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Left and right ventricular structure and function in subclinical hypothyroidism: The effects of one-year levothyroxine treatment

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Background: The aim of this study was to investigate left ventricular (LV) and right ventricular (RV) structure, function, and mechanics in patients with subclinical hypothyroidism (SHT), and to evaluate the effect of a 1-year levothyroxine treatment.

Material/Methods: We compared 45 untreated women with subclinical hypothyroidism and 35 healthy control women matched by age. All the subjects underwent laboratory analyses, which included a thyroid hormone levels (free T3, free T4, and TSH) test, and a complete 2-dimensional echocardiographic study. All the SHT patients received levothyroxine therapy and were followed for a year after euthyroid state was achieved.

Results: The LV mass index in the SHT participants before and after replacement therapy was significantly higher than in controls. In the SHT patients before the treatment, LV diastolic function and global function estimated by the Tei index were significantly impaired, whereas the LV systolic function was decreased. The results show that LV mechanics was significantly impaired in the SHT patients at baseline. Additionally, the SHT participants before levothyroxine substitution had increased RV wall thickness and significantly impaired RV diastolic and global function in comparison with the controls or the SHT subjects after the treatment. Furthermore, RV mechanics was also significantly deteriorated in the SHT patients before the treatment.

Conclusions: Subclinical hypothyroidism significantly affected LV and RV structure, systolic, diastolic and global function, and LV and RV mechanics. Levothyroxine replacement therapy significantly improved cardiac structure, function, and mechanics in the SHT patients.

Key words: subclinical hypothyroidism • left ventricle • right ventricle • mechanics • diastolic function • levothyroxine therapy

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Background

Thyroid hormones have significant influence on the cardiovascular system [1]. Hypothyroidism is associated with impaired cardiac function [2]; studies have shown that subclinical hypothyroidism (SHT) and mild hypothyroidism are associated with left ventricular (LV) dysfunction, especially diastolic dysfunction [3–8], but the mechanisms of this relationship are still insufficiently investigated. Although researchers revealed that substitution therapy with levothyroxine in the SHT patients could improve LV function and cause reversion of LV diastolic dysfunction [9–12], many controversies remain about the favorable influence of therapy on LV remodeling.

The impact of thyroid hormones on right ventricular (RV) structure and function, especially in the SHT patients, is still unknown. The RV has long been considered as an "insignificant" heart chamber, as long as studies showed that RV hypertrophy and dysfunction are related with cardiovascular morbidity and mortality [13,14]. However, because of its complex geometry, the RV could be very difficult to assess echocardiographically, which is why cardiac MR has long been considered as a gold standard for RV imaging. The estimation of RV function and mechanics became available and reliable after the introduction of new echocardiographic tools such as tissue Doppler and speckle tracking imaging. A few studies have shown that RV remodeling, particularly RV diastolic dysfunction, occurs parallel to LV changes, and that levothyroxine therapy also has favorable influence on reversibility of RV diastolic dysfunction [15,16].

To our knowledge, ours the first study to use 2-dimensional speckle tracking imaging to assess the effect of SHT and levothyroxine replacement therapy on LV and RV mechanics. In the present study, we investigated LV and RV structure, function, and mechanics in SHT patients and evaluated the effect of replacement therapy on LV and RV remodeling.

Material and Methods

We enrolled 45 female patients with untreated subclinical hypothyroidism and 35 age-matched healthy female volunteers. The study was conducted at the Endocrinology and Cardiology Department, University Clinical Hospital Centre "Dr Dragisa Misovic" in Belgrade, Serbia, between January 2010 and May 2013. The cause of SHT in all patients was chronic autoimmune thyroiditis (diagnosed by increased circulating antiperoxidase and/or anti-thyroglobulin autoantibodies and diffuse hypoechogenicity imaged by thyroid ultrasound). The inclusion criteria were age (≤45 years) and increased serum TSH level with normal levels of FT3 and FT4. Subjects with symptoms or signs of cardiovascular disease (arterial hypertension, myocardial infarction, atrial fibrillation, heart failure, congenital heart disease, valvular disease), obesity (BMI ≥30 kg/m^2), asthma, chronic obstructive lung disease, neoplastic disease, cirrhosis of the liver, kidney failure, sleeping disorders, or type 2 diabetes mellitus were excluded from the study.

