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The effect of L-thyroxine treatment on ventricular dysfunction and pulmonary arterial stiffness in patients with subclinical hypothyroidism

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Abstract. – OBJECTIVE: In our study, we aimed at evaluating the change in biventricular functions and pulmonary arterial stiffness (PAS) in patients with subclinical hypothyroidism (SH) in whom euthyroidism was achieved with L-thyroxine therapy.

PATIENTS AND METHODS: 70 SH patients and 75 healthy volunteers were included in our study consecutively. Baseline demographic and echocardiographic data of the participants were recorded. The data obtained in the control evaluation 6 months after the euthyroidism were achieved in the SH group patients started on L-thyroxine treatment and then compared with the baseline measurements.

RESULTS: The mean age of patients in the SH group was 44.1 ± 9.4 years and 47.1% were women. Euthyroidism in SH patients was achieved with a mean daily L-thyroxine treatment of 59 μg/day for a mean of 16.1 ± 4.5 weeks. Positive changes in metabolic and hormonal profiles were achieved after L-thyroxine treatment in SH patients. It was determined that left ventricular and right ventricular isovolumetric relaxation and myocardial performance index were higher in SH patients compared to the control group, and these measurements were observed to decrease significantly with L-thyroxine treatment ($p < 0.05$ for each). While PAS was 16.9 ± 3.1 kHz/ms in the control group, it was 25.2 ± 5.3 kHz/ms in the SH group ($p < 0.05$). After L-thyroxine treatment, PAS measurements decreased to 17.2 ± 3.2 kHz/ms ($p < 0.05$) in the SH group and showed a positive change. Thyroid-stimulating hormone (TSH) change (Δ TSH) with Δ E/A ratio (r: -0.407, $p < 0.001$), right ventricular myocardial performance index (Δ RV MPI) change (r: 0.404, $p < 0.001$) and PAS change (Δ PAS) (r: 0.458, $p < 0.001$) found to be correlated.

CONCLUSIONS: SH is associated with dysfunction in the biventricular and pulmonary vascular bed. Biventricular functions and PAS change positively in SH patients with L-thyroxine treatment.

Key Words:
L-thyroxine treatment, Pulmonary arterial stiffness, Subclinical hypothyroidism, Ventricular dysfunction.

Introduction

Subclinical hypothyroidism (SH) is a biochemical definition that can be observed in 4-10% of the general population, in which serum thyroid-stimulating hormone (TSH) levels are high (> 4 mIU/L), free triiodothyronine (FT3) and free thyroxine (FT4) hormone levels are within normal limits[1,2]. Thyroid hormones can cause important functional changes in the cardiovascular system by the transcription of some structural and regulatory proteins and/or hemodynamic changes in arterial wall smooth muscles and/or predisposing to chronic inflammatory processes[3-6]. SH has been identified as an independent risk factor for cardiovascular diseases, as well as being associated with many cardiovascular diseases[3]. It has been previously shown that SH can have adverse effects on right ventricular (RV) and left ventricular (LV) systolic, diastolic and global functions[6]. It has even been found that these negative effects can be improved with L-thyroxine treatment[7,8].

Global myocardial performance index (MPI) (Tei index) is an echocardiographic parameter used to evaluate left ventricular systolic and diastolic functions together. It has been previously demonstrated that MPI predicts morbidity and mortality in patients with cardiovascular pathologies[9]. Scholars[10] have shown that MPI in SH patients is higher than in healthy participants in the control group and that MPI value may improve after L-thyroxine treatment.

Pulmonary arterial stiffness (PAS) indicates the functional and structural status of the pulmonary vascular bed. It has previously been shown to be successful in demonstrating adverse cardiovascular outcomes[11]. In literature, changes in RV and LV systolic, diastolic, and global functions in SH patients and the positive effects of L-thyroxine treatment in these patient groups have been shown. However, there

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is no study evaluating the PAS measurement in SH patients and investigating the effect of L-thyroxine treatment on PAS. In our study, we aimed at evaluating the relationship of SH with ventricular functions and PAS and to examine the changes in these parameters after euthyroidism was achieved with L-thyroxine treatment.

Patients and Methods

Study Design

Our study included SH patients aged 18 and over, newly diagnosed in endocrinology and internal medicine clinics, referred to our cardiology outpatient clinics due to cardiovascular risk assessment and/or planned outpatient follow-up, and healthy participants with similar demographic characteristics as the control group. Inclusion criterion for the SH group: not receiving thyroid hormone replacement therapy. Exclusion criteria were determined as: pregnancy, malignancy, coronary artery disease, cardiomyopathies, moderate/severe valve diseases, cardiac arrhythmias, diabetes mellitus, hypertension, kidney or liver failure, chronic lung disease, and drug use history that may affect thyroid hormone levels. The same exclusion criteria were applied to healthy participants. Subjects over 60 years of age and participants with significant hypothyroidism (TSH level equal to or greater than 10 mIU/L) were excluded from the study because they had been previously reported to be at high risk of diastolic dysfunction[12]. It has been previously shown that obesity can increase TSH and FT3 levels independently of autoimmune thyroiditis and hypothyroidism[13]. Therefore, patients with BMI > 30 kg/m^2 were not included in our study. In our previous study, in which we evaluated the relationship between left ventricular dysfunction and fragmented QRS in patients with subclinical hypothyroidism, those who needed L-thyroxine treatment were determined[14]. Additional patients who needed L-thyroxine treatment from the internal medicine clinic in accordance with our study protocol were also included in our study. After applying the inclusion and exclusion criteria, 75 SH patients and 75 healthy volunteers who were similar in terms of the age-sex-body mass index (BMI) were included in the study. Patients with SH were classified according to their etiology as follows: (I) SH occurring after thyroidectomy (n = 9) (II) SH due to Hashimoto's thyroiditis (n = 56), (III) SH due to other causes (not due to surgery and with negative thyroid autoantibodies) (n = 10).

SH was defined as the TSH level > 4.0 mIU/L, FT3 and FT4 values within normal limits in 2 separate fasting blood samples taken 2 to 6 weeks apart[15]. Baseline demographic and echocardiographic data of the participants were recorded. Fasting venous blood samples were taken between 08:00 and 09:00 in the morning. Serum TSH, FT3, and FT4 levels were measured by electrochemiluminescence immunoassay (ECLIA) on a Cobos e601 analyzer (Roche HITACHI, Germany). BMI (kg/m²) of the study and control groups were calculated. Thyroid hormone normal ranges were accepted as TSH: 0.36-4.0 mIU/L, FT4: 7.64-19.7 pmol/L, FT3: 3.5-7.9 pmol/L.

In SH group patients who were treated with 25 µg/day of L-thyroxine daily, the data obtained in the control evaluation 6 months after euthyroidism was achieved by dose titration every 8 weeks were compared with baseline measurements. The data of 5 patients who did not attend recommended follow-up visits in accordance with our study protocol or who did not regularly use/tolerate the recommended L-thyroxine treatment were not included in the analysis. As a result, 70 patients in the SH group and 75 patients in the control group were evaluated in the analyses. The relationship between TSH change (Δ TSH) and PAS change (Δ PAS) and demographic and echocardiographic data was evaluated by correlation analysis.

Echocardiographic Measurements

All echocardiographic examinations were performed by experienced operators (Vivid S5, GE, Horten, Norway) blinded to the data of the patients included in the study. Echocardiographic measurements were taken in the left lateral decubitus position after the patients rested for at least 15 minutes. All measurements were taken in at least three consecutive cycles and mean values were calculated. All echocardiographic evaluations were performed according to the recommendations of the European Association of Cardiovascular Imaging/American Society of Echocardiography[16].

Ejection fraction was calculated using the modified Simpson's method. Left ventricular end-diastolic and end-systolic diameters (LVEDD, LVESD) were measured from the parasternal long-axis view with M-mode. Left ventricular end-systolic and end-diastolic volumes were measured from apical four-chamber and two-chamber views. RV end-diastolic di-

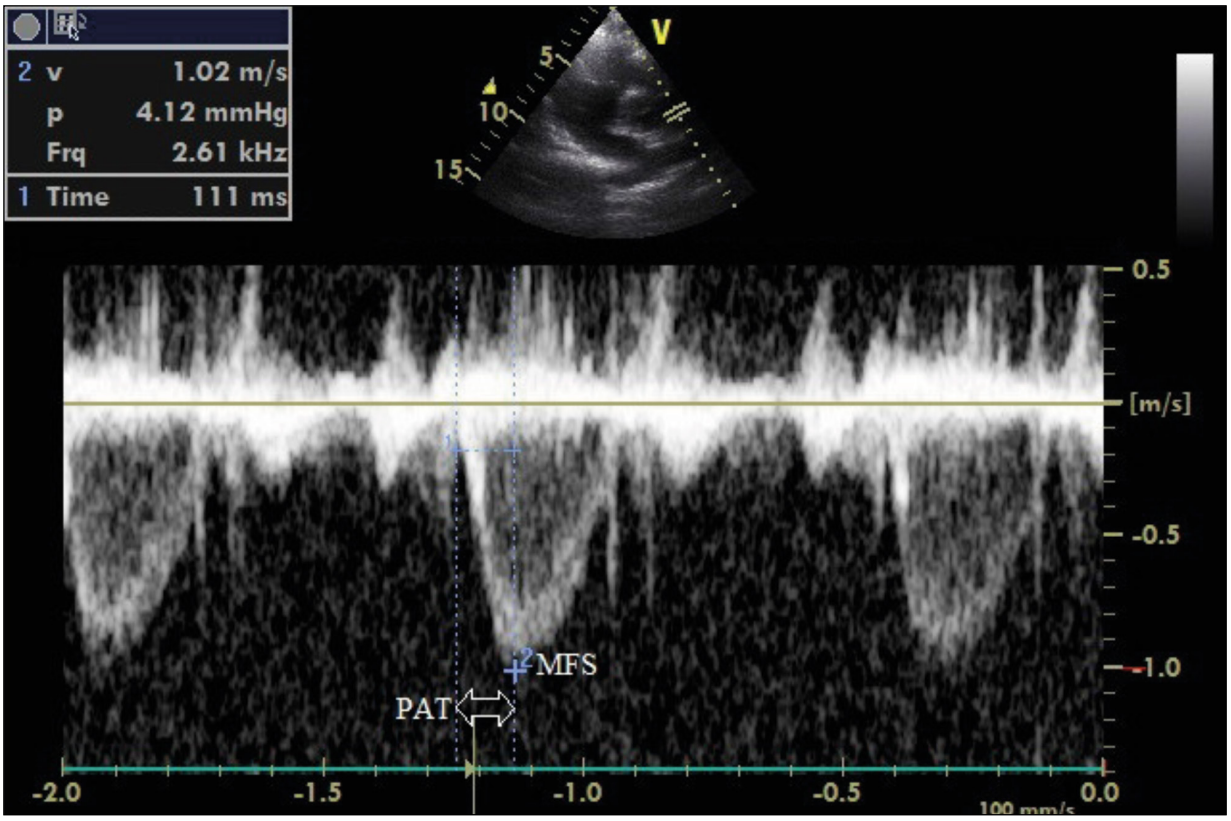

Figure 1. Measurement of pulmonary arterial stiffness (PAS) by echocardiography.
PAS (kHz/ms) = maximum frequency shift (MFS)/pulmonary flow acceleration time (PAT).

ameter was calculated from the basal segment in apical four-chamber view. RV end-diastolic and end-systolic areas (RVEDA, RVESA) were calculated from the apical four-chamber view. RV fractional area change (RVFAC) was calculated with the formula (RVEDA-RVESA)/RVEDA. Tricuspid annular plane systolic excursion (TAPSE) was measured as the distance at which the tricuspid annular ring was displaced between end-systole and end-diastole in M-mode imaging. RV peak systolic S velocity was calculated by pulsed wave (PW) tissue Doppler imaging (TDI) of the lateral tricuspid annulus. Mean pulmonary artery pressure (mPAP) was calculated from systolic PAP (sPAP) with the formula: mPAP = 0.61 × sPAP + 2 mmHg[17]. LV and RV MPI were calculated with the formula: isovolumic contraction time (IVCT) + isovolumic relaxation time (IVRT)/ejection time (ET). The components of the MPI formula were evaluated by PW TDI.

PW Doppler recordings of pulmonary artery blood flow were taken 1 cm below the pulmonary valve ring in parasternal short-axis view. Peak velocity of pulmonary flow (maximum frequency shift = MFS) and time to peak from the onset of pulmonary flow ejection (pulmonary flow acceleration time = PAT) were calculated by averaging at least three consecutive beat measurements. PAS (kHz/ms) calculated with the formula: maximum frequency shift (MFS) / pulmonary flow acceleration time (PAT)[11] (Figure 1).

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences 21.0 (SPSS, IBM Corp., Armonk, NY, USA) package program. Numerical variables were expressed as mean ± standard deviation (SD), categorical variables as numbers (n) and percentages (%). The conformity of the data to the normal distribution was determined by the Kolmogorov-Smirnov test. The Chi-square test was used for categorical variables. Student's *t*-test was used to compare groups with normal distribution for numerical variables, and the Mann-Whitney U test was used for groups that did not show normal distribution. TSH change before and after L-thyroxine treatment was expressed as Δ TSH. The correlation between Δ TSH and changes (Δ) in other variables was evaluated.

Table I. Baseline and post-treatment demographic data of study patients.

Variables	Control group (n = 75)	SH pre-treatment (n = 70)	SH post-treatment (n = 70)
Age (years)	43.7 ± 9.4	44.1 ± 9.4	-
Gender (female), n (%)	36 (48%)	33 (47.1%)	-
Body mass index (kg/m²)	27.4 ± 4.2	27.3 ± 5.8	27.8 ± 3.9
Systolic blood pressure (mmHg)	118.9 ± 10.4	118.3 ± 10.9	120.3 ± 9.9
Diastolic blood pressure (mmHg)	73.1 ± 6.4	73.6 ± 6.6	72.7 ± 5.9
Total cholesterol (mg/dL)	167.06 ± 21.02[a,c]	186.72 ± 30.67[a,b]	173.21 ± 24.19[b,c]
LDL cholesterol (mg/dL)	103.61 ± 19.22[a]	117.34 ± 27.4[a,b]	103.51 ± 19.82[b]
HDL cholesterol (mg/dL)	48.43 ± 9.2	46.94 ± 9.6	48.12 ± 9.9
Triglycerides (mg/dL)	99.62 ± 24.16	103.76 ± 27.83	100.93 ± 26.82
Thyroid-stimulating hormone (mIU/L)	2.39 ± 0.87[a]	7.95 ± 1.44[a,b]	2.28 ± 0.7[b]
Free T3 (pmol/L)	4.66 ± 0.61	4.81 ± 0.94	4.70 ± 0.79
Free T4 (pmol/L)	13.26 ± 2.42	12.82 ± 2.73	13.69 ± 3.04
Heart rate (bpm)	75.6 ± 10.8	73.2 ± 11.1[b]	76.9 ± 10.7[b]

[a]: $p < 0.05$ for the numerical difference between the control group and the SH pre-treatment group. [b]: $p < 0.05$ for the numerical difference between the SH pre-treatment and SH post-treatment groups. [c]: $p < 0.05$ for the numerical difference between the control group and the SH post-treatment group. SH: Subclinical hypothyroidism, LDL: Low-density lipoprotein, HDL: High-density lipoprotein.

These relationships between numerical variables were evaluated with Pearson's correlation analysis. The relationship of high TSH measurements with high PAS measurements was evaluated with relative risk (RR) and odds ratio (OR). The hypotheses were two-sided and a p-value < 0.05 was considered statistically significant.

Results

The mean age of the control group participants included in our study was 43.7 ± 9.4 years, while the mean age of the SH patients was 44.1 ± 9.4 years. Euthyroidism in SH patients was achieved with a mean daily L-thyroxine treatment of 59 µg/day for a mean of 16.1 ± 4.5 weeks. The female gender was similar between the groups and was 47.1% in the SH group. There were no differences between the control and study groups in terms of BMI, systolic and diastolic blood pressures. Compared to the control group, SH patients had higher total cholesterol, low-density lipoprotein (LDL) cholesterol, and TSH hormone levels ($p < 0.05$ for each), and positive changes were achieved in this metabolic and hormonal profile after L-thyroxine treatment. There were no significant differences between the groups in other lipid profiles, FT3 and FT4 levels. It was determined that the heart rate increased significantly in the post-treatment SH group. Demographic and laboratory data of the control and SH groups before and after treatment are presented in Table I.

There were no significant differences between the groups in the diameters of the LV, LV ejection fraction (LVEF), interventricular septum, and left atrium (LA). The E wave was significantly lower in the pre-treatment SH group compared to the control and post-treatment SH groups. The A wave was significantly higher in the pre-treatment SH group than in the control and post-treatment SH groups. In addition, the E/A ratio was found to be significantly lower in the pre-treatment SH group compared to the control and post-treatment SH groups. LV and RV IVRT and MPI measurements were higher in the SH group than in the control group ($p < 0.05$ for each). It was observed that these measurements decreased significantly with L-thyroxine treatment ($p < 0.05$ for each). There were no significant differences between the groups in TAPSE, S', and FAC measurements expressing RV systolic functions. While there was no significant difference between mPAP groups, PAS was 16.9 ± 3.1 kHz/ms in the control group, while it was 25.2 ± 5.3 kHz/ms in the SH group ($p < 0.05$). After L-thyroxine treatment, PAS measurements decreased to an average of 17.2 ± 3.2 kHz/ms ($p < 0.05$) in the SH group and showed a positive change. Echocardiographic data of the control group and SH group before and after treatment are presented in Table II.

The correlation of Δ TSH before and after treatment with other demographic, laboratory, and echocardiographic data was evaluated. There was a significant positive correlation of Δ

Table II. Baseline and post-treatment echocardiographic data of study patients.

Variables	Control group (n = 75)	SH pre-treatment (n = 70)	SH post-treatment (n = 70)
LVEF (%)	61.2 ± 5.4	62.3 ± 5.7	63.1 ± 4.4
LVEDD (mm)	48.6 ± 8.1	47.9 ± 7.8	48.3 ± 8.5
LVESD (mm)	35.1 ± 5.2	34.8 ± 5.6	34.6 ± 5.7
LA (mm)	37.64 ± 5.32	37.25 ± 5.41	36.82 ± 6.02
IVS (mm)	9.82 ± 1.8	9.79 ± 1.6	9.86 ± 1.4
E (m/s)	0.94 ± 0.17[a]	0.78 ± 0.14[a,b]	0.96 ± 0.16[b]
A (m/s)	0.71 ± 0.13[a]	0.86 ± 0.16[a,b]	0.74 ± 0.14[b]
DT (ms)	191.4 ± 26.8	189.6 ± 26.4	190.8 ± 27.6
E/A ratio	1.41 ± 0.25[a]	1.14 ± 0.22[a,b]	1.39 ± 0.27[b]
LV IVRT (ms)	82.1 ± 16.9[a]	96.8 ± 18.8[a,b]	84.2 ± 17.7[b]
LV IVCT (ms)	54.6 ± 9.9	58.6 ± 11.2	55.2 ± 10.1
LV ET (ms)	290.6 ± 35.6	286.8 ± 38.2	289.8 ± 36.7
LV MPI	0.43 ± 0.09[a]	0.49 ± 0.11[a,b]	0.44 ± 0.08[b]
RVEDD (mm)	34.7 ± 6.3	35.2 ± 6.4	35.5 ± 5.9
RVESD (mm)	21.4 ± 4.7	20.9 ± 4.2	21.5 ± 4.6
TAPSE (mm)	20.9 ± 4.7	21.2 ± 4.9	21.5 ± 4.1
FAC (%)	50.6 ± 8.8	49.7 ± 8.9	50.4 ± 9.1
S' (cm/s)	15.1 ± 3.3	14.9 ± 3.7	14.8 ± 3.8
RV IVRT (ms)	63.3 ± 13.4[a,c]	80.5 ± 16.2[a,b]	74 ± 14.3[b,c]
RV IVCT (ms)	64.8 ± 14.2	66.2 ± 13.2	64.2 ± 14.6
RV ET (ms)	285.2 ± 36.7[a]	277.9 ± 37.8[a,b]	282.6 ± 36.1[b]
RV MPI	0.43 ± 0.08[a]	0.52 ± 0.09[a,b]	0.42 ± 0.08[b]
mPAP (mmHg)	22.6 ± 4.1	21.9 ± 4.3	22.8 ± 4.5
PAS (kHz/ms)	16.9 ± 3.1[a]	25.2 ± 5.3[a,b]	17.2 ± 3.2[b]

[a]: $p < 0.05$ for the numerical difference between the control group and the SH pre-treatment group. [b]: $p < 0.05$ for the numerical difference between the SH pre-treatment and SH post-treatment groups. [c]: $p < 0.05$ for the numerical difference between the control group and the SH post-treatment group. SH: Subclinical hypothyroidism, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LA: Left atrium, IVS: Interventricular septum, DT: Deceleration time, E: Early filling peak velocity, A, Late diastolic filling velocity, LV: Left ventricle, IVRT: Isovolumic relaxation time, IVCT: Isovolumic contraction time, ET: Ejection time, MPI: Myocardial performance index, RVEDD: Right ventricular end-diastolic diameter, RVESD: Right ventricular end-systolic diameter, TAPSE: Tricuspid annular plane systolic excursion, FAC: Fractional area change, S': Tricuspid lateral annulus systolic flow velocity, RV: Right ventricle, mPAP: Mean pulmonary arterial pressure, PAS: Pulmonary arterial stiffness.

TSH with Δ total cholesterol but not with Δ LDL. Δ TSH and Δ E (r: -0.321, *p:* 0.012), Δ E/A ratio (r: -0.407, $p < 0.001$), Δ RV MPI (r: 0.404, $p < 0.001$), and Δ PAS (r: 0.458, $p < 0.001$) were found to be significantly correlated. Δ LV and Δ RV IVRT were also observed to have a significant positive correlation with Δ TSH. Δ RV ET was observed to have a significant negative correlation with Δ TSH (r: -0.302, $p = 0.001$). The pre-and post-treatment change of PAS (Δ PAS) measurement, which is the focal point of our hypothesis, was determined and its correlation with other demographic, laboratory, and echocardiographic data was investigated. Δ PAS and Δ E/A ratio [r: -0.322, $p = 0.008$], Δ LV IVRT (r: 0.366, $p < 0.001$), Δ RV IVRT (r: 0.358, $p < 0.001$), and Δ RV MPI (r: 0.412, $p < 0.001$) was also found to be significantly correlated (Table III). The correlation relationship between Δ TSH and Δ PAS, Δ RV MPI, and Δ E/A is also graphically shown in Figure 2.

Relative risk and odds ratio were calculated to evaluate the relationship between PAS elevation and TSH elevation. Since there was no clear cut-off value for PAS measurement, 21.1 was accepted as the cut-off value with a 75% quartile limit. The SH patient group was divided into two groups, as PAS values below and above 21.1. For the TSH value, the cut-off value of the quartile limit of 75% was accepted with the same method. The SH group was again divided into two groups as TSH measurements below 6.71 and above. In the analysis performed by accepting exposure: TSH > 6.71 and disease: PAS > 21.1, the relative risk of high TSH levels causing high PAS measurements was calculated as: 6.34, while OR: 17.09.

Table III. Correlation of TSH level change with demographic characteristics and echocardiographic data.

