Echocardiographic Examination

Conventional Echocardiography

A commercially available ultrasound system (iE33, Philips, The Netherlands), equipped with a broadband (1-5 MHz) S5 transducer was used to obtain 2D grayscale harmonic images at a frame rate of 60-80 frames/s. Two-dimensional and M-mode echocardiography was used to measure left ventricular end-diastolic and end-systolic diameter, end-diastolic septal and posterior wall thickness, ejection fraction (EF), shortening fraction (FS) according to the guidelines of American Society of Echocardiography recommendations [15].

Tissue Doppler Imaging

Tissue Doppler imaging measurements were performed on the basal septum, LV and RV lateral wall. Filters were set to exclude high frequency signals. Gain was minimized to obtain clear signals, and images were recorded at a velocity of 100 mm/s. The maximal systolic myocardial velocity (S_m), early and late diastolic myocardial velocity (E_m and A_m) were measured. The isovolumetric contraction time (IVCT) was calculated from the beginning of QRS in the echocardiogram until the beginning of S_m wave, isovolumetric relaxation time (IVRT) was calculated from the end of S_m wave until the beginning of E_m wave. Ejection time (ET) was measured from the beginning to the end of S_m wave. Mean values were recorded by averaging the results of 3 consecutive measurements. Myocardial performance index (MPI; Tei index), a Doppler-derived index, including both systolic and diastolic time intervals to generate a combined index of global ventricular function, was calculated according to the formula; (IVCT+IVRT)/ET [16].

Speckle Tracking Echocardiography

All two-dimensional STE analyses were performed by the same investigator to avoid inter-observer variability. Myocardial deformation parameters (S and SR) were measured using commercially available software (QLAB ver. 6.0, TMQ, Philips Medical systems) on standard 2D grayscale left ventricle images from the standard apical 4-chamber view (AP4) for longitudinal strain and standard parasternal short axis at the papillary muscle level (PML) for circumferential strain. Two consecutive beats synchronized to a continous electrocardiography (ECG) were recorded with frame rate set to >60 frames/s. The data were transferred to a software system (QLAB, Philips Systems) for off-line analysis. The endocardial borders were identified manually to include the entire myocardium in all view area.The following peak systolic LV and RV STE parameters were measured in the context:

- LVGLS: Left ventricular global longitudinal strain at AP4
- LVGLSR: Left ventricular global longitudinal strain rate at AP4
- LVGCS: Left ventricular global circumferential strain at PML
- LVGCSR: Left ventricular global circumferential strain rate at PML
- RVGLS: Right ventricular global longitudinal strain at AP4
- RVGLSR: Right ventricular global longitudinal strain rate at AP4

Statistical Analysis

SPSS for Windows (version 18; SPSS Inc.,Chicago, IL, USA) was used for the statistical analysis. Kolmogorov-Smirnov test was used to analyze the distribution of continuous variables. Continuous variables are expressed as the mean ± standard deviation. Chi-square analysis was used to determine whether there is a difference in terms of gender between patients and controls. Comparisons of demographic data and echocardiographic parameters between patients and controls were performed using Mann-Whitney U test for non-normally distributed variables. A difference was considered statistically significant at a p values of < 0.05. Sperman's correlation coefficient was used to disclose possible correlations between thyroid volumes, Tg-Ab, TPO-Ab and all echocardiographic data.

The number of patients that would be included to the study was calculated by Russ Lenth's power analysis software. Control group of the study is less than study group, for this reason the Power analysis was based on the "mean LVGLS levels" as main outcome, when the mean levels for the study and control groups was given as -23 and -25, respectively, and a common standard deviation of 3, the difference between the two groups can be compared with 34 cases in each group (total 68 cases) using the independent samples t-test with an effect size of 0.7 (medium), a two-sided p-value of 0.05, and a power of 81%.

Results

Clinical Characteristics of the Study Population

A totally of 50 patients with eHT and 35 healthy controls were evaluated. The mean age of patients was 12.5 ± 3.2 years and who were 37 girls (74%) and 13 boys (26%). There was no significant difference in age, gender and body mass index (BMI; m^2) between eHT group and the controls. Heart rate, systolic and diastolic blood pressures were similar in both groups. No significant differences in fT3, fT4 and TSH levels were found between the groups. Compared to the control group, patients with eHT had significantly higher Tg and TPO antibody levels ($p<0.001$**).** There was stage 1a goiter in 16 (32%) and stage 1b goiter in 34 patients (68%). The mean thyroid volume was 10.1± 3.5 mL (min-max: 4.9-16.0 mL). The patient and control groups had no specific ECG findings. Baseline characteristics and laboratory results of study groups are given in Table 1.

Association of Thyroid volume and Tg and TPO antibody levels

There was no correlation between Tg-Ab, TPO-Ab levels and thyroid volume in patients with eHT.

