities were obtained by pulsed wave Doppler recording in apical four-chamber view, placing the sample volume at the tips of the tricuspid valve leaflets. The peak early (E; meters per second) and late (A; meters per second) tricuspid inflow velocities and E wave deceleration time (DT; milliseconds) were measured.

A 3-mm sample volume was placed at the level of basal RV free wall in four-chamber apical view. Three waves were obtained in each cycle: a systolic wave (S_m), an early diastolic wave (E_m), and a late diastolic wave (A_m). Isovolumic acceleration (IVA) (precedes S_m and begins before the R wave on electrocardiogram) was calculated by dividing myocardial peak velocity during isovolumic contraction by the time interval from the onset of this wave to the time at peak velocity. Peak S_m (centimeters per second), E_m (centimeters per second), and A_m (centimeters per second) velocities, their ratio (E_m to A_m), IVA (meters per second squared), myocardial precontraction time (PCT_m; milliseconds; from the onset of electrocardiogram QRS to the beginning of S_m), contraction time (CT_m; milliseconds; from the beginning to the end of S_m), their ratio (PCT_m to CT_m), and myocardial relaxation time (RT_m; milliseconds; time interval between the end of S_m and the onset of E_m) were calculated. All measurements were averaged for three consecutive cycles.

Statistical analysis

All continuous data were expressed as mean ± SD. Data were analyzed by SPSS (version 11.0; SPSS Inc., Chicago, IL). χ^2 analysis was used to assess the differences between dichotomous variables. Comparisons between controls and patients were performed by independent-samples *t* test. Data before and after L-T_4 therapy were compared by paired samples *t* test. Correlations were determined by the Pearson rank correlation test. $P < 0.05$ was considered significant.

Results

The clinical and echocardiographic characteristics of the study population are shown in Table 1. TSH levels were significantly higher in patients than controls with comparable free thyroid hormone levels. Peak E inflow velocity and peak E to A ratio were significantly lower, DT was significantly prolonged, and peak A inflow velocity was significantly higher in patients with SH. Other standard echocardiographic parameters were similar among the two groups.

CT_m, E_m velocity, and IVA were significantly lower in patients with SH. A_m and S_m velocities and E_m to A_m ratio did not differ among the two groups. PCT_m, RT_m, and PCT_m to CT_m ratio were significantly higher in SH patients.

The thyroid hormone levels and echocardiographic variables after L-T_4 therapy are shown in Table 2. Heart rate, BMI, and blood pressures were similar before and after L-T_4 therapy (data not shown). RV diastolic dimension, RV wall thickness, and pulmonary artery pressures (PAP) were similar after treatment. Peak E inflow velocity, IVA, E_m velocity, and CT_m increased, whereas peak A inflow velocity, E to A ratio, DT, S_m velocity, A_m velocity, and E_m to A_m ratio did not

TABLE 1. The clinical and echocardiographic characteristics of the patients and controls

Parameters	Patients with SH (n = 53)	Control subjects (n = 25)	*P* value
Age (yr)	45.6 ± 10.8	44.4 ± 10.5	0.64
Gender (male/female)	4/49	2/23	0.94
BMI (kg/m^2)	28.3 ± 5.3	27.8 ± 3.8	0.66
SBP (mm Hg)	118.7 ± 13.3	121.6 ± 7.3	0.31
DBP (mm Hg)	75.8 ± 9.3	78.4 ± 7.2	0.23
Heart rate (beats/min)	72.4 ± 10.9	68.4 ± 8.5	0.11
TSH (mIU/ml)	11.1 ± 6.8	2.1 ± 1.3	<0.001
Free T_3 (pmol/liter)	4.6 ± 0.6	4.5 ± 0.8	0.35
Free T_4 (pmol/liter)	13.4 ± 1.9	14.4 ± 3.1	0.07
RVEDD (mm)	19.3 ± 1.0	19.8 ± 1.7	0.07
RVFWT (mm)	2.8 ± 0.4	2.8 ± 0.5	0.47
PAP (mm Hg)	23.0 ± 2.9	23.6 ± 2.7	0.45
E wave (m/sec)	0.63 ± 0.17	0.72 ± 0.14	0.023
A wave (m/sec)	0.66 ± 0.14	0.57 ± 0.15	0.008
E to A ratio	0.97 ± 0.3	1.33 ± 0.3	<0.001
DT (msec)	224.8 ± 33.5	201.0 ± 9.8	0.001
Tissue Doppler echocardiographic variables			
S_m (cm/sec)	13.0 ± 2.0	13.9 ± 1.7	0.067
IVA (m/sec^2)	4.2 ± 1.0	5.2 ± 0.9	<0.001
E_m (cm/sec)	12.3 ± 2.6	14.2 ± 3.3	0.005
A_m (cm/sec)	14.1 ± 3.1	15.0 ± 3.7	0.24
E_m to A_m ratio	0.9 ± 0.3	1.0 ± 0.3	0.21
PCT_m (msec)	88.3 ± 14.7	77.2 ± 12.6	0.002
CT_m (msec)	270.5 ± 29.1	292.4 ± 18.9	0.001
PCT_m to CT_m ratio	0.33 ± 0.06	0.27 ± 0.05	<0.001
RT_m (msec)	85.7 ± 19.1	73.2 ± 7.6	0.002