	Δ TSH		Δ PAS	
	r	*p*-value	r	*p*-value
Δ Total cholesterol	0.328	**0.018**	0.212	**0.007**
Δ LDL cholesterol	0.192	0.073	0.166	0.524
Δ IVS	0.182	0.254	0.164	0.302
Δ E	-0.321	**0.012**	-0.193	0.266
Δ A	0.254	**0.009**	0.204	0.194
Δ E/A ratio	-0.407	**< 0.001**	-0.322	**0.008**
Δ LV IVRT	0.354	**0.002**	0.366	**< 0.001**
Δ LV MPI	0.223	0.168	0.203	0.304
Δ RV IVRT	0.336	**< 0.001**	0.358	**< 0.001**
Δ RV ET	-0.302	**0.001**	-0.206	0.157
Δ RV MPI	0.404	**< 0.001**	0.412	**< 0.001**
Δ PAS	0.458	**< 0.001**	-	-

Δ: Changes in follow-up, r: Correlation coefficient. TSH: Thyroid stimulating hormone, PAS: Pulmonary arterial stiffness, LDL: Low-density lipoprotein, IVS: Interventricular septum, E: Early filling peak velocity, A: Late diastolic filling velocity, LV: Left ventricle, IVRT: Isovolumic relaxation time, MPI: Myocardial performance index, RV: Right ventricle.

Discussion

The main results of our study were as follows: (I) IVRT and MPI values measured from both ventricles were higher in SH patients compared to the control group. After L-thyroxine treatment, biventricular IVRT and MPI measurements in SH patients decreased significantly and showed a positive change; (II) PAS measurements were higher in the SH group compared to the control group. There was a significant and positive decrease in PAS measurements of SH patients with L-thyroxine treatment. (III) TSH change in SH patients after L-thyroxine treatment showed a significant positive correlation with LV IVRT, RV IVRT, RV MPI, and PAS; (IV) high TSH levels was found to increase the risk of high PAS measurements.

Thyroid hormones have various effects on the cardiovascular system. They have important effects on atherosclerosis through mechanisms, such as effects on transcription of structural proteins, stimulation of chronic inflammation and dehydration, and effects on collagen tissue change[4,5]. Therefore, SH has been found to be associated with blood pressure and lipid metabolism disorders, and other cardiovascular risk factors[3]. The presence of dyslipidemia and cardiovascular risk factors in SH patients are important components for the initiation of treatment[18]. As a result of our analysis, we found that SH patients had a tendency to hyperlipidemia compared to healthy individuals in the control group, and the lipid profile in the SH group could be improved with L-thyroxine treatment, which was consistent with similar publications in the literatüre[19,20]. In addition, after L-thyroxine treatment in SH patients, TSH change showed a positive and significant correlation with total cholesterol changes.

Thyroid hormones bind to the thyroid hormone receptor alpha in cardiac myocytes to regulate gene expression. They also affect cardiac contractility by mechanisms such as down-regulation of myosin heavy chain beta and up-regulation of myosin heavy chain alpha affecting the contractile apparatus, induction of SERCA2a and down-regulation of phospholamban, and increasing adrenergic response as a result of up-regulation of β1-adrenergic receptor[21]. In our study, we found that the mitral E and E/A ratios used to evaluate LV diastolic dysfunction were lower in the SH group compared to the control group of healthy participants. We observed that the mitral E and E/A ratio increased, and the A wave level decreased after L-thyroxine treatment in the SH patient group. In accordance with similar examples in the literature in which Doppler echocardiographic evaluations of SH patients were made, LV diastolic dysfunction tendencies of SH patients can be improved with L-thyroxine treatment[7,10]. In addition, TSH change in SH patients after L-thyroxine treatment was found to have a significant negative correlation with E and E/A changes. LV IVRT and LV MPI were found to be significantly higher in SH patients compared to the control group. Significant reductions in LV IVRT and LV MPI were obtained after L-thyroxine treatment. There were no significant differences in RV dimensions and functional measurements such as TAPSE, FAC,

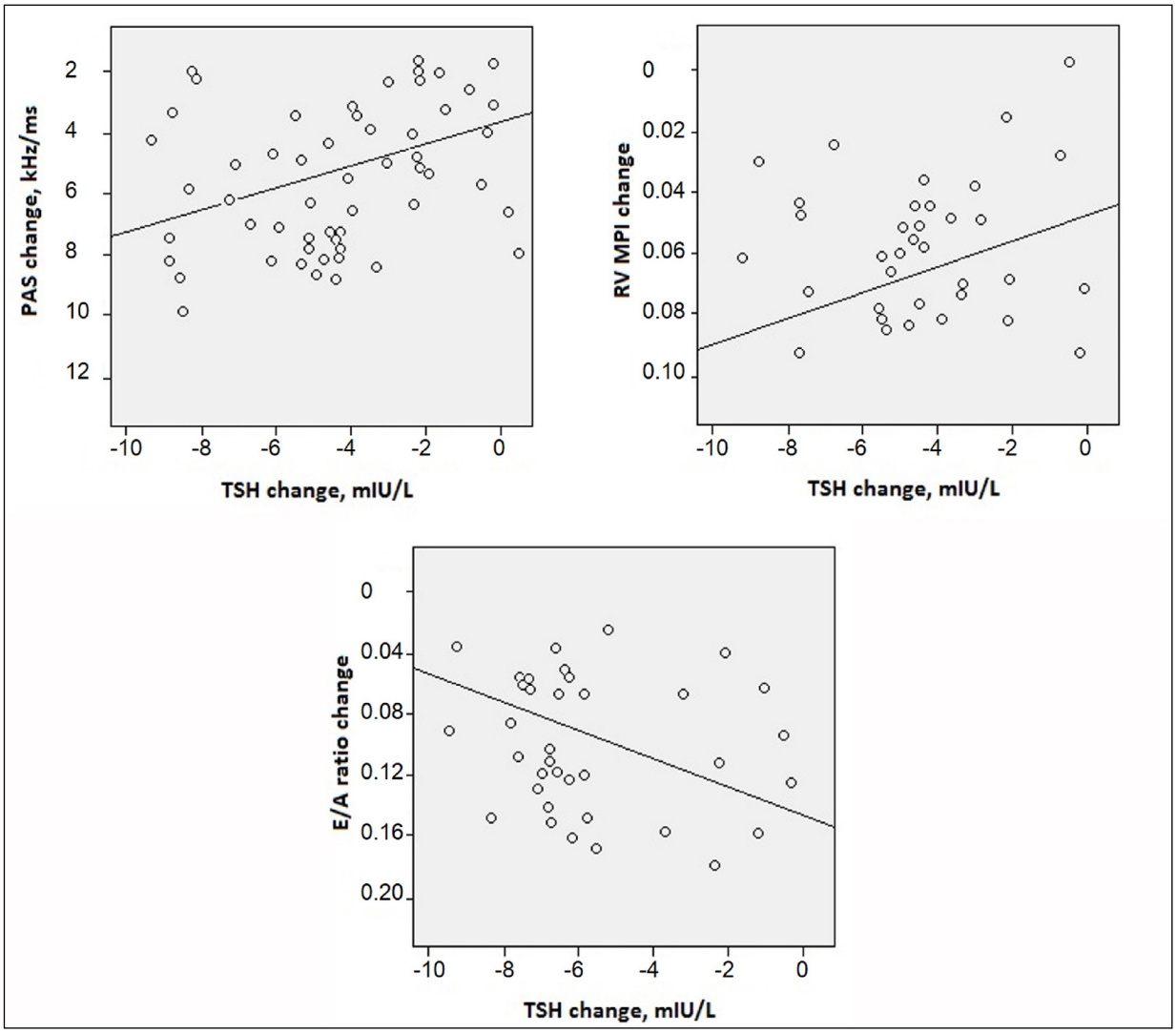

Figure 2. Representation of TSH change and PAS, RV MPI, and E/A ratio changes with correlation graph. TSH: Thyroid stimulating hormone, PAS: Pulmonary arterial stiffness, RV MPI: Right ventricular myocardial performance index.

or S' between the groups. On the other hand, RV IVRT and RV MPI were significantly higher in the SH group compared to the control group. L-thyroxine treatment resulted in a significant reduction in RV IVRT and RV MPI measurements. In a study by Oner et al[7], LV MPI was found to be significantly higher in SH patients compared to the control group, while LV IVRT was found to be numerically higher, although not at a significant level. The authors found no significant change in LV MPI in SH patients after L-thyroxine treatment, but in our study, we found that both LV and RV MPI were significantly reduced in SH patients after treatment. In the Doppler study by Ilic et al[10] on SH patients, it was found that LV IVRT and LV MPI were significantly higher in the SH group before L-thyroxine treatment than in the control group, and these measurements decreased significantly after treatment, thus supporting our results. In a previous study[14] conducted on SH patients, we reported that LV IVRT and LV MPI measurements were higher in SH patients compared to the control group, and the presence of fragmented QRS, which is an electrocardiographic indicator of cardiac fibrosis, was detected more frequently in SH patients. In our study, we found that LV MPI and LV IVRT measurements were also higher in SH patients with fragmented QRS compared to SH patients without fragmented QRS. We found that high TSH, MPI, and IVRT in SH patients are risk factors for the presence of fragmented QRS[14]. From these results, we can conclude that cardi-

ac fibrosis is also a possible etiological cause for the increased LV and RV IVRT and MPI in SH patients. In this study, electrocardiographic follow-up or cardiac fibrosis assessment was not performed on our patients. However, with our previous experience, positive changes obtained from echocardiographic parameters, which are risk factors for cardiac fibrosis, suggest that L-thyroxine treatment may indirectly improve the progression to cardiac fibrosis. The thyroid hormone signaling pathway is quite complex and is formed by the conversion of hormones to their active forms, binding to thyroid hormone receptors and interacting with numerous coactivators and coreceptors. The increase in TSH hormone level may increase triiodothyronine (T3) hormone receptor sensitivity at the cell level[22]. This may explain the cardiac effects observed in patients with SH when FT3 and FT4 levels are normal. The increase in the sensitivity of the hormones at the receptor level while the hormone levels are normal may be another mechanism of action of the systolic and diastolic interaction observed in the right and left ventricles.

