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*Original Article*

# Comparison of myocardial deformation indices during rest and after activity in untreated hyperthyroid patients with normal population

Maryam Shojaeifard[1], Zahra Davoudi[2], Azam Erfanifar[2], Fatemeh Karamali[1], Hamed Fattahi Neisiani[1], Shirin Habibi Khorasani[1,3], Khadije Mohammadi[1,3]

[1]*Echocardiography Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran;* [2]*Department of Endocrinology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran;* [3]*Cardiovascular Research Center, Kerman University of Medical Sciences, Kerman, Iran*

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**Abstract:** Background: Thyroid hormones play an essential role on the cardiovascular system. Also, thyroid diseases have a prominent adverse effect on myocardial and vascular functions. Therefore, the aim of this study was to compare myocardial deformation indices during resting and after activity between the untreated hyperthyroid patients and normal population. Methods: We included 26 untreated participants who were newly diagnosed with hyperthyroidism and 26 healthy participants matched in terms of age and sex. The left ventricular end-diastolic volume index (LVEDVI), Heart Rate (HR), Cardiac Output (CO), systolic and diastolic blood pressures, Global Longitudinal Strain (GLS), Global Circumferential Strain (GCS), Rate-Pressure Product (RPP), systolic and diastolic strains rates were measured in rest and peak of exercise in stress echocardiography. Results: Age and sex distributions were similar among the groups. Also, mean serum TSH was 0.08 ± 0.08 ng/dL in the case group. The participants with the untreated hyperthyroidism had lower Ejection Fraction change (ΔEF), GLS, peak stress systolic and diastolic strains rates compared to the control group. Also, there was a positive association between TSH levels and basal HR, RPP, CO, as well as a negative correlation with basal and maximum GLS, ΔHR, ΔEF, and ΔCO. Also, a duration of symptoms had a linear association with rest HR, CO, and LVEDVI, as well as a negative correlation with rest and maximal GLS, ΔHR, and ΔGLS. Conclusion: Myocardial deformation assessed by 2DE imaging are significantly impaired in the hyperthyroid patients. In this regard, further studies with a larger sample size are required to confirm the results of this study.

**Keywords:** Hyperthyroidism, tissue Doppler imaging, myocardial deformation, global longitudinal strain, global circumferential strain

## Introduction

Thyroid hormones affect the most of the body parts, especially the cardiovascular system [1]. The cardiovascular consequences of hyperthyroidism have been defined in the last centuries, which are known as the cornerstone of its diagnosis in medical practice. The patients with manifest, subclinical, and even compensated hyperthyroidism are significantly at a higher risk for myocardial involvement compared to general population [2, 3]. In this regard, various mechanisms have been proposed for the effect of thyroid hormones on cardiac parameters. However, most of these side effects appear to be due to molecular mechanisms by which triiodothyronine (T3) affect the myocardium and cardiovascular arteries. In fact, thyroid hormones can affect the tissue and function of the heart through both genetic and non-genetic mechanisms. Moreover, due to the lipophilic properties of thyroid hormones, they have the ability of crossing the cytoplasmic membrane of cardiac tissue, and after entering the nucleus of heart cells and binding to specific receptors (thyroid hormone receptors (THRs)), they cause the formation of special complexes and then initiate the transcription process [4]. Currently, in cardiology, diagnostic approaches deserve special attention, which allow you to record the earliest preclinical signs of heart and vascular dysfunctions. Therefore, to assess the contractile function of the LV, the speckle tracking method is used, based on the determination of systolic deformation of the LV walls [5, 6]. For myocardial deformation evaluation, a video sequence of LV ultrasound images synchronized with an ECG that was recorded during contraction, is used. In addition, the analysis program automatically monitors the trajectory of the control points of the LV segments, and then builds a model of LV systolic deformation reflecting local (segmental) and global contractility (LV global systolic longitudinal strain (GLS)). Violation of the longitudinal contractile function is known as the earliest manifestation of LV mechanical dysfunction [7, 8]. Previous studies have shown that, in some diseases such as amyloidosis and diabetes, myocardial contractile function decreases to subclinical changes, which were diagnosed using the special tracking [9, 10]. Moreover, it has been reported that, the echocardiographic evaluation of myocardial function mainly depends on the assessment of regional wall motion abnormality (RWMA) and left ventricular ejection fraction. However, in recent years, the limitations of this method, specially subjective and operator-dependent ones that require the complete visualization of endocardium and being affected by changes in cardiac loading and heart rate, have led to attempts for introducing new methods. The introduction of two-dimensional (2D) speckle tracking echocardiography (STE) has enabled LV GLS assessment, which currently serves as a useful and well established robust marker of systolic myocardial function [11, 12]. Especially, LV GLS was proved as a useful tool for the evaluation of subclinical myocardial dysfunction despite normal LV ejection fraction (LVEF) [13, 14]. On the other hand, clinicians can obtain valuable information from LV GLS in several cardiac diseases including acute myocardial infarction, heart transplantation, and other acute and chronic cardiac disorders [15]. Exercise stress echocardiography (SE) is a useful method that allows a rapid evaluation of myocardial function under the conditions of physiological stress. Accordingly, clinicians mostly use this method to assess the inducible ischemia or myocardial viability. Moreover, in recent years, SE was used for the evaluation of non-ischemic heart diseases. In addition, it has been reported that with LV GLS assessment under the stressful condition provided, myocardial deformation capacity can provide an additional value to rest strain assessment by allowing further recognition of early subtle myocardial dysfunction or incipient damage [16, 17]. Correspondingly, these methods have dramatically increased the accuracy of myocardial function assessment [18, 19]. Despite the expanded use of LV GLS, only limited data currently exit on the application of LV strain in the patients with hyperthyroidism.