SBP, Systolic blood pressure; DBP, diastolic blood pressure; RVEDD, RV end diastolic dimension; RVFWT, RV free wall thickness.

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TABLE 2. Effects of L-T_4 therapy on thyroid hormone levels and echocardiographic variables of the RV in patients with SH

Parameters	Before therapy	After therapy	*P* value
TSH (mIU/ml)	11.1 ± 6.8	2.9 ± 0.9	<0.001
Free T_3 (pmol/liter)	4.6 ± 0.6	4.8 ± 1.1	0.308
Free T_4 (pmol/liter)	13.4 ± 1.9	16.9 ± 4.1	<0.001
RVEDD (mm)	19.3 ± 1.0	19.3 ± 1.1	0.659
RVFWT (mm)	2.8 ± 0.4	2.8 ± 0.3	0.070
PAP (mm Hg)	23.0 ± 2.9	22.8 ± 2.9	0.746
E wave (m/sec)	0.63 ± 0.17	0.72 ± 0.14	0.001
A wave (m/sec)	0.66 ± 0.14	0.70 ± 0.16	0.103
E to A ratio	0.97 ± 0.3	1.08 ± 0.3	0.052
DT (msec)	224.8 ± 33.5	221.4 ± 34.6	0.450
Tissue Doppler echocardiographic variables			
S_m (cm/sec)	13.0 ± 2.0	13.3 ± 2.0	0.24
IVA (m/sec^2)	4.2 ± 1.0	5.2 ± 1.2	<0.001
E_m (cm/sec)	12.3 ± 2.6	12.9 ± 2.5	0.05
A_m (cm/sec)	14.1 ± 3.1	14.5 ± 2.8	0.35
E_m to A_m ratio	0.9 ± 0.3	0.9 ± 0.2	0.77
PCT_m (msec)	88.3 ± 14.7	78.5 ± 12.1	<0.001
CT_m (msec)	270.5 ± 29.1	289.3 ± 28.3	<0.001
PCT_m to CT_m ratio	0.33 ± 0.06	0.27 ± 0.06	<0.001
RT_m (msec)	85.7 ± 19.1	69.4 ± 15.7	<0.001

RVEDD, RV end diastolic dimension; RVFWT, RV free wall thickness.

change after therapy. PCT_m, PCT_m to CT_m ratio, and RT_m decreased significantly.

There was a weak negative correlation between TSH and E to A ratio ($r = -0.23$, $P = 0.042$), IVA ($r = -0.24$, $P = 0.037$), S_m ($r = -0.25$, $P = 0.026$), and E_m velocities ($r = -0.27$, $P = 0.019$) and a weak to moderate positive correlation between TSH and DT ($r = 0.29$, $P = 0.011$), PCT_m ($r = 0.29$, $P = 0.01$), PCT_m to CT_m ratio ($r = 0.40$, $P < 0.001$), and RT_m ($r = 0.35$, $P = 0.002$).