Anthropometric measures (height and weight), and laboratory analyses (level of thyroid hormones, total cholesterol, triglycerides, and HDL and LDL cholesterol) were taken from all study subjects. Fasting venous blood samples were drawn between the hours of 0800 and 0900. None of the participants used any medication one year before inclusion in the study or during the study. The normal ranges for FT3, FT4, and TSH are 1.5–4.1 pg/ml, 11.5–22.7 pmol/l, and 0.4–4 mIU/l, respectively. FT3 level was determined by IMMULITE 1000 (a competitive analog-based immunoassay); FT4 level was assessed by IMMULITE 2000 enzyme-labeled chemiluminescent competitive immunoassay; and TSH level was determined by using IMMULITE 2000 (a third-generation TSH, 2-site chemiluminescent immunometric assay). After baseline assessment, patients with SHT were assigned to receive levothyroxine replacement starting with 25 μg/d. TSH was measured every 8 weeks for dose adjustment. Euthyroid state was achieved with a mean dose of 71 μg/d in 19.6±5.8 weeks. Echocardiographic examination was performed before starting the treatment, and by levothyroxine therapy 1 year after euthyroid state was achieved. Body mass index (BMI) and body surface area (BSA) were calculated for each patient. The study was approved by the local Ethics Committee, and informed consent was obtained from all the participants.

Echocardiography

Echocardiographic examination was performed by using a Vivid 7 ultrasound machine (GE Healthcare, Horten, Norway) equipped with a 2.5 MHz transducer with harmonic capability.

Standard two-dimensional (2DE) echocardiographic examination

The values of all 2DE parameters were obtained as the average value of 3 consecutive cardiac cycles. The LV end-systolic and end-diastolic (LVEDD) diameters, the left ventricle posterior wall (PWT), and interventricular septum thickness were determined according to the current recommendations [17]. Relative wall thickness was calculated as (2xPWT)/LVEDD. Left ventricular ejection fraction (EF) was estimated by using the biplane method. Left ventricular mass was calculated by using the Devereux formula [18], and was indexed for height powered to 2.7.

Transmitral Doppler inflow and tissue-pulsed Doppler were obtained in the apical 4-chamber view. Pulsed Doppler

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measurements included the transmitral early diastolic peak flow velocity (E), late diastolic flow velocity (A), their ratio (E/A), and E velocity deceleration time (DT) [19]. Tissue Doppler imaging was used to obtain left ventricular myocardial velocities in the apical 4-chamber view, with a sample volume placed at the septal segment of the mitral annulus during early and late diastole (e' and a') and systole (s). Using tissue Doppler, we also determined early diastolic velocity across a lateral segment of the mitral annulus and computed the average early diastolic relaxation velocity (e'_{av}) of the septal and lateral mitral annulus; this was used for further calculation of the E/e'_{av} ratio.

The parameters necessary for calculating the Tei index were obtained by the tissue Doppler in the apical 4-chamber view. A 2-mm sample volume was placed at the lateral corner of the mitral annulus. Isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) were measured from the end of the mitral annular velocity pattern to the onset of the systolic wave, and from the end of the systolic wave to the onset of the mitral annular velocity pattern, respectively. The ejection time (ET) was defined as the duration of the left ventricle outflow Doppler velocity profile. The Tei index was then calculated according to the formula: Tei index = (IVCT + IVRT)/ET [20].

Two-dimensional left ventricular strain

2DE strain imaging was performed by using 3consecutive cardiac cycles of 2DE LV images in apical (long-axis 4-chamber view) [21]. The frame rate ranged between 50 and 70Hz. A commercially available software, 2DE Auto LVQ software (EchoPAC 110.1.2, GE-Healthcare, Horten, Norway), was used for 2DE strain analysis. The 2DE longitudinal strain and strain rate were calculated by averaging all 6 values of the regional peak longitudinal strain obtained in 4-chamber apical view. We separately estimated peak longitudinal strain of the LV, interventricular septum, and LV lateral wall.

Right ventricle and atrium

The RV internal end-diastolic diameter was measured in M-mode in the parasternal long-axis view [22]. RV end-diastolic thickness was measured in the subcostal view [22]. Two-dimensional RV volumes and ejection fraction were calculated by using the modified Simpson's rule [22]. The right atrial (RA) diameters were measured in the apical 4-chamber view at the ventricular end-systole [22].

Pulsed Doppler measurements across the tricuspid annulus included early and late diastolic flow velocity, their ratio (E/A_t), and deceleration time (DT_t). Tissue Doppler imaging was used to obtain the RV myocardial velocities in the apical 4-chamber view with a sample volume placed at the lateral segment of the tricuspid annulus [22]. Acquisition was performed at end-expiration during quite breathing. RV global systolic function was assessed as the tricuspid annular plane systolic excursion (TAPSE) [22].

The parameters necessary for calculation of the Tei index of the right ventricle were obtained by the tissue Doppler in the apical 4-chamber view. The RV Tei index was calculated similarly as for the LV, according to the current guidelines [22].

RV systolic blood pressure (SPAP) was assessed in a subset of patients with minimal/mild tricuspid regurgitation.

Two-dimensional right ventricular strain

Two-dimensional strain imaging was performed by using 3 consecutive cardiac cycles in the apical 4-chamber view [22]. The frame rate ranged between 60 and 80 frames/s. EchoPAC 110.1.2 (GE-Healthcare, Horten, Norway) commercially available software was used for the 2DE strain analysis. Longitudinal peak strain was the variable used for evaluation of systolic function and contractility. We separately estimated peak strains of the RV and free wall.

Statistical analysis

Normal distribution of all variables was verified using the Kolmogorov-Smirnov test. Continuous variables are presented as mean ± standard deviation (SD) and were compared by using the 2-tailed t-test. Comparisons between the controls and the patients were performed by an independent-samples t-test. The data before and after L-thyroxin therapy were compared by a paired-samples t-test. The differences in proportions were compared by using the χ^2 test. The correlations were determined by the Pearson rank correlation test. Inter- and intra-observer variability was examined by using Bland-Altmann analysis. We reported relation coefficients, 95% confidence intervals, and percent errors. P-value <0.05 was considered statistically significant.

Results

The SHT patients and the controls had similar age, heart rate, blood pressure, BMI, BSA, triglycerides, and HDL-cholesterol level (Table 1). FT3 and FT4 levels were similar between the controls and the SHT patients, but TSH level was significantly elevated in the SHT group in comparison with the controls and the treated patients. The total cholesterol and LDL-cholesterol levels were increased in the SHT patients before the treatment in comparison with the controls and the SHT patients after levothyroxine treatment (Table 1).

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Table 1. Demographic characteristics and clinical parameters of study population.

	Controls (n=35)	Baseline SHT (n=45)	SHT after 12 months (n=45)
Age (years)	39±6	40±5	–
BMI (kg/m^2)	24.8±4.5	25.2±4.3	24.7±4.6
BSA (m^2)	1.73±0.15	1.76±0.17	1.74±0.16
Heart rate (beats/min)	74±11	73±10	74±12
Clinic systolic BP (mmHg)	119±9	121±10	120±9
Clinic diastolic BP (mmHg)	72±7	74±8	75±8
FT3 (pmol/l)	2.7±0.6	2.53±0.49	2.61±0.52
FT4 (pmol/l)	13.7±2.2	13.17±1.94	13.45±2.48
TSH (mIU/ml)	2.13±0.87[b]	8.54±2.58[b,f]	1.91±0.65[f]
Triglycerides (mmol/l)	1.33±0.65	1.39±0.7	1.25±0.62
Total cholesterol (mmol/l)	4.69±0.79[b,d]	5.5±1.04[b]	5.2±0.82[d]
LDL cholesterol (mmol/l)	2.93±0.66[b,d]	3.83±0.95[b]	3.5±0.76[d]
HDL cholesterol (mmol/l)	1.43±0.32	1.38±0.38	1.39±0.41

BMI – body mass index; BSA – body surface area; BP – blood pressure; FT3 – free tri-iodothyronine; FT4 – free thyroxine, TSH – thyroid-stimulated hormone; STA – subclinical hypothyroidism. [a] p<0.05 for controls *vs.* baseline SHT; [b] p<0.01 for controls *vs.* baselinel [d] p<0.01 for controls *vs.* SHT after 12 months; [f] p<0.01 for baseline *vs.* SHT after 12 months.

Left ventricular structure, function, and mechanics

The LV diameters and volumes were similar among the SHT patients and the controls (Table 2), but LV EF was lower in the SHT patients at baseline in comparison with the controls and the SHT patients after the therapy. IVS and PWT were significantly increased in the SHT patients before the therapy in comparison with the controls (Table 2). The LV mass index was significantly increased in the SHT patients before the therapy in comparison with the controls and the treated SHT subjects (Table 2). There was no important difference in LA diameter between the SHT patients and the controls. Transmitral E/A and e'/a' ratios were decreased in the SHT patients before the therapy in comparison with the controls and the SHT patients after therapy. Additionally, DT_m and $IVRT_m$ were significantly prolonged, and E/e'_{av} was increased, in the SHT patients before the treatment (Table 2). Mitral s was significantly decreased, whereas the LV Tei index was increased in the patients before substitution therapy.

The LV global longitudinal strain was significantly decreased in the SHT patients at baseline in comparison with the controls and the SHT patients after the levothyroxine therapy (Table 2). Similar results were obtained for septal and LV lateral wall strain.

Right ventricular structure, function, and mechanics

The RV diameter and volumes did not differ between the SHT patients and the controls, regardless of therapy; whereas RV wall thickness was significantly increased in the SHT patients before the treatment (Table 3). Interestingly, RV EF assessed by the biplanes rule was lower in the SHT patients before the treatment in comparison with the controls.

The RA diameters were similar between the controls and the SHT patients (Table 3). Tricuspid E/A and e'/a' ratio were decreased in the SHT patients before the therapy in comparison with the controls or with the SHT patients after the therapy. There was no difference in E/e'_t, s_t, TAPSE, and SPAP between the SHT patients and the controls (Table 3). Global RV function obtained by the Tei index was significantly impaired in the SHT patients before the therapy in comparison with the SHT participants after the therapy or the controls (Table 3).

Longitudinal RV strain was decreased in the untreated SHT patients in comparison with treated SHT subjects or healthy volunteers (Table 3). Similar results were obtained for free wall strain (Table 3).

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Table 2. Echocardiographic parameters of left ventricular structure and function in the study population.

	Controls (n=35)	Baseline SHT (n=45)	SHT after 12 months (n=45)
LVEDD (mm)	46.3±4.8	47.1±5.1	46.8±5
LVESD (mm)	31.8±3.6	32.6±4.2	32.5±4.4
IVS (mm)	9.2±0.9[a]	9.8±1.1[a]	9.6±1
PWT (mm)	8.8±0.8[a]	9.3±0.9[a]	9.15±1
RWT	0.38±0.03	0.39±0.04	0.39±0.03
LA (mm)	35.4±3.8	36.1±4	35.9±4.1
LVM/Ht$^{2.7}$ (g/m$^{2.7}$)	41.6±4.2[b,d]	46±4.8[b]	44.5±4.7[d]
EDV (ml)	89.5±9.2	92.8±9	91±8.8
ESV (ml)	31.3±6.8	34±7	32±7.4
EF (%)	65±5a	63±4[a,e]	65±4[e]
$(E/A)_m$ ratio	1.43±0.35[b]	1.16±0.33[b,f]	1.36±0.3[f]
DT_m (ms)	193±26[b]	221±32[b,f]	201±29[f]
$IVRT_m$ (ms)	78±13[b]	93±21[b,f]	82±15[f]
$(e'/a')_m$	1.2±0.22[b]	0.93±0.13[b,f]	1.14±0.18[f]
E/e'_{av}	5.14±1.47[b]	6.25±1.8[b,e]	5.48±1.65[e]
s_m (cm/s)	13.5±1.8[a]	12.7±1.6[a]	13.3±1.8
LV Tei index	0.43±0.05[b]	0.53±0.07[b,f]	0.45±0.06[f]
LV strain (%)			
GLS	22.5±2.1[b]	20.4±2.5[b,f]	22.1±2.4[f]
Septum	23±2.8[b]	21.1±2.7[b,f]	22.8±2.7[f]
Lateral wall	22.2±2.6[b]	19.9±2.6[b,f]	21.6±2.5[f]

a' – late diastolic mitral flow across septal segment of the mitral annulus (tissue Doppler); A_m – late diastolic mitral flow (pulse Doppler); DT – deceleration time; E_m – early diastolic mitral flow (pulse Doppler); e' – early diastolic mitral flow across septal segment of the mitral annulus (tissue Doppler); e'_{av} – average of the peak early diastolic relaxation velocity of the septal and lateral mitral annulus (tissue Doppler); EDV – end-diastolic volume; EF – ejection fraction; ESV – end-systolic volume; Ht – height; GLS – global longitudinal strain; IVRT – isovolumic relaxation time; IVS – interventricular septum; LA – left atrium; LVM – left ventricle mass; LVEDD – left ventricle end-diastolic dimension; LVESD – left ventricle end-systolic dimension; PWT – posterior wall thickness; RWT – relative wall thickness. [a] p<0.05 for controls *vs.* baseline SHT; [b] p<0.01 for controls *vs.* baseline; [d] p<0.01 for controls *vs.* SHT after 12 months; f – p<0.01 for baseline *vs.* SHT after 12 months.

Correlation and regression analyses

Considering the entire study population (the SHT patients before and after levothyroxine therapy, and controls), TSH level correlated with LV mass index (r=0.47, p<0.01), E/A_m ratio (r=–0.32, p<0.01), E/e'_m ratio (r=0.37, p<0.01), LV Tei index (r=0.43, p<0.01), and LV global longitudinal strain (r=–0.51, p<0.01) among LV parameters; and also correlated with E/A_t ratio (r=–0.28, p=0.02), E/e'_t (r=0.39, p<0.01), RV Tei index (r=0.4, p<0.01), and RV global longitudinal strain (r=–0.48, p<0.01) among RV parameters. However, after adjustment for LV mass index and RV wall thickness, in the whole study population, TSH was associated only with LV Tei index (β=0.39, p<0.01), LV longitudinal strain (β=–0.47, p<0.01), and RV longitudinal strain (β=–0.32, p=0.025).

Interobserver variability

Bland-Altman analyses was: Mitral E/e'_{av} (95% CI ±2.7; percentage error 5.1%); LV Tei index (95% CI ±2.4; percentage error 4.5%); global LV strain (95% CI ±2; percentage error 4.1%); Tricuspid E/e' (95% CI ±2.9; percentage error 5.5%); RV Tei

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Table 3. Echocardiographic parameters of right ventricular structure and function in the study population.

	Controls (n=35)	Baseline SHT (n=45)	SHT after 12 months (n=45)
RVDd outflow (mm)	23.1±2.2	23.8±2.5	23.4±2.3
RVTd subcostal (mm)	3.8±0.5[a]	4.1±0.6[a]	3.9±0.6
RV EDV (ml)	86±8.5	89.2±8.9	86.6±8.7
RV ESV (ml)	32.8±6.6	35.5±6.9	33.7±6.8
RV EF (%)	62±4[a]	60±4[a]	61±4
RA long axis (mm)	37.5±6.1	38.3±6.6	37.9±6.5
RA short axis (mm)	30.1±4.2	30.7±4.4	30.3±4.3
$(E/A)_t$	1.52±0.4[b]	1.23±0.32[b,f]	1.44±0.35[f]
$(e'/a')_t$	1.29±0.22[b]	0.97±0.19[b,f]	1.2±0.2[f]
DTt (ms)	203±26[b]	228±34[b,f]	206±28[f]
E/e'_t	4.42±1.19	4.82±1.3	4.5±1.22
st (cm/s)	14.3±2.8	13.4±2.5	14±2.7
TAPSE (mm)	25±4	24±4	25±3
SPAP (mmHg)	20±6	22±5	20±5
RV Tei index	0.4±0.04[b]	0.51±0.06[b,f]	0.42±0.05[f]
RV strain (%)			
Global	27.6±3.3[b]	25±3[b,f]	27.2±3.1[f]
Free wall	32±3.9[b]	29.1±3.6[b,f]	31.7±3.8[f]