PAS is an index that shows pulmonary artery elasticity and was developed to evaluate the structural features and functions of the pulmonary vascular bed. The deterioration in cardiac functions affects the pulmonary vascular system. In cases of chronic pressure elevation in the left ventricle, an increase in pressure also occurs in the pulmonary vascular system and remodeling is induced in the vessel wall[23]. As a result of this pressure increase, chronic inflammation, a decrease in nitric oxide levels, an increase in neurohormones occur, and endothelial function is impaired. In time, smooth muscle cell proliferation in the pulmonary vascular structure, increased fibrosis in the intimal layer, and deterioration in elastic fibers occur. As a result, the elasticity of the pulmonary vascular bed decreases, and the stiffness increases[24-26]. The gold standard in PAS measurement is right heart catheterization, which is an invasive method, and magnetic resonance imaging, computed tomography, and echocardiography are other alternative measurement techniques[11,27,28]. We preferred PAS measurement with echocardiography in our study because it is a safe, inexpensive, and easily applicable technique without the use of noninvasive and contrast agents. In the study of Görgülü et al[11] in patients with pulmonary hypertension due to congenital heart disease, PAS measurements made by transthoracic echocardiography were found to be compatible with right heart catheterization measurements[11]. Transthoracic echocardiography has been successfully used in PAS measurement in many subsequent studies[29-31]. PAS was studied in different designs in patients with heart failure with reduced ejection fraction (HFrEF) and congenital heart disease and was found to be higher than the control groups[11,23]. It has been shown that PAS measurements positively decreased after compensation with sodium-glucose co-transporter-2 inhibitor or angiotensin-receptor neprilysin inhibitor therapies in patients with HFrEF who were symptomatic despite optimal medical treatment[29,31]. It was previously shown that systemic arterial stiffness, which is an indicator of endothelial dysfunction, can be improved by hormone replacement therapy in patients with SH[32]. However, there is not enough data in the literature on PAS evaluation in the SH patient group compared to the control group and the change in PAS measurements with L-thyroxine treatment. In our study, we found that PAS measurement was higher in the SH group compared to the healthy individuals in the control group. We also found a significant and positive decrease in PAS measurements of SH patients with L-thyroxine treatment, and that TSH change after L-thyroxine treatment in SH patients had a positive and significant correlation with LV IVRT, RV IVRT, RV MPI, and PAS. In addition, we observed that high TSH levels increase the risk of detection of high PAS measurements.

To emphasize the importance of PAS measurements in the follow-up of the SH patient group, we compared the changes in PAS measurement results after L-thyroxine treatment with other echocardiographic parameters in which we evaluated LV and RV diastolic and systolic functions. The change in PAS measurement after L-thyroxine treatment in SH patients has a negative correlation with the change in the E/A ratio, and a positive correlation with the changes in LV IVRT, RV IVRT, and RV MPI.

Limitations

Our study had some limitations. The small number of patients included in the study was our main limitation. However, excluding patients aged > 60 years and/or patients with TSH levels ≥ 10 mIU/L is an advantageous aspect to prevent echocardiographic erroneous measurements. On the other hand, the fact that placebo control was not performed in a double-blind randomized design in the choice of L-thyroxine treatment is another important limitation of our study.

Conclusions

SH is associated with dysfunction in the biventricular and pulmonary vascular bed. Biventricular functions and PAS also change positively in SH patients who have hormonal and metabolic improvements with L-thyroxine treatment. High TSH levels increase the risk of high PAS measurements. Ventricular and pulmonary vascular dysfunctions should be considered when making a treatment decision in SH patients, and echocardiographic evaluation/follow-up should be recommended. For ventricular and pulmonary vascular dysfunctions not to be permanent, it is recommended to start appropriate hormone replacement therapy in risky groups.

Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this paper.

Ethics Approval

The Clinical Research Ethics Committee of Ordu University approved the study (Approval No.: 2022/146). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent

All patients were informed about the investigation protocol and signed informed consent.

Data Availability

Data are available upon request from the corresponding author.

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Authors' Contributions

Concept – SÇ and EY; Design – SÇ, EY, and MY; Supervision – SÇ and EY; Materials – EY, SÇ, and MY; Data collection and/or processing – EY, SÇ, and MY; Analysis and/or interpretation – EY and SÇ; Literature search – EY, SÇ, and MY; Writing – SÇ and EY; Critical review – SÇ, EY, and MY.

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