Discussion

Hypothyroidism can affect myocardial function by decreasing the activity of some enzymes involved in intracellular calcium handling and changing the contractile protein expression (13, 14). SH can alter collagen, myocardial fiber orientation, tissue water content, and capillary blood flow distribution (5). Recent argument is that SH is a mild form of thyroid failure associated with initial signs of cardiovascular hypothyroidism. Although benefits and risks of L-T_4 therapy for SH have been discussed for two decades, the indication is still controversial (1, 3, 15).

Lack of thyroid hormones is associated with poor LV contractility and relaxation (2–5). Several studies using conventional echocardiography and PWTDI investigated the effects of L-T_4 therapy on LV functions in patients with SH, and controversial results have been reported (4, 8, 9, 16). To date, only two studies have investigated RV functions in patients with SH (10, 11). However, these studies did not examine the effects of L-T_4 therapy.

In our study, among the indices of RV systolic function, IVA and CT_m were significantly reduced, whereas PCT_m and PCT_m to CT_m ratio were significantly prolonged in SH patients. These suggest RV contractile dysfunction. S_m velocities were similar in controls and patients and did not change after L-T_4 therapy, whereas IVA and CT_m significantly increased. PCT_m and PCT_m to CT_m ratio significantly decreased after L-T_4 therapy. These results are in contrast to a previous study by Kosar *et al.* (11), who reported that RV systolic functions were preserved in SH patients. Conflicting results might be related to differences in patient selection (age, inclusion of patients with previous hyperthyroidism, small sample size, and etiology of SH). We strictly selected newly diagnosed stable SH patients without history of thyroid disorders. Furthermore, we used somewhat different methods to assess RV systolic function. Although S_m velocities were similar among patients and controls in both studies, we found that IVA was lower in the SH patients. Moreover, IVA increased significantly with L-T_4 therapy, whereas S_m velocities remained unchanged. Recently it has been shown that IVA is a sensitive index of RV contractile function that is unaffected by ventricular shape or loading conditions (17, 18). It may be suggested that IVA reflects an earlier isovolumic event and is more sensitive to changes in contractile state than S_m velocities. IVA can be used as a practical, noninvasive parameter for early determination of RV contractile dysfunction in SH patients. Thyroid disease may affect RV contractile functions by altering PAP, but in our study PAP was not changed by L-T_4 therapy. These findings may suggest that the favorable effect of L-T_4 therapy is directly on myocardium, not on PAP.

In our study, the lower peak E inflow velocity, E to A ratio, and E_m velocity and prolonged DT and RT_m in patients with SH indicate RV diastolic dysfunction. These results are consistent with the findings of Kosar *et al.* (11). After L-T_4 therapy, peak E inflow velocity was significantly increased, E_m velocity slightly increased, and RT_m significantly decreased, but peak A inflow velocity, E to A ratio, and DT did not change. These findings suggest the reversibility of RV diastolic dysfunction after L-T_4 therapy. Right atrial filling pressures might be changed by thyroid status and alter RV diastolic functions. E to E_m ratio is a valuable index to estimate right atrial filling pressures (19). E to E_m ratios were unaffected by L-T_4 therapy in our patients; thus, improvement in diastolic functions cannot be attributed to right atrial filling pressures. SH may impair diastolic function directly by the reduction of sarcoplasmic reticulum calcium-adenosine

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triphosphatase enzyme activity and the hyperexpression of phospholamban, its negative regulatory protein (20). We cannot explain why only some parameters are normalized with L-T_4 therapy. Probably it takes longer for some parameters to normalize after euthyroid state is achieved.

The small number of patients is a limitation of our study; also velocities measured by PWTDI are limited by rotational and restraining forces in the contracting and relaxing heart. Strain rate imaging is a new technology that measures segmental tissue deformation and may be useful in resolving these limitations.

In conclusion, this is the first study specifically examining the effects of L-T_4 therapy on RV function using PWTDI in patients with SH. PWTDI might be a reliable and simple tool in diagnosis and follow-up of RV dysfunction in SH patients. IVA may be a useful parameter and an early indicator for evaluating RV systolic dysfunction. Our data suggest that SH is a condition of minimal tissue hypothyroidism rather than a compensated state and is associated with RV systolic and diastolic dysfunction that may be reversible by a substitutive L-T_4 therapy.

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