a' – late diastolic mitral flow across the lateral segment of tricuspid annulus (tissue Doppler); A_t – late diastolic tricuspid flow (pulse Doppler); DT – deceleration time; E_t – early diastolic tricuspid fow (pulse Doppler); e' – peak early diastolic relaxation velocity of the lateral segment of tricuspid annulus (tissue Doppler); EDV – end-diastolic volume; EF – ejection fraction; ESV – end-systolic volume; GLS – global longitudinal strain; RA – right atrium; RV – right ventricle; RVD – right ventricular diameter; RVT – right ventricular wall thickness; RWT – relative wall thickness; st – systolic flow velocity across lateral segment of tricuspid annulus (tissue Doppler); SPAP – systolic pressure in pulmonary artery; TAPSE – tricuspid annular plane excursion. [a] p<0.05 for controls *vs.* baseline SHT; [b] p<0.01 for controls *vs.* baseline; [f] p<0.01 for baseline *vs.* SHT after 12 months.

index (95% CI ±3.1; percentage error 5.8%); Global RV strain (95% CI ±2.9; percentage error 5.4%).

Intraobserver variability

Bland-Altman analyses was: Mitral E/e'_{av} (95% CI ±2.1; percentage error 4.1%); LV Tei index (95% CI ±1.8; percentage error 3.9%); Global LV strain (95% CI ±1.5; percentage error 3.4%); Tricuspid E/e' (95% CI ±2.2; percentage error 4.7%); RV Tei index (95% CI ±2.4; percentage error 5.2%); Global RV strain (95% CI ±2.2; percentage error 4.6%).

Discussion

There are several important findings in our study: (i) LV undergoes structural and functional remodeling in SHT, which means that LV structure, as well as systolic, diastolic and global function, are impaired in these patients; (ii) LV mechanics is compromised in the SHT patients; (iii) RV structure and diastolic and global function are affected by SHT; (iv) RV mechanics is also affected by SHT; and (v) TSH level is associated with LV and RV mechanics independently of LV mass index and RV wall thickness.

Hypothyroidism could induce cardiac remodeling in 3 ways. Firstly, by decreasing activity of some enzymes included in intracellular calcium handling, which further changes the expression of contractile protein [2,22,24]. Secondly, chronic inflammation [25] and tissue changes (e.g., collagen alteration, dehydration, myocardial fiber orientation or capillary distribution) in a condition of SHT could be responsible for cardiac dysfunction [26,27]. It has been speculated that SHT and mild hypothyroidism are related to initial signs of cardiovascular

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hypothyroidism [26]. Thirdly, SHT is associated with hemodynamic changes that could also induce cardiac impairment [26].

Our results show that the SHT patients had increased LV mass index in comparison with the controls, as confirmed by some authors [11,15,28], but our results disagree with those of others [3,6,7,29]. Similarly, levothyroxine therapy induced the reduction of LV wall thickness and LV mass in some investigations [11], but it did not cause significant improvement in other studies [10]. The more recent studies agree with our results. In addition to the above-mentioned mechanism that could induce LV hypertrophy in a condition of SHT, increased systemic vascular resistance [30,31] and activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system could also have a significant role in hemodynamic and structural changes of the LV [2,32].

Although more investigators have demonstrated that SHT has an unfavorable influence on LV diastolic function [4,10,12,16,28], which also concurs with our results, there is still a lack of agreement on this topic because many studies disagree with these findings [5–7,9]. However, a recently published meta-analysis that included 675 SHT participants younger than 60 years of age has concluded that LV diastolic dysfunction is significantly more prevalent in the SHT patients than in the healthy, age- and gender-matched controls [33]. Studies that evaluated the effects of levothyroxine therapy in SHT patients show the positive influence of this therapy on LV diastolic function [4,10,11], which agrees with our findings and confirms the favorable relationship between thyroid hormones and LV function.

The impact of SHT on LV systolic function is more controversial. Ripoli et al. used cardiac MR for estimation of LV function, and, even if the difference in ejection fraction was 4% (65% *vs.* 61%) between the SHT patients and the controls, it was not enough to reach statistical significance due to small sample size [31]. In our study, a difference of only 2% in LV ejection fraction was sufficient to show a statistically significant difference between the SHT patients at baseline and the controls or the SHT patients after the treatment. However, Ripoli et al. succeeded in showing that SHT patients had reduced end-diastolic volume, stroke volume, and cardiac index in comparison with the controls [31]. Similar results regarding unchanged LV ejection fraction among the SHT patients were also obtained by other researchers [6,7,11,12,28]. However, tissue Doppler analysis showed impaired LV systolic function in the SHT population [3,34]. Additionally, global LV function estimated by the Tei index is also impaired in SHT and is significantly improved after levothyroxine substitution [11].

Interest in LV mechanics has been increasing. Tiryakioglu et al. showed that patients with overt hypothyroidism have impaired LV longitudinal function as assessed by tissue Doppler and strain imaging [35]. In another study, LV deformation of all 16 segments of the LV was impaired in hypothyroid patients in comparison with controls [35], and to our best knowledge a similar study has not been previously done in the SHT population. Our results showed depression of LV global longitudinal strain and strain of the LV lateral wall and interventricular septum in the SHT patients. We demonstrated that LV mechanical disturbances disappeared after levothyroxine treatment, and TSH level was found to be associated with LV global strain independently of LV mass index. These results show that LV hypertrophy is not the only mechanism responsible for LV dysfunction in SHT patients. Hemodynamic changes in SHT, led by increased systemic vascular resistance, have a very important, maybe crucial, role in the relationship between thyroid hormones and LV mechanics.

The RV has been significantly less studied, mostly because of its complicated anatomy and lack of a reliable and accessible imaging tool. Only a few studies have examined RV structure and function in SHT patients. Turhan et al. showed that SHT is associated with RV systolic and diastolic dysfunction, and revealed that levothyroxine therapy improves these abnormalities [16]. Kosar et al. demonstrated an association between clinical hypothyroidism and RV diastolic dysfunction [15], but Niafar et al. did not find any difference in RV systolic or diastolic function between SHT subjects and controls [6]. Several studies failed to detect any difference in RV wall thickness between the observed groups [15,16]. Our results demonstrate that RV wall thickness was increased, and RV diastolic and global functions were impaired in the SHT patients. Interestingly, Kosar et al. found an even greater difference than we did in RV wall thickness between the patients with clinical hypothyroidism and the controls, but this still was insufficient to reach statistical significance due to small sample size [15]. In our study, levothyroxine treatment improved diastolic and global RV functions, but did not significantly reduce RV wall thickness.

To date, RV mechanics has not been estimated in the SHT population. Our research revealed that RV mechanics assessed by speckle tracking imaging is significantly impaired in the SHT subjects. Specifically, global RV strain and strain of RV free wall were decreased in the SHT patients in comparison with the healthy controls. A mechanism that can explain the relationship between RV remodeling and SHT is elevated RV filling pressure, which is reflected by the increased E/e'_t that we obtained in our study. Other possible mechanisms are RV hypertrophy, endothelial dysfunction in pulmonary circulation, increased sympathetic and RAAS activity, and impaired Ca^{2+} handling in SHT, which could induce elevated pulmonary vascular resistance. Finally, the interaction between LV and RV is certainly one of the most important causes of RV impairment in SHT patients due to transmission of increased LV filling pressure through pulmonary circulation to the RV. However, our

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study revealed that TSH is associated with RV mechanics independently of LV mass index and RV wall thickness. Additionally, we showed that impairment of RV mechanics is completely reversible after adequate replacement therapy.

Limitations

Our study has several limitations. Firstly, the relatively small number of patients could be a limitation to our study. Secondly, our investigation included only women (SHT is mostly seen in females, which is why we decided to include only women), which restricts our results to this population. Thirdly, the existence of coronary artery disease (CAD) was not excluded by coronary angiography; however, our study included young females without other cardiovascular risk factors and expected prevalence of CAD in this population is very low.

Conclusions

LV and RV structure and systolic, diastolic, and global function are impaired in SHT patients. LV and RV mechanics are also damaged in the SHT subjects. Impairments in LV and RV function and mechanics were reversed after adequate treatment with levothyroxine, whereas structural cardiac damage did not significantly improve. This shows that a longer time of treatment is probably needed to achieve this kind of improvement. TSH level correlates with LV and RV structure, diastolic and global function, and LV and RV mechanics. However, after adjustment for LV and RV hypertrophy, TSH was associated only with LV global function and LV and RV mechanics. Further longitudinal analyses with a greater number of patients are needed to validate the possible impact of LV and RV mechanical changes on morbidity and mortality in SHT subjects.

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