Echocardiographic Findings

Conventional Echocardiographic Findings

The eHT and control groups were not significantly different LV end-diastolic diameter (LVDd), diastolic thickness of the interventricular septum (IVSd) and LV posterior wall (LVPWd), and left ventricular FS and EF. Shortening fraction and EF were within normal limits in both groups. Conventional echocardiographic findings are summarized in Table 1.

Tissue Doppler Imaging Findings

TDI assesment of LV showed statiscally significantly higher values of IVRT and MPI at IVS and LV, in eHT group compared to control group. Additionally, ET values at LV were significantly lower in patients with eHT. There was no

significant differences in S_m, E_m and A_m values between the groups ($p<0.05$, Table 2). There were no significant differences in TDI values at RV in eHT group compared to controls.

Speckle Tracking Echocardiographic Findings

The eHT group had statically significantly lower LVGLS and LVGCS values compared to controls. Also LVGLSR and LVGCSR values were significantly lower in eHT patients. There were no statistically significant differences for RVGLS and RVGLSR values between patients and controls (Table 3, Figure 1,2).

Association of LV STE Parameters with Laboratory Markers and Thyroid Volume

There was a negative correlation between Tg-Ab, TPO-Ab levels and LV global longitudinal and circumferential strain and strain rates (Table 4, Figure 3,4). However, there was no correlation between Tg-Ab, TPO-Ab levels and RVGLS and RVGLSR. In addition, thyroid volume showed no significant correlation with left ventricular global longitudinal and circumferential strain and strain rates (Table 4).

Discussion

Thyroid hormones have prominent adverse effects on the heart and cardiovascular system. Thyroid dysfunction is a condition which effects cardiac performance and it is related with the risk of heart failure. There are two main thyroid hormone receptor genes on human heart. Triiodothyronine (T3) is biologically active form of thyroid hormone and effects heart by increasing some of these genes [1-4,17-20]. The impact of hyperthyroidism or hypothyroidisim on the cardiovascular system is well known and there are many studies on this topic. Hyperthyroid patients have increased heart rate and stroke volume that result in high cardiac output state. An increased prevalence of LV hypertrophy and increased LV contractility has been reported in patients with overt hyperthyroidism. Hypothyroid patients have low heart rate and low stroke volume that results in low cardiac output. Additionaly, overt hypothyroidism has been reported as associated with decreased cardiac contractility [15-18]. A Recent study showed that long-term thyroid hormone replacement in euthyroid patients after myocardial infarction significantly improves LV contractility [21-23].

We know much about cardiovascular effects of eHT in adults [6,10]. However, reasons for changes in cardiac performance in euthyroid patients remain unclear and children with eHT may be at higher risk for developing cardiovascular diseases [10,24].

There were deleterious effects of eHT on LV and RV systolic and diastolic functions. This indicates that Hashimoto's thyroiditis affects myocardial function regardless of thyroid hormone levels [6,10]. The conventional echocardiography and TDI can be used to evaluate the systolic and diastolic function of heart in hypothyroid and hyperthyroid state, but diagnostic value of conventional echocardiography is limited in the early phase of cardiac dysfunction [25,26]. The impact of Hashimoto's thyroiditis on myocardial systolic and diastolic functions has been studied using TDI in some previous studies [5,6,10]. In this study, TDI of the IVS showed significant longer IVRT and shorter ET, consequently a higher Tei index. Additionally, LV-Tei index was significantly increased in eHT group, and this increase is more related to prolongation of IVRT than shortening of ET, thus reflecting both the impairment of systolic and diastolic function. Tei index was found to be more sensitive in the evaluation of diastolic relaxation than parameters such as the deceleration time and the E/A ratio, as previously reported [23,24]. Akgul et al. also reported an impairment of global LV performance in adult patients with eHT. They showed an impaired Tei index and TDI-derived diastolic parameters despite normal findings by conventional echocardiography [6].

Recently new imaging techniques have been introduced to evaluate myocardial mechanics. STE is a novel echocardiographic method and strain and strain rate obtained by STE gives opportunity of quantitative assessment of cardiac function. STE can be used as a diagnostic method in the early stages of many cardiomyopathic diseases, myocardial global longitudinal strain values were shown to have reduced without any changes in conventional echocardiographic parameters [27]. Subclinical myocardial dysfunction can be detected early by TDI and STE methods, especially in early stage of many diseases. STE appeared to be sensitive diagnostic method for subclinical diseases for early detection of myocardial involvement in asymptomatic patients. STE is a more recent technique that provide a global approach to ventricular myocardial mechanics and cardiac deformation [6,8,27].

The many people have both cardiovascular diseases and thyroid diseases. We could not find any literature that investigated myocardial functions by STE in children with eHT. This study aimed to detect myocardial involvement in the euthyroid stage of HT. Recently studies showed that eHT is associated with an increased pulsed-wave velocity, independent of arterial atheromatosