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Original Article

Right Ventricular Function Indices at Rest and During Exercise in Hyperthyroid Patients: A Cross-sectional Study

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Abstract

Background: Since hyperthyroidism could be associated with right ventricular dysfunction, this study intended to investigate right ventricular (RV) function using strain echocardiography in hyperthyroid patients both at rest and in maximum-stress conditions.

Methods: This cross-sectional study was conducted at Rajaie Cardiovascular Medical and Research Center, Tehran, Iran, from January 2019 to January 2020. All study participants completed a maximum treadmill exercise test, as well as a complete two-dimensional echocardiogram at rest and the peak of stress test. The data were analyzed using SPSS statistical software. The independent samples *t* test and Mann–Whitney U test were used for numerical, and the Chi square test was used for nominal variables. P<0.05 was considered statistically significant.

Results: The final analysis included 52 participants (26 subjects in each group). In a maximal stress situation, we found that among the RV function indices, RV global longitudinal strain (P=0.0001), systolic strain rate (P=0.0001), diastolic strain rate (P=0.0002), and tricuspid annular plane systolic excursion (P=0.019) were reduced significantly in the hyperthyroid patients compared to the control group. There was also a linear correlation between RV size and thyroid stimulating hormone (TSH) level (P=0.009, r=0.36). Moreover, we found a negative linear correlation between TSH level with maximum stress RV strain and diastolic strain rate (P<0.001).

Conclusion: The findings of the present study revealed a significant change in RV function indices among hyperthyroid patients. Therefore, it highlights the necessity of early diagnosis and treatment of hyperthyroidism, as well as RV function evaluation in these patients.

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Keywords ● Ventricular function, right ● Hyperthyroidism ● Exercise test ● Echocardiography

What's Known

- Thyroid hormones have significant effects on the heart and cardiovascular system, and hyperthyroidism affects left ventricular systolic and diastolic function differently.

What's New

- The study indicated that although right ventricular function indices may be normal at rest in hyperthyroid patients, they are impaired during the stress tests, and these patients lack a normal right cardiac reserve.

Introduction

Hyperthyroidism is a common disorder that is more prevalent in adults.[1] In recent years, hyperthyroidism-associated cardiac dysfunctions were more widely recognized. Elevated levels of thyroid hormones are associated with impaired ventricular contractility and relaxation.[2-4] Thyroid Hormones significantly affect the heart and cardiovascular system through a variety of direct and indirect mechanisms. Thyroid hormones have substantial cardiovascular consequences such as decreased peripheral vascular and post-load resistance and elevated heart rate, myocardial contractility, blood pressure, and cardiac output.[5]

There are conflicting findings from studies investigating the impact of hyperthyroidism on cardiovascular events.[6-8] As many studies supported the hypothesis that right ventricular (RV) disorders are correlated with increased risk of morbidity and mortality, RV function assessments are pushed to the forefront of clinical work.[9]

Another common complaint in patients with hyperthyroidism is pulmonary arterial hypertension (PAH), which affects 30 to 65% of these patients.[10, 11] It was reported that RV function was reduced in patients with pulmonary hypertension.[12]

With recent evidence demonstrating the critical role of RV in a number of disorders, including pulmonary hypertension (PH), congenital heart disease, ischemic heart disease, and left ventricular (LV) dysfunction prognosis, the determination of the RV feature becomes quickly essential in clinical practice.[13, 14] Therefore, Medical research concentrated on investigating RV size, feature, and myocardial dynamics as clinical outcome predictors.[15] An echocardiogram of heart function revealed that thyroid dysfunction could have a negative impact on left ventricular function. There are little and conflicting evidence on the influence of thyroid disease on the structure and function of the RV.[4, 16] In addition, the RV has a complex structure, and echocardiographic evaluation is challenging.[17, 18]

In recent years, researchers and clinicians have widely used tissue Doppler echocardiography to assess systolic and diastolic ventricular activity. The two-dimensional speckle tracking echocardiography (STE) is one of the most recent and precise methods of measuring RV function.[19, 20] Despite the high prevalence of cardiovascular dysfunction in hyperthyroid patients, few studies investigated the association between thyroid hormone concentrations with systolic and diastolic RV dysfunction and deformation indices in these patients.

Hence, the present study aimed to assess the right ventricular function in untreated hyperthyroid patients and compare the results to that of healthy individuals.

