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Left ventricular strain and strain rate by two-dimensional speckle tracking echocardiography in patients with subclinical hypothyroidism

M. SUNBUL, E. DURMUS, T. KIVRAK, H. YILDIZ[1], B.G. KANAR, B. OZBEN, I. SARI, B. MUTLU

Department of Cardiology, Marmara University Faculty of Medicine, Istanbul, Turkey
[1]Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey

Abstract. – AIM: Subclinical hypothyroidism (SH) is an asymptomatic condition defined by increased serum thyroid-stimulating hormone (TSH) with normal free thyroid hormone levels. Heart is a major target organ for thyroid hormone action. The aim of this study was to evaluate cardiac functions in patients with SH by speckle tracking imaging.

PATIENTS AND METHODS: We included 23 consecutive patients with untreated SH (Group A; 7 male, mean age: 40.9±1.6 years) and 21 patients with treated SH (Group B; 6 male, mean age: 40.2±2.1 years). The control group included 25 healthy volunteers (8 male, mean age: 39.9±2.8 years). Left ventricular (LV) functions were assessed with speckle tracking imaging.

RESULTS: Age and sex distributions were similar among the groups. Mean serum TSH and free T4 levels were 11.7±2.9 μIU/mL, 1.16±0.06 ng/dL for group A; 2.6±0.3 μIU/mL, 1.35±0.09 ng/dL for group B; 1.4±0.3 μIU/mL, 1.31±0.09 ng/dL for controls, respectively (p = 0.001, p = 0.122). The untreated SH patients had significantly lower LV strain and strain rate values compared to controls. The treated SH patients had higher LV strain and strain rate values compared to untreated SH patients although the difference was not statistically significant. The treated SH patients had lower LV strain and strain rate values compared to controls but the difference was not statistically significant.

CONCLUSIONS: Untreated SH is associated with impairment in LV longitudinal myocardial function. Speckle tracking echocardiography appears to be useful both for early detection of LV impairment in patients with SH and documentation of improvement in myocardial deformation parameters with treatment.

Key Words:
Subclinical hypothyroidism, Left ventricular function, Speckle tracking echocardiography.

Introduction

Thyroid hormones act an important role on the cardiovascular system and thyroid diseases have a prominent adverse effect on myocardial and vascular functions. Frequency of thyroid dysfunction increases with aging. The prevalence of subclinical hypothyroidism (SH) is 10% and subclinical hyperthyroidism is 1.5%[1]. SH is characterized by normal serum free L-thyroxine (fT_4) and free triiodothyronine ($fT_{3)}$ levels and an increased thyroid stimulating hormone (TSH) level, usually without any clinical signs[2]. Heart is a major target organ for thyroid hormone action. T_3 is the bioactive hormone that is known to affect tissue oxygen consumption, vascular resistance, blood volume, cardiac contractility and heart rate[3]. Subclinical thyroid disease has been associated with systolic and diastolic cardiac dysfunction, and previous studies have shown that thyroxine replacement improved cardiac function in subjects with SH[4].

In overt hyperthyroidism, increased cardiac contractility, heart rate and altered left ventricular (LV) loading conditions result in a hyperdynamic state, with high cardiac output at rest and a suboptimal response to exertion[5]. SH may have similar but more subtle effects on cardiac function. Patient with overt hypothyroidism have bradycardia, decreased ventricular filling, decreased cardiac contractility, which lead to decreased cardiac output[6]. In SH, effects of thyroid hormone replacement on clinical symptoms are still unclear[7]. Previous studies showed that patients with SH have metabolic, neuromuscular and neuropsychiatric deficiencies. Previous studies indicated that lipid alteration can be one of eventual risk factors accompanied with thyroid disorder such as SH. The increase in serum cholesterol

Corresponding Author: Murat Sunbul, MD; e-mail: drsunbul@yahoo.com.tr

levels reflects increase of the serum TSH levels in patients with SH[8]. Hence, SH may also be considered as a risk factor for atherosclerosis[9].

Left ventricular (LV) diastolic and systolic dysfunction may lead to increased morbidity, exercise intolerance and heart failure[10]. Non-invasive techniques such as standard echocardiography indirectly provide information about LV global functions. Standard echocardiography, therefore, provides limited data regarding changes of LV function in hypothyroidism. The impact of SH on LV diastolic and systolic dysfunction has been studied using tissue Doppler echocardiography in previous studies[11,12]. Recently, new echocardiographic techniques have been introduced to evaluate myocardial mechanics. Strain and strain rate imaging is a novel non-invasive method for assessment of myocardial function. Speckle tracking echocardiography is a more recent technique that provides a global approach to LV myocardial mechanics, giving information about the three spatial dimensions of cardiac deformation[13]. The aim of this study was to evaluate cardiac functions in patients with SH by strain and strain rate imaging and effect of treatment on these parameters.

Patients and Methods

Study Population

We included 23 consecutive patients with untreated SH (Group A; 7 male, mean age: 40.9 ± 1.6 years) and 21 patients with treated SH (Group B; 6 male, mean age: 40.2 ± 2.1 years). The control group included 25 healthy volunteers (8 male, mean age: 39.9 ± 2.8 years). Patients with impairment of LV systolic function (ejection fraction < 55%), significant valvular heart disease, cardiomyopathy, history of coronary artery disease, malignancy, diabetes mellitus and patients with poor echogenecity were excluded. All subjects underwent a resting electrocardiography and a two dimensional (2D) transthoracic echocardiography examination. We obtained medical histories from all patients and performed physical examination. The investigation complies with the principles outlined in the Declaration of Helsinki. The study was approved by the local Ethics Committee and written informed consent was obtained from all participants.

Standard Echocardiography and 2D Speckle Tracking Echocardiography

Standard echocardiographic examinations were performed in accordance with the recommendations of the American Society of Echocardiography guidelines[14] using an ultrasound system (Vivid 7, General Electric, Horten, Norway). 2D speckle tracking echocardiographic data for LV was obtained from the apical-four chamber view. A single cardiac cycle was stored in cineloop format with a frame rate of 40-80 Hz for the analysis. The S and SR data analysis was performed as previously described[15]. The endocardium of LV was manually drawn in end-systolic single frame, a region of interest was automatically mapped to the endocardial border (Figure 1). The LV myocardium was automatically divided into six segments (basal, mid and apical

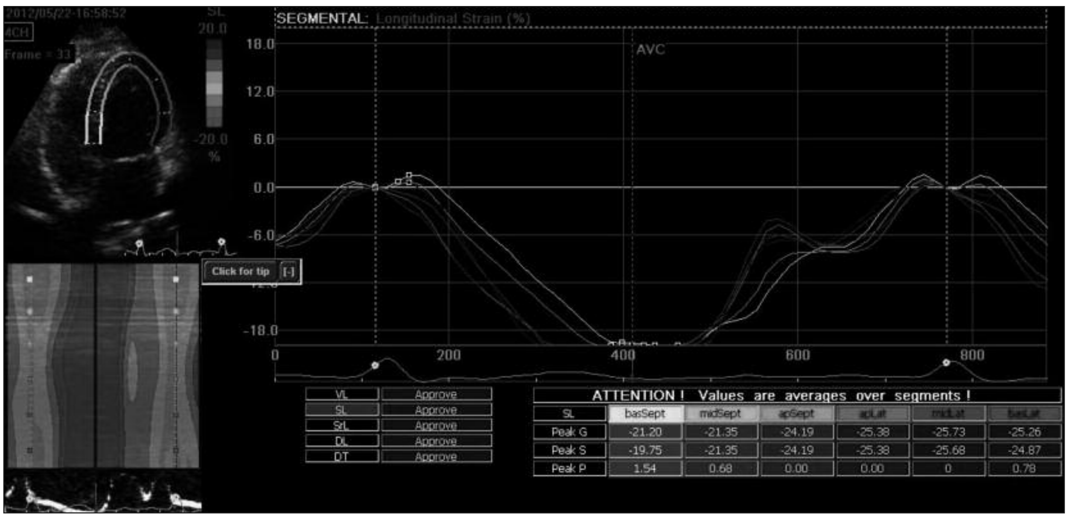

Figure 1. Left ventricular 2D speckle tracking echocardiography pattern in a patient with subclinical hypothyroidism.

segments of the septum and LV lateral wall). Only the images that demonstrated appropriate tracking in all myocardial segments in echocardiograms were used in the analysis.

Laboratory Findings

Thyroid hormone parameters were assessed by a Roche Elecsys 1010/2010 (Mannheim, Germany) using immuno-chemiluminescence assay method. SH was diagnosed with increased level of serum TSH and normal fT3 and fT4 levels. The normal reference levels of the thyroid panel were: TSH: 0.27-4.30 mIU/mL, fT3: 1.80-4.60 pg/ml, fT4: 0.93-1.70 ng/dl according to the standards of the biochemistry laboratory of our clinic. Cases with SH were defined as having a TSH level above 4.2 mIU/mL and fT4 value within normal range.

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 statistical package for Windows (SPSS Inc., Chicago, IL, USA). Continuous data are expressed as mean ± standard deviation. Chi-square test was used for comparison of categorical variables while Mann Whitney U and Kruskal-Wallis test was used to compare non-parametric continuous variables. Intra- and inter-observer variabilities were calculated as the absolute difference between two measurements in percent of their mean. A value of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics and laboratory findings are shown in Table I. Age and sex distributions were similar among the groups. Age and sex distributions were as: 23 patients with untreated SH (Group A; 7 male, mean age: 40.9 ± 1.6 years), 21 patients with treated SH (Group B; 6 male, mean age: 40.2 ± 2.1 years) and 25 healthy volunteers (8 male, mean age: 39.9 ± 2.8 years) ($p = 0.329$, $p = 0.969$, respectively). Mean serum TSH and free T4 levels were 11.7 ± 2.9 uIU/mL and 1.16 ± 0.06 ng/dL for group A; 2.6 ± 0.3 uIU/mL and 1.35 ± 0.09 ng/dL for group B; 1.4±0.3 uIU/mL and 1.31±0.09 ng/dL for control group, respectively ($p = 0.001$ and $p = 0.122$, respectively). All patients and controls had normal LV ejection fraction (group A = 63.7 ± 5.6%, group B = 65.3 ± 3.5%, group C = 66.2 ± 3.9%, $p = 0.150$). LV strain and strain rate data of the groups are shown in Table II. The untreated SH patients had significantly lower LV strain and strain rate values compared to controls. The treated SH patients had higher LV strain and strain rate values compared to untreated SH patients although the difference was not statistically significant. The treated SH patients had lower LV strain and strain rate values compared to controls but the difference was not statistically significant.

Discussion

We showed that patients with untreated SH had significantly lower LV strain and strain rate values and the treated SH patients had lower LV strain and strain rate values without statistical significant differences compared to controls.

Thyroid dysfunction is a condition which effects cardiac performance. Triiodothyronine (T3) is biologically active form of thyroid hormone and effects heart by increasing transcriptions of some genes. There are two main thyroid hormone receptor (TR) genes in human heart (TRα and TRβ)[16,17]. Most of the structural and functional proteins such as sarcoplasmic reticulum calcium adenosine triphosphatase (ATP-ase) (SERCA2), α mysosin heavy chain (α MHC), β1 adrenergic receptors, sodium-potassium ATP-ase and atrial brain natriuretic hormone and

Table I. Baseline characteristics and laboratory findings.

	Group A n = 23	Group B n = 21	Control n = 25	*p*
Age (years)	40.9 ± 1.6	40.2 ± 2.1	39.9 ± 2.8	0.329
Sex (male-%)	7 (30.4%)	6 (28.6%)	8 (32%)	0.969
TSH Levels (mIU/mL)	11.7 ± 2.9	2.6 ± 0.3	1.4 ± 0.3	0.001
Free T4 Levels (ng/dl)	1.16 ± 0.06	1.35 ± 0.09	1.31 ± 0.09	0.122
LVEF (%)	63.7 ± 5.6	65.3 ± 3.5	66.2 ± 3.9	0.150

TSH: Thyroid-Stimulating Hormone; T4: L-Thyroxine; LVEF: Left Ventricular Ejection Fraction.

Table II. Left ventricular strain and strain rate data.

	Strain (%)				Strain rate (1/s)			
	Group A	Group B	Control	*p*	Group A	Group B	Control	*p*
$Septal_{basal}$	–17.2 ± 3.7	–18.1 ± 3.3	–19.8 ± 2.4	0.020*	–1.3 ± 0.2	–1.3 ± 0.3	–1.4 ± 0.2	0.022*
$Septal_{mid}$	–18.7 ± 3.5	–19.0 ± 3.7	–21.2 ± 2.8	0.023*	–1.3 ± 0.2	–1.3 ± 0.1	–1.4 ± 0.2	0.001*,+
$Septal_{apical}$	–19.2 ± 5.4	–20.8 ± 3.7	–23.0 ± 5.3	0.035*	–1.3 ± 0.2	–1.4 ± 0.2	–1.6 ± 0.4	0.004*
$Lateral_{basal}$	–15.8 ± 5.7	–18.2 ± 3.6	–20.0 ± 4.7	0.012*	–1.4 ± 0.3	–1.5 ± 0.2	–1.6 ± 0.4	0.070
$Lateral_{mid}$	–15.9 ± 3.9	–18.8 ± 3.0	–19.3 ± 4.4	0.009*	–1.2 ± 0.3	–1.3 ± 0.1	–1.5 ± 0.3	0.018*
$Lateral_{apical}$	–17.3 ± 4.5	–19.5 ± 3.0	–21.7 ± 5.0	0.004*	–1.3 ± 0.3	–1.4 ± 0.2	–1.5 ± 0.4	0.035*
Global	–17.3 ± 3.3	–19.0 ± 2.3	–20.8 ± 2.9	< 0.001*				

Posthoc analysis: *$p < 0.05$ Group A vs Control group; $^{+}p < 0.05$ Group B vs Control group.

phospholamban are regulated by thyroid hormones. T3 leads to upregulation of SERCA2 and downregulation of phosplolamban and improve diastolic relaxation of the heart. So that, alterations of serum T3 level may cause cardiac dysfunction[16,17].

Thyroid dysfunction is related with risk of heart failure. Increased and decreased level of TSH was associated with higher risk of heart failure development, especially for TSH ≥ 10 mIU/L and for TSH < 0.10 mIU/L (HR: 1.86, $p < 0.01$ and HR:1.94, $p < 0.047$ respectively)[18]. Hyperthyroid patients have increased heart rate and stroke volume that result in high cardiac output state. But long term exposure to high thyroid hormone level and high cardiac output state may cause atrial fibrillation, ventricular dilatation and initiates the development of heart failure[19]. Heart failure risk is increased with underlying cardiovascular disease in hyperthyroid patients. On the contrary, hypothyroid patients have low heart rate and low stroke volume that results in low cardiac output[16]. Low T3 level leads to increased phospholamban and decreased SERCA activity, and results in decreased systolic and diastolic function of the heart[16]. Liu et al[20] showed that decreased thyroid hormone levels after thyroidectomy lead to cardiac atrophy and severe cardiac dysfunction and loss of the arterioles. These findings suggested that hypothyroidism is associated with low cardiac output. To evaluate the systolic and diastolic function of heart in hypothyroid and hyperthyroid state, standard 2D echocardiography and Doppler measurements can be used.

In a study, the mean peak systolic strain, the mean peak systolic strain rate, the mean peak early diastolic strain rate and the mean peak late diastolic strain rate were lower in overt hypothyroidism compared to controls by tissue Doppler imaging[21]. In a meta-analysis, association between SH and LV function was evaluated. SH was associated with LV diastolic dysfunction. There were significant differences between SH patients and normal controls in LV late diastolic filling flow velocity (Weighted mean difference: WMD = 4.51, 95% CI: 2.41 to 6.61), E/A (WMD = –0.22, 95% CI: –0.30 to –0.13) and the left ventricular isovolumic relaxation time (WMD = 6.13, 95%CI: 2.79 to 9.48). Whereas there was not observed difference in LV systolic function[22].

Although standard echocardiographic measurements and tissue Doppler imaging can be useful to evaluate systolic and diastolic function of heart, diagnostic value of standard echocardiography is limited in early phase of cardiac dysfunction. Therefore, a more precise assessment of cardiac function, 2D speckle tracking echocardiography, can be used as a diagnostic method. Speckle tracking echocardiography is a quantitative technique to evaluate myocardial function by analyzing spots on the two-dimensional gray-scale ultrasound images of myocardium. It is not user dependent and not affected from angle. To be independent in terms of the Doppler method enables you to examine all the regions in the short axis. "Strain" and "strain rate" values are not affected by the movement of heart. Strain shows regional deformation of myocardium, "strain rate" shows the relationship between the time and deformation. Speckle tracking also provides information about the segmental wall function[23].

In a study, myocardial strain was evaluated during transition from exogenous hyperthyroidism to overt hypothyroidism in patients with differentiated thyroid carcinoma. Longitudinal and circumferential myocardial strain improved during changes from hyperthyroid state to euthyroid state and deteriorated again in hypothyroid conditions without significant changes in LV dimensions or systolic function[24].

In our study, we used 2D speckle tracking echocardiography to evaluate cardiac function in hypothyroid state. As shown in previous studies, untreated SH was associated with impairment in LV longitudinal myocardial function compared to healthy controls (p value < 0.001). In fact, cardiac functions improve with the replacement of thyroid hormone level in hypothyroid state. We also found that there was no significant difference in myocardial strain and strain rate values except mid septal strain rate between healthy controls and treated SH patients. So, our findings support this hypothesis. In the present study, by using speckle tracking echocardiography LV systolic dysfunction can be early assessed in SH patients who have normal ejection fraction values. Because our study is a cross-sectional study, prospective investigations must be done in order to conclude this issue.

Conclusions

Although standard echocardiography can demonstrate LV systolic function impairment in patients with SH, it does not provide information regarding myocardial systolic and diastolic properties. Untreated SH is associated with impairment in LV longitudinal myocardial function. In this work, we demonstrated that speckle tracking echocardiography is not only useful for early detection of LV impairment in SH but also might be useful to show reversal of impairment.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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