The present study aimed to compare the myocardial deformation indices during resting and after activity between the untreated hyperthyroid patients and normal population.

## Materials and methods

### *Study population*

The present trial was a case control study conducted in the Rajaie Cardiovascular Medical and Research Center, Tehran, Iran. In this study, 52 participants were recruited from January 2019 to January 2020. The study protocol was approved by local research ethics committee and the informed consent was obtained from all the participants. The case group included 26 newly diagnosed hyperthyroid patients and the control group consisted of 26 healthy subjects. Notably, hyperthyroidism was diagnosed based on the higher than normal concentration of serum free Thyroxin (T4) and T3 and Thyroid stimulating hormone (TSH) < 0.4 mIU/mL. The included subjects had no history of heart failure, hypertension, coronary artery disease, previous cerebrovascular insult, atrial fibrillation, congenital heart disease, valvular heart disease, pulmonary hypertension, diabetes mellitus, anemia, pulmonary, and neuromuscular disease and they consumed no medication. The control subjects were chosen among people with normal stress echocardiography results who were referred to our echo lab for checkup or non-anginal chest pain, and they had no past medical history with normal lab test's results for thyroid function, lipid profile, blood sugar, and hemoglobin. In the screening phase, the patients were assessed by electrocardiography (ECG) and conventional echocardiography. Accordingly, those with valvular heart disease, any structural heart disease, left ventricular (LV) systolic dysfunction by means of LV ejection fraction of less than 55% in terms of the Simpson method, pulmonary hypertension (systolic pulmonary artery pressure more than 35 mmHg using tricuspid regurgitation (TR) velocity), and non-sinus rhythm were excluded from this study.

*Exercise stress test protocol*

All the participants included in this study underwent a treadmill exercise test in terms of the Bruce protocol under the supervision of a board certified cardiologist. End points for exercise were chest pain, dyspnea, exhaustion, target heart rate of more than 90% adjusted by age, and a significant ST segment deviation. Moreover, heart rate, blood pressure, and other ECG were assessed and then reported before the beginning of exercise (rest situation) and at any stage. Also, the rate-pressure product (RPP) was calculated as the product of heart rate (beats per minutes) and systolic arterial pressure (mmHg).

*Stress echocardiography*

Standard echocardiography using a complete two dimensional (2D) and Doppler echocardiography was performed for the subjects who were at rest in left lateral decubitus position, by an expert operator using the same machine (affinity 70 Philips with 1-5 MHz transducer) in terms of the American society of echocardiography recommendation. LV end diastolic and end systolic volumes and EF were calculated from apical two and four chamber views based on the modified Simpson method. For global 2D strain analysis, a digital loop was acquired from parasternal short axis views at the apex, mid-papillary, and mitral valve levels for circumferential strain, and also from apical 4-chamber, 2-chamber, and apical long axis views for longitudinal strain. Afterward, the patients and control subjects underwent an exercise stress echocardiography by treadmill for the evaluation of their functional class, ischemia, and arrhythmia. Peak stress images including 5 standard echocardiographic views (parasternal long and short axis views, apical 4 chamber, 3 chamber, and 2 chamber views) were obtained immediately after the cessation of test during one minute for the evaluation of ischemia and for the analysis of speckle tracking strain. All the images were then transferred to Q-lab and retrospectively analyzed. Also, we traced along the LV endocardial border at the end-systolic frame. Accordingly, the strain curve was extracted from the grayscale images using dedicated software. Peak strain was defined as the peak negative value on the strain curve during the entire cardiac cycle. Moreover, Peak GLS and Global Circumferential Strain (GCS) were calculated from the entire U-shaped (GLS) and circular-shaped (GCS) LV myocardium as follows: global strain (%) = (L [end-systole] - [end-diastole])/L (end-diastole) × 100. In this regard, GLS was averaged from global strains from the apical 4-, 3- and 2-chamber views. In addition, GCS was averaged from 3 short axis (basal, mid, and apical) views.

*Biochemical assessment*

In this study, we used the radioimmunoassay method for the evaluation of T3 and T4 and Enzyme-Linked Immunosorbent Assay (ELISA) method for TSH using some commercially available kits for TSH (Pishgaman Sanjesh-IRAN).

*Statistical analysis*

The normality of quantitative data was evaluated by Kolmogorov-Smirnov test. To analyze the qualitative variables, we applied the chi-square test. Baseline characteristics of the participants in the case and control groups are shown as mean ± SD for quantitative variables, and as frequency (%) for descriptive variables. Several significant differences were evaluated in general characteristics of the categories of the case and control groups using one-way analysis of variance or Chi-square test, based on the type of variables, as quantitative or qualitative, respectively. Moreover, we used the "independent samples t-test" and "Mann-Whitney U test" for the evaluation of the numerical variables with and without normal distribution, respectively. One-way analysis of variance (ANOVA) and LSD post-hoc tests were used to compare the groups in terms of quantitative variables. Also, analysis of covariance (ANCOVA) was used to adjust the effect of confounding variables. Statistical analysis of the obtained data was done using SPSS version 22 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY). *P*-value < 0.05 was considered as statistically significant.

## Results

The final analyses were conducted on 52 participants (26 cases and 26 controls) with complete information. In this regard, baseline char-

**Table 1.** Baseline characteristics of the hyperthyroid patients

| Characteristics | Value |
|---|---|
| Age, mean ± SD (years old) | 39.77 ± 12.00 |
| Female sex, n (%) | 14 (53.8%) |
| BSA ($m^2$) | 1.81 ± 0.20 |
| TSH, mean (range) | 0.081 (0.001-0.4) |
| Duration of symptoms (month), median (IQR) | 5.5 (3.7-12) |
| Etiology of hyperthyroidism, n (%) | |
| Graves | 21 (80.76%) |
| Toxic multi nodular goiter | 3 (11.54%) |
| Toxic adenoma | 1 (3.85%) |
| Sub-acute hyper thyroiditis | 1 (3.85) |
| Symptoms, n (%) | |
| Palpitation | 12 (46.2%) |
| Exertional dyspnea | 16 (61.52%) |
| Atypical chest pain | 5 (19.2%) |

SD: Standard Deviation, n: number, BSA: Body Surface Area, TSH: Thyroid Stimulating Hormone, IQR: Inter-Quartile Range.

acteristics of the hyperthyroid patients are presented in the **Table 1**. Mean age of the participants in the case group was 39.77 ± 12.00 years old, and in the control group, it was 40.53 ± 10.34 years old, and no significant difference was observed between these two groups (P=0.8). Also, 53.8% of the participants in both groups were women and 46.2% of them were men. The etiology of hyperthyroidism was Graves (80.76%), toxic multi nodular goiter (11.54%), toxic adenoma (3.85%), and sub-acute thyroiditis (3.85%). Moreover, cardiovascular symptoms and signs were as follows: palpitation (46.2%), exertional dyspnea (61.5%), and atypical chest pain (19.2%).

The comparison of myocardial indices between the hyperthyroid patients and control subjects is shown in **Table 2**. Notably, TSH concentration in the hyperthyroid patients was 0.08 ± 0.08 mU/l. There was no significant difference between these two groups in Body Surface Area (P=0.43) and sex.

*Hemodynamic parameters findings*

The indices of SBP, DBP, and RPP are presented in **Table 2**. In the rest and maximum exercise situation, there was no significant difference in SBP and DBP between the case and control groups (P > 0.05). Also, there was no significant difference between the two groups in ΔSBP (29.53 ± 15.85 vs. 40.07 ± 25.92; P=0.08) and ΔDBP (9.92 ± 7.51 vs. 12.92 ± 10.43; P=0.24). Moreover, RPP value was higher in the hyperthyroid patients compared to the control group in the rest position (10778.61 ± 1739.53 vs. 8636.15 ± 1347.45; P < 0.01); however, it was not significantly different in the maximal exercise (P=0.93). In addition, the hyperthyroid patients had a higher CO than control group in the rest situation (3.11 ± 0.59 vs. 2.62 ± 0.44; P=0.001); however, ΔCO was significantly lower in the hypothyroid patients compared to the control subjects (2.20 ± 1.27 vs. 2.89 ± 0.96; P=0.03). Moreover, we found no significant difference between these two groups in EF in the rest situation (P=0.11); however, the participants with hyperthyroidism had a lower EF in the maximal exercise situation (61.68 ± 4.58 vs. 64.51 ± 4.04; P=0.02). Accordingly, ΔEF was significantly lower in the hyperthyroid patients compared to the control group (3.29 ± 6.50 vs. 7.96 ± 4.15; P=0.03).

*Myocardial deformation indices*

The amount of LVEDVI, and systolic and diastolic strains rates data of the participants are shown in **Table 2**. The patients with hyperthyroidism had a significantly higher LVEDV than control group (48.64 ± 7.41 vs. 43.62 ± 5.78; P=0.003). Also, they had significantly lower systolic and diastolic strains rates compared to the control group in the maximal exercise situations (**Figure 1**). Furthermore, Speckle tracking analysis showed that GLS values were significantly lower in the hyperthyroid group compared to the controls in both rest (18.37 ± 1.60 vs. 20.18 ± 0.90; P < 0.001) and maximal exercise situations (19.33 ± 2.48 vs. 23.01 ± 1.36; P < 0.001) (**Figure 2**). Also, the hyperthyroid patients in the maximal exercise situation had a lower GCS value compared to the control group. Moreover, there was a significant difference in terms of ΔGCS between the hyperthyroid patients and the control subjects (0.15 ± 3.95 vs. 2.84 ± 2.42; P=0.005).

*Association of myocardial parameters with TSH concentration and clinical symptoms*

As shown in **Table 3**, there was a positive correlation among TSH concentration and

**Table 2.** Comparison of clinical and echocardiographic variables between hypothyroid and control group

| Variables | Case | Control | *P*-value |
|---|---|---|---|
| Age (year) | 39.77 ± 12.00 | 40.53 ± 10.34 | 0.8 |
| BSA ($m^2$) | 1.81 ± 0.2 | 1.77 ± 0.14 | 0.43 |
| Sex, n (%) | | | |
| Female | 14 (53.8%) | 14 (53.8%) | 1.00 |
| Male | 12 (46.2%) | 12 (46.2%) | 1.00 |
| HR (bpm) | | | |
| Rest | 86.38 ± 10.13 | 72.23 ± 7.95 | < 0.001 |
| Maximal exercise | 165.73 ± 13.12 | 169.07 ± 10.85 | 0.321 |
| ΔHR | 79.34 ± 13.41 | 96.84 ± 10.43 | < 0.001 |
| SBP (mmHg) | | | |
| Rest | 124.69 ± 10.48 | 115.61 ± 23.69 | 0.08 |
| Maximal exercise | 154.23 ± 14.74 | 155.69 ± 19.12 | 0.75 |
| ΔSBP | 29.53 ± 15.85 | 40.07 ± 25.92 | 0.08 |
| DBP (mmHg) | | | |
| Rest | 77.61 ± 7.91 | 73.84 ± 9.29 | 0.122 |
| Maximal exercise | 87.53 ± 7.44 | 86.76 ± 11.35 | 0.77 |
| ΔDBP | 9.92 ± 7.51 | 12.92 ± 10.43 | 0.24 |
| RPP | | | |
| Rest | 10778.61 ± 1739.53 | 8636.15 ± 1347.45 | < 0.001 |
| Maximal exercise | 25595.92 ± 3465.72 | 25488.92 ± 5321.89 | 0.93 |
| ΔRPP | 14817.30 ± 3410.36 | 16852.76 ± 4861.84 | 0.08 |
| EF (%) | | | |
| Rest | 58.38 ± 5.15 | 56.54 ± 2.58 | 0.11 |
| Maximal exercise | 61.68 ± 4.58 | 64.51 ± 4.04 | 0.02 |
| ΔEF | 3.29 ± 6.50 | 7.96 ± 4.15 | 0.003 |
| CO index | | | |
| Rest | 3.11 ± 0.59 | 2.62 ± 0.44 | 0.001 |
| Maximal exercise | 5.32 ± 1.16 | 5.51 ± 1.11 | 0.551 |
| ΔCOI | 2.20 ± 1.27 | 2.89 ± 0.96 | 0.03 |
| LVEDVI | 48.64 ± 7.41 | 43.62 ± 5.78 | 0.003 |
| GLS (%) | | | |
| Rest | -18.37 ± 1.60 | -20.18 ± 0.90 | < 0.001 |
| Maximal exercise | -19.33 ± 2.48 | -23.01 ± 1.36 | < 0.001 |
| ΔGLS | -0.96 ± 1.90 | -1.64 ± 0.82 | < 0.001 |
| sys SR | | | |
| Rest | 1.93 ± 0.36 | 1.96 ± 0.28 | 0.71 |
| Maximal exercise | 3.16 ± 0.86 | 3.61 ± 0.8 | 0.05 |
| Δsys SR | 1.23 ± 0.72 | 1.64 ± 0.82 | 0.05 |
| dia SR | | | |
| Rest | 2.07 ± 0.63 | 2.28 ± 0.55 | 0.21 |
| Maximal exercise | 2.82 ± 0.75 | 3.51 ± 0.55 | < 0.001 |
| Δdia SR | 0.74 ± 0.79 | 1.23 ± 0.60 | 0.01 |
| GCS (%) | | | |
| Rest | -25.00 ± 5.02 | -25.92 ± 4.18 | 0.47 |
| Maximal exercise | -25.16 ± 4.57 | -28.77 ± 3.48 | 0.002 |
| ΔGCS | -0.15 ± 3.95 | -2.84 ± 2.42 | 0.005 |

CO: Cardiac Output Index; EF: Ejection Fraction; HR: Heart Rate; LVEDVI: Left Ventricular End Diastolic Volume Index; GCS: Global Circumferential Strain; GLS: Global longitudinal Strain; DBP: Diastolic Blood Pressure; dia SR: diastolic Strain Rate; SBP: Systolic Blood Pressure; RPP: Rate-Pressure Product; sys SR: Systolic Strain Rate.

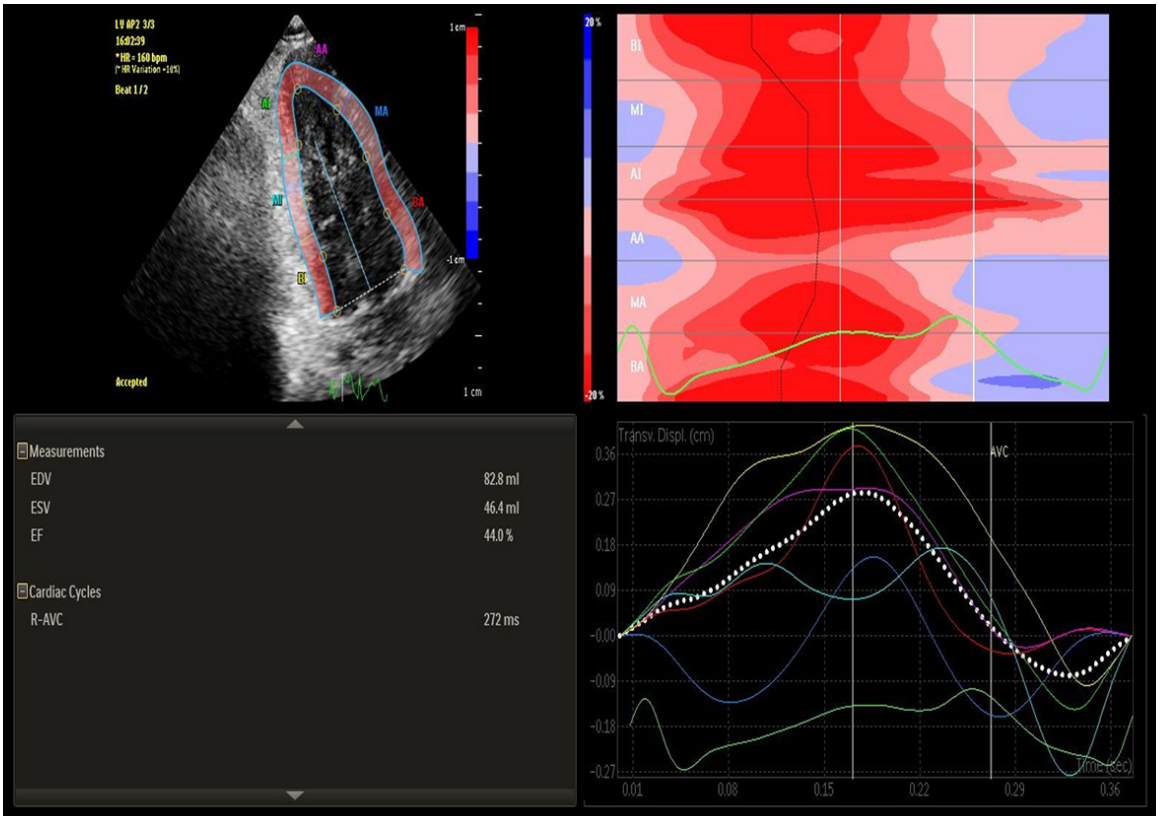


**Figure 1.** Left ventricular strain rate in a hyperthyroid patient at peak of stress test (heart rate about 160 bpm). Systolic strain rate is about 0.27 $s^{-1}$ that is significantly lower than control subjects.

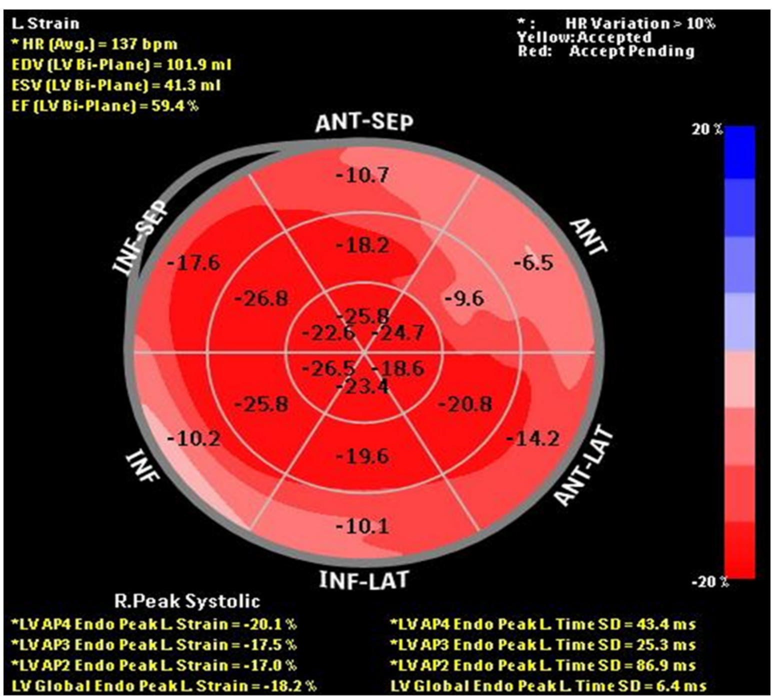


**Figure 2.** Left ventricular Global Longitudinal Strain (GLS) in a hyperthyroid patient at peak of stress test (-18.2%) that showed a subtle increase in GLS from resting GLS (not showed here) compared to control subjects.

basal HR (r=0.36, P=0.009), RPP (r=0.34, P=0.01), EF (r=0.3, P=0.03), and CO (r=0.27, P=0.04), as well as a negative correlation with maximum EF (r=-0.28, P=0.03), ΔEF (r=-0.43, P=0.001), ΔHR (r=-0.3, P=0.02), and basal and maximum GLS and ΔCO (r=-0.34, P=0.01), respectively. Also, there was a positive association among the duration of symptoms with basal HR (r=0.5, P < 0.001), RPP (r=0.49, P < 0.001), and LVEDVI (r=0.4, P=0.003), as well as a negative correlation with basal GLS (r=-0.53, P < 0.001), maximum GLS (r=-0.55, P < 0.001), maximum dia SR (r=-0.33, P=0.01), ΔHR (r=-0.61, P < 0.001), ΔRPP (r=-0.31, P=0.02), and ΔGLS (r=-0.35, P=0.009).

**Table 3.** Pearson correlation coefficients between TSH level and duration of symptoms of participants with hemodynamic and echocardiographic data

| Myocardial deformation indices | TSH levels | | Duration of symptoms | |
|---|---|---|---|---|
| | r | P | r | P |
| TSH | 1 | - | 0.36 | 0.008 |
| Duration of symptoms | 0.36 | 0.008 | 1 | - |
| HR-1 | 0.36 | 0.009 | 0.5 | < 0.001 |
| HR-2 | -0.03 | 0.8 | -0.27 | 0.05 |
| SBP-1 | 0.13 | 0.328 | 0.2 | 0.137 |
| SBP-2 | -0.003 | 0.98 | -0.06 | 0.62 |
| DBP-1 | 0.14 | 0.3 | 0.18 | 0.2 |
| DBP-2 | 0.07 | 0.61 | 0.05 | 0.68 |
| RPP-1 | 0.34 | 0.014 | 0.49 | < 0.001 |
| RPP-2 | 0.04 | 0.74 | -0.09 | 0.51 |
| LVEDVI-1 | 0.07 | 0.59 | 0.4 | 0.003 |
| EF-1 | 0.3 | 0.03 | -0.06 | 0.64 |
| EF-2 | -0.28 | 0.03 | -0.15 | 0.27 |
| CO-1 | 0.27 | 0.04 | 0.34 | 0.01 |
| CO-2 | -0.21 | 0.12 | 0.04 | 0.74 |
| GLS-1 | -0.37 | 0.007 | -0.53 | < 0.001 |
| GLS-2 | -0.3 | 0.02 | -0.55 | < 0.001 |
| sys SR-1 | -0.007 | 0.96 | -0.008 | 0.95 |
| sys SR-2 | -0.1 | 0.46 | -0.16 | 0.25 |
| dia SR-1 | -0.09 | 0.52 | -0.25 | 0.06 |
| dia SR-2 | -0.15 | 0.26 | -0.33 | 0.01 |
| GCS-1 | 0.02 | 0.86 | -0.07 | 0.59 |
| GCS-2 | -0.17 | 0.21 | -0.22 | 0.1 |
| ΔHR | -0.3 | 0.02 | -0.61 | < 0.001 |
| ΔSBP | -0.12 | 0.39 | -0.23 | 0.09 |
| ΔDBP | -0.06 | 0.65 | -0.11 | 0.42 |
| ΔRPP | -0.1 | 0.47 | -0.31 | 0.02 |
| ΔEF | -0.43 | 0.001 | -0.07 | 0.6 |
| ΔCO | -0.34 | 0.01 | -0.12 | 0.37 |
| ΔGLS | -0.13 | 0.33 | -0.35 | 0.009 |
| Δsys SR | -0.1 | 0.44 | -0.17 | 0.22 |
| Δdia SR | -0.08 | 0.55 | -0.12 | 0.36 |
| ΔGCS | -0.25 | 0.07 | -0.18 | 0.18 |

CO: Cardiac Output; EF: Ejection Fraction; HR: Heart Rate; GCS: Global Circumferential Strain; GLS: Global longitudinal strain; DBP: diastolic Blood Pressure; dia SR: diastolic Strain Rate; SBP: systolic blood pressure; RPP: Rate-Pressure product; sys SR: systolic Strain Rate.

## Discussion

In those subjects suffering from the hyperthyroidism, with a higher frequency than the general population; hypertension, LVH, and LV systolic and diastolic dysfunctions were detected. The present study provided new insights into the effects of thyroid hormone on myocardial mechanical under both rest and stressful conditions by 2D-STE.

We assessed the myocardial deformation response to exercise stress testing in the patients with hyperthyroidism, and we reported the following three main findings: (1) The hyperthyroid patients had higher RPP, CO, LVEDV in the rest situation as well as lower EF, systolic and diastolic strains rates, and GLS and GCS in the exercise stress testing; (2) There was a positive correlation between TSH concentrations and basal HR, RPP, and CO as well as a negative association with EF, ΔEF, ΔHR, and basal and maximum GLS and ΔCO, respectively, and (3) There was a positive association among the duration of symptoms and basal HR, RPP, and LVEDVI, as well as a negative correlation with basal and maximum GLS, maximum diastolic SR, ΔHR, ΔRPP, and ΔGLS.

Myocardial function evaluation is one of the most important factors in diagnosing and monitoring of the patients with various cardiovascular diseases. Moreover, it has been reported that, new mayocardial function related parameters, especially the long axis parameters, can provide a comprehensive insight on LV systolic function, which has been proved as valuable in detecting subtle myocardial dysfunction in the patients with normal LVEFs [20]. Accordingly, this feature may be correlated with the longitudinal orientation of subendocardial muscle fibers as well as their responsiveness to ischemic injury, edema, and fibrosis [21, 22].

Thyroid hormones exert some significant effects on the cardiovascular system. In this regard, T3 is known as the biologically active form of thyroid hormone, which exerts some of its effects by affecting the TRα and TRβ receptors expressions. Various studies have evaluated the changes in the structure and function of the cardiovascular system in the patients with hyperthyroidism. Therefore, it has been shown that, hyperthyroidism increase HR and stroke volume, which result in a high CO state. In line with our findings, Zhou et al. reported that in the rest situation, HR and CO slightly increased in young adults who were newly diagnosed with hyperthyroidism due to Graves' disease [23]. Also, it has been shown in several other studies that, a higher concentration of thyroid hormones usually results in the increased CO with the reduced systemic vascular resistance as well as an increase in resting heart rate, blood volume, and left ventricular contractility [24, 25]. Recent studies revealed that, the long-term thyroid hormone replacement in the thyroid patients after myocardial infarction can lead to a significant improvement in the LV contractility [26-28]. Maor et al. in a case control study conducted on 70 patients with subclinical hyperthyroidism and 273 patients with hypothyroidism, reported that the patients in the hyperthyroidism group experienced a higher resting HR as well as a significantly lower HR at the end of the test [29]. However, some of the other studies revealed that, HR and CO in the hyperthyroid patients increased at both rest and exercise stress and also decreased during reserve situation [30, 31]. In our study, we showed a significant increase in CO in the rest situation as well as a significant difference between the two groups in ΔCO. This result was in line with that of the George et al.' study [32].

Prolonged exposure with a higher concentration of thyroid hormone and a higher CO can cause atrial fibrillation, ventricular dilation, and the increased risk of heart failure [33]. The negative association between serum T3 level and EF in the patients with hyperthyroidism is supported from this hypothesis that impaired functional left ventricular reserve is seen in these patients. Accordingly, these subjects had a less than expected increase in left ventricular contractility during doing exercise (markedly the reduced Δ end-systolic volume index); however, they showed the appropriate response after the antithyroid treatment, which suggests a direct effect on the myocardium of an excess of circulating T3 [34, 35].

One of the cardiac complications observed in the hyperthyroid patients, which was also reported in some studies, was subclinical LV systolic dysfunction as evaluated by multidirectional strains. The results of our study showed that, in the hyperthyroid patients, GLS, peak stress GCS, and systolic and diastolic strains rates were less than the control group. In a study conducted by Tadic et al. the association between subclinical hyperthyroidism (SCH) and left ventricular deformation was evaluated between the 35 untreated women with SCH and 35 healthy subjects. They found that 2DE LV longitudinal and circumferential strains have significantly reduced in the patients with SCH. Also, in line with our findings, they found that systolic and diastolic strains rates have reduced in the SCH group. As shown, many studies on the patients with hyperthyroidism showed a decrease in the global strain or in the strain rate. Regional dysfunction that occurs at different segments or levels of LV walls may be considered as the early signature of the patients exposed to the elevated levels of thyroid hormones. Oxygen intake, endothelial dysfunction, and localized or diffuse myocardial inflammation may also lead to cardiac dysfunction in the patients with hyperthyroidism, along with neurohumoral and genetic factors [36, 37].

Some previous studies have suggested that, LV twist is the most common indicator of the LV systolic function, while LV untwisting rate is known as the common indicator of the LV diastolic dysfunction. Moreover, hyperthyroidism can affect both systolic and diastolic LV mechanical activities. On the other hand, LV systolic mechanics assessed by 2DE and 3DE strains is also impaired in the hyperthyroid patients [23, 38].

Our results also revealed the correlation among the serum TSH levels and duration of the symptoms, and LV structure, function, and mechanics. The progressive decrease in serum concentration of TSH was associated with a decrease in the basal and maximum exercise GLS, ΔEF, ΔHR, and ΔCO. Abdulrahman et al. reported a borderline correlation between 2DE longitudinal and circumferential strains with the TSH concentration [39]. Also, Tadic et al. showed a positive association among TSH and mitral E/A ratio, and LV longitudinal and circumferential strains [40]. Although the exact mechanism of changes in myocardial function in the patients with hyperthyroidism has not been determined yet, several mechanisms have been proposed in some studies. Accordingly, it has been reported that higher levels of thyroid hormones can decrease peripheral resistance and cause peripheral vasodilatation, the impaired the function of renin-angiotensin-aldosterone system, the reduced kidney perfusion, and the impaired LV and CO volumes [41-43].

Recently, some new imaging techniques have been introduced to evaluate the myocardial mechanics. In this regard, two dimensional (2D) speckle tracking echocardiography is a novel echocardiographic technique and strain rate gives researchers the opportunity to quantitatively evaluate myocardial function. Moreover, it has been reported that myocardial GLS have reduced with no changes in conventional echocardiographic values. Therefore, using this technique gives researchers and clinicians the opportunity to diagnose subclinical myocardial dysfunction at early stages [44].

The present study had several limitations as follows: firstly, considering that we exclude the patients with any comorbidity and those who were newly diagnosed ones, the main limitation of our study was a low sample size. Secondly, we selected our cases from outpatient clinic and did not include more severe cases who may need hospitalization.

## Conclusion

Although LV systolic function can be detected using standard echocardiography, it does not determine more accurate data on myocardial systolic and diastolic deformations. Untreated hyperthyroidism is associated with the impaired LV longitudinal myocardial function. In this case control study, we showed that some of the myocardial indices were impaired in the hyperthyroid patients. Also, we showed that, there was a significant association among TSH levels and GLS, ΔEF, ΔHR, and ΔCO. Further studies with larger sample sizes are required to confirm the results of this study.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Khadije Mohammadi, Cardiovascular Research Center, Shafa Hospital, Shafa Avenue, Kerman, Iran. Tel: +983432115758; E-mail: khma_65@yahoo.com

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