Patients and Methods

Study Population

This cross-sectional study was conducted from January 2019 to January 2020 at Rajaie Cardiovascular Medical and Research Center (Tehran, Iran). The study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.RHC.REC.1398.057). Written informed consent was obtained from all the participants.

The study population comprised all patients with newly diagnosed hyperthyroidism. An expert endocrinologist diagnosed hyperthyroidism based on the higher levels of serum-free Thyroxin (T4) and (T3) (more than normal levels) and thyroid-stimulating hormone (TSH) <0.1 mIU/mL. There was no history of any other chronic diseases in any of the patients. Participants with 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 diseases were excluded. The control group included healthy peers of the same age and sex. They had normal stress echocardiography results and came to our echo laboratory department for a checkup and had no previous medical history. Besides, they had normal laboratory tests for thyroid function, lipid profile, blood sugar, and hemoglobin.

Patients were evaluated by a clinician, and those with valvular heart disease, any structural heart disease, LV systolic dysfunction (measured by an LV ejection fraction of less than 55% using the modified Simpson method), pulmonary hypertension (measured by a systolic pulmonary artery pressure greater than 35mmHg using tricuspid regurgitation (TR) velocity), and non-sinus rhythm were excluded from the study during the screening stage.

Exercise Stress Test Protocol

All study participants performed the maximum treadmill exercise test according to Bruce protocol and under the supervision of a board-certified cardiologist.[21] At rest and during each test stage, the heart rate, blood pressure, and electrocardiography (ECG) were measured. Chest pain, dyspnea, exhaustion, a target heart rate of more than 90% adjusted by age, and a significant ST-segment deviation were the exercise endpoints. Heart rate response was calculated as the maximum heart rate divided by the age-predicted maximal rate.

Stress Echocardiography

All participants underwent a complete two-dimensional (2D) and Doppler echocardiogram using the same equipment (Philips, affinity 70 echocardiography machine with 1-5MHz transducer), in accordance with the American society of echocardiography recommendation.[22] The RV function indices were evaluated using the apical four-chamber and RV-focused views. At the end-systolic frame, the RV endocardial border was followed. The strain curve was extracted from grayscale images using specialized software. The peak negative value on the strain curve during the cardiac cycle was defined as the peak strain. The size of the RV was measured in an apical four-chamber view using mid-ventricular diameter. To assess the right systolic function, peak systolic myocardial velocity(Sm) and tricuspid annular plane systolic excursion (TAPSE) were measured. TAPSE was defined as the variance in the displacement of the RV base between the diastole and the systole and was calculated in M-mode using apical four-chamber view images and a cursor oriented to the junction of the tricuspid valve plane and the RV free wall. Moreover, the tricuspid regurgitation velocity (TRV) was used to determine the pulmonary artery pressure.

With regard to biochemical evaluation, T3 and T4 serum concentrations were measured using a radioimmunoassay, and TSH concentration was determined using an immunometric method.

Statistical Analysis

All statistical analyses were performed with the statistical package for social sciences (SPSS), version 27.0 (IBM Corp., Armonk, NY, USA). Quantitative data with normal distribution were expressed as mean±SD, whereas variables without normal distribution were reported as median with interquartile range. Qualitative data were expressed by numbers and percentages. Quantitative variables with and without normal distribution were compared using independent samples *t* test and Mann-Whitney U test, respectively. Additionally, Chi square test was used to compare qualitative variables. Spearman's rho correlation test was used to evaluate the relationship between TSH level, disease duration, and the RV indices.

Results

Of 29 patients who were referred to Rajaie Cardiovascular Medical and Research Center, three patients were excluded due to LV dysfunction, atrial fibrillation rhythm, and pulmonary hypertension. Thus, the study was conducted on 26 newly diagnosed hyperthyroid patients and 26 healthy peers of the same age and sex. The mean age of the participants in the case and control groups was not significantly different. Totally, 53.8% of the participants in both groups were women, and 46.2% were men. The main cause of hyperthyroidism in patients was Graves' disease, which accounted for more than 80% of hyperthyroidism etiology. Other causes include toxic multi-nodular goiter (11.54%), toxic adenoma (3.85%), and sub-acute thyroiditis (3.85%). Palpitation (46.2%), exertional dyspnea (61.52%), and atypical chest pain (19.2%) were just a few of the cardiac symptoms reported by patients.

Hemodynamic parameters such as systolic and diastolic blood pressures (SBP, DBP) did not differ significantly between the two groups (table 1). However, hyperthyroid patients had higher Heart Rates (HR) than the control group at rest.

RV Function Indices

The right mid-ventricular diameter was significantly higher in the hyperthyroid patients than the control group (P=0.007). The rest and maximum RV strain indices in the hyperthyroid patients and the control group were presented in table 2. In the rest situation, the RV Global

Table 1: Comparison of clinical and hemodynamic variables between hyperthyroid and control group

Variables		Case (N=26) (mean±SD)	Control (N=26) (mean±SD)	P value
Age (year)		39.77±12.00	40.54±10.34	0.806[a]
Sex, n (%)	Female	14 (53.80%)	14 (53.80%)	>0.999[b]
	Male	12 (46.2%)	12 (46.2%)	>0.999[b]
HR (bpm)	Rest	86.38±10.13	72.23±7.95	<0.001[a]
	Maximal	165.73±13.12	169.07±10.85	0.321[a]
	Exercise	79.34±13.41	96.84±10.43	<0.001[a]
SBP (mmHg)	Rest	124.69±10.48	115.61±23.69	0.080[a]
	Maximal exercise	154.23±14.74	155.69±19.12	0.750[a]
	ΔSBP	29.53±15.85	40.07±25.92	0.083[a]
DBP (mmHg)	Rest	77.61±7.91	73.84±9.29	0.122[a]
	Maximal exercise	87.53±7.44	86.76±11.35	0.774[a]
	ΔDBP	9.92±7.51	12.92±10.43	0.240[a]

HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; [a]Independent samples *t* test, [b]Chi square test, P<0.05 was considered statistically significant.

Longitudinal Strain (GLS) did not significantly differ between the two groups. However, it was shown that in the maximal exercise situation, RV GLS was significantly lower in the hyperthyroid patients than the control group (figure 1).

In the rest situation, hyperthyroid patients had lower systolic SR (P=0.006). However, there were no significant differences between the two groups in diastolic SR, peak systolic myocardial velocity (Sm), Tricuspid Annular Plane Systolic Excursion (TAPSE), and tricuspid regurgitation velocity (TRV). In the maximal stress situation, however, a significantly lower rate of systolic SR, diastolic SR, and TAPSE was observed in the case group than the control group.

Association of RV Function Parameters with TSH Concentration and Clinical Symptoms

As shown in table 3, there was a linear correlation between RV size and TSH concentration (P=0.009), as well as an inverse correlation between TSH concentration and maximum stress RV GLS (r=-0.58, P<0.001), systolic SR (r=-0.39, P=0.004), and diastolic SR (r=-0.47, P<0.001). Moreover, it wasreported that the duration of hyperthyroidism symptoms had an inverse relationship with RV GLS, systolic SR at rest, peak stress test, and maximum stress diastolic SR.

Discussion

The findings of the present study indicated that hyperthyroidism affected markers associated with RV function. Moreover, TSH concentration and the duration of hyperthyroidism symptoms had a significant correlation with RV function indices. Thyrotoxicosis was considered to aggravate pre-established cardiovascular issues or resulted in thyrotoxic cardiomyopathy.

Table 2: Comparison of echocardiographic data between the two groups

Variables		Case (N=26)	Control (N=26)	P value
RV GLS(%)	Rest	22.25 (20.12-24.37)	23.15 (21-25.57)	0.074
	Maximal exercise	21.85 (20.52-23.97)	25.45 (23.30-26.65)	0.0001
	Δ strain	0.25 (-1.30-2.00)	2.80(1.70-3.40)	0.002
Systolic SR (S^{-1})	Rest	2.05 (1.90-2.92)	2.60 (2.20-3.02)	0.006
	Maximal exercise	3.00 (2.60-4.00)	5.00 (4.00-6.00)	0.0001
	Δ strain	1.00 (0.30-2.02)	1.95 (1.15-3.35)	0.010
Diastolic SR	Rest	2.00 (1.57-2.70)	2.25(1.85-2.95)	0.122
	Maximal exercise	2.55 (2.00-3.20)	4.00 (3.00-5.00)	0.0002
	Δ Diastolic SR	0.50 (0.17-1.00)	1.50 (0.85-2.50)	0.002
Sm (cm/s)	Rest	12.25 (11.82-14.75)	12.50 (11.00-14.00)	0.080
	Maximal exercise	16.00 (14.00-18.22)	16.00 (15.00-18.00)	0.750
	ΔSm	2.7 (1.80-5.32)	3.60 (2.57-4.17)	0.332
TAPSE (mm)	Rest	20.00 (19.00-21.70	19.66 (18.82-23.00)	0.905
	Maximal exercise	22.00 (20.92-24.500)	24.30 (22.87-26.55)	0.019
	ΔDBP	2.00 (0.25-3.40)	3.50 (1.60-6.12	0.044
TRV (m/s)	Rest	2.27 (1.97-2.30)	2.20 (1.97-2.30)	0.286
	Maximal exercise	2.60 (2.39-2.88)	2.57 (2.46-2.70)	0.627
	ΔDBP	0.40 (0.33-0.55)	0.40 (0.30-0.57)	0.797

RV: Right Ventricle; GLS: Global Longitudinal Strain; SR: Strain Rate; TAPSE: Tricuspid Annular Plane Systolic Excursion; Sm: Peak systolic myocardial velocity; TRV: Tricuspid Regurgitation Velocity, Mann–Whitney test was used for statistical analysis. *The numbers in parenthesis are presented as the interquartile range (25-75).

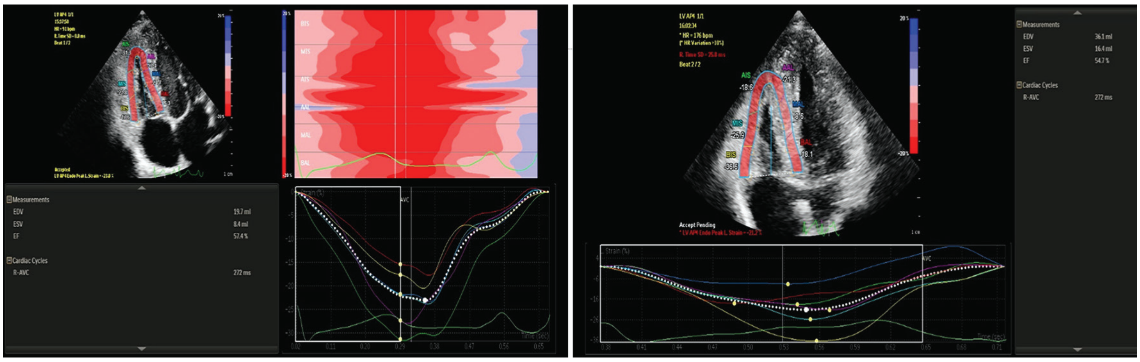

Figure 1: Left: In the rest situation (heart rate:91 bpm), RV Global longitudinal strain was -23% in the hyperthyroid patient (no significant difference with the control group), Right: in the peak of stress test (heart rate:176bpm), RV GLS was -21.2% that showed significantly lower value than the control group.

Table 3: Correlation between thyroid stimulating hormone level (TSH) and duration of symptoms in participants with Right Ventricular indices

RV indices	TSH levels		Duration of symptoms	
	r	P value	r	P value
RV size	0.36	0.009	0.32	0.021
Indexed RV size	0.24	0.08	0.30	0.029
RV GLS-1	-0.20	0.14	-0.37	0.007
RV GLS-2	-0.58	<0.001	-0.51	0.0001
∆Strain	-0.47	0.0004	-0.29	0.03
Systolic SR-1	-0.34	0.013	-0.45	0.001
Systolic SR-2	-0.39	0.004	-0.49	<0.001
∆ Systolic SR	-0.39	0.004	-0.49	0.0002
Diastolic SR-1	-0.18	0.18	0.22	0.11
Diastolic SR-2	-0.47	0.0003	-0.60	<0.001
∆ Diastolic SR	-0.36	0.008	-0.51	0.0001
TAPSE-1	-0.00	0.97	-0.03	0.82
TAPSE-2	-0.27	0.049	-0.34	0.011
∆TAPSE	-0.20	0.154	-0.30	0.02
Sm-1	0.11	0.401	-0.02	0.85
Sm-2	0.05	0.69	-0.12	0.39
∆Sm	-0.14	0.30	-0.15	0.26
TRV1	0.17	0.204	0.03	0.78
TRV2	0.13	0.34	-0.02	0.88
∆TRV	-0.03	0.81	0.01	0.89

RV: Right Ventricle; GLS: Global Longitudinal Strain; SR: Strain Rate; TAPSE: Tricuspid Annular Plane Systolic Excursion; Sm: Peak systolic myocardial velocity; TRV: Tricuspid Regurgitation Velocity, in each parameter 1 and 2 are representative of rest and stress situation, respectively. *Spearman's rho correlation coefficients test was used

It was due to thyrotoxicosis-induced higher cardiac output. The T3 and T4 exert inotropic and chronotropic effects on the heart tissue, which reduces systemic vascular resistance and leads to hyper-dynamic circulation with increased cardiac output. The combination of these changes eventually causes cardiac output impairment, and the right and left ventricles become dysfunctional.[23, 24]

Based on the findings of the present study, the RV global systolic function at rest, as evaluated by the TAPSE and Sm, did not differ significantly between the two groups. Similar to our findings, Tadic and others found that there was no significant difference in TAPSE and systolic velocity between hyperthyroid patients and the control group.[25] Furthermore, the results of this study were consistent with those of other studies in patients with subclinical hyperthyroidism.[26]

There is not much information available about how hyperthyroidism affects RV structure and function. Arinc and colleagues found that diastolic RV function was reduced in patients with overt hyperthyroidism, whereas RV systolic function measured by tissue Doppler imaging increased in these patients, which was not consistent with the findings of the present study.[27] Besides, another study reported that RV volume indexes were increased in patients with hyperthyroidism, however, it was not statistically significante.[28]

The mechanism by which hyperthyroidism might cause right heart failure is unknown. The right ventricle, which is pressure- and volume-sensitive, is thought to receive more blood flow and venous return as a result of hyperthyroid patients' excessive circulatory dynamics.[29] As a result, the pulmonary arterial and right ventricular pressures rise, and the right ventricle dilates.[29]

There are some theories that explain the causes of alterations in RV structure and function in hyperthyroid patients. These conditions are caused by a mild hyperkinetic cardiac state, which causes chronic hemodynamic overload, and as demonstrated in previous studies, leads to RV hypertrophy without alterations in RV dimensions.[30, 31]

The present study indicated that in hyperthyroid patients, the maximal stress condition, right ventricular systolic and diastolic strain rates were also decreased. It is important to note that these minor changes in RV systolic function were not detected by conventional 2DE parameters such as Doppler tissue indices, but only by speckle-tracking 2DE, demonstrating the superiority of these modern techniques over conventional ones. In other words, only a small portion of the global RV function is reflected by tricuspid annular plane systolic excursion and tricuspid annular systolic velocity, which is angle-dependent. The altered RV systolic activity could be attributed to a hemodynamic imbalance and a disruption in Ca^{2+} processing.[25]

Based on the findings of the present study, under conditions of maximum stress, the indices of RV function, including RV strain, systolic SR, diastolic SR, and TAPSE were lower in the hyperthyroid patients than the control group. Teasdale and others reported statistically significant changes in RV function indices in post-walk situations among the patients with Graves' Hyperthyroidism,[32] which was consistent with our findings. Moreover, Suk and colleagues demonstrated that patients with Graves' disease had reduced TAPSE and RV Sm values.[12] Although there was conjecture on this point, it was proposed that strain measurements were less dependent on loading conditions than TAPSE, RV Sm, or RVEF.[33]

To the best of our knowledge, the function and mechanics of the RV during stress tests in hyperthyroid patients have not been evaluated so far. Our study, however, had several limitations. The quality of the sonograms, particularly throughout the full-volume acquisition, may have had a significant impact on RV feature prediction, and the quality depends on the investigator. The study population was selected from the outpatient clinic and did not include more severe cases who may require hospitalization. We didn't perform follow-up echocardiograms for patients who became euthyroid.

Conclusion

The findings of the current study showed that RV structure and function indices in hyperthyroid patients were lower than the control group. There was also a significant correlation between TSH concentrations, disease duration, and RV-related indices. Thus, it highlights the necessity of early hyperthyroidism diagnosis and treatment, as well as the need to evaluate RV function in these patients. However, further studies with larger sample sizes are required to confirm the findings of this study.

Authors' Contribution

K.M and M.S: study concept and final revision of the manuscript. All authors contributed to the writing of the manuscript, data collection, and the review of the literature. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Conflict of Interest: None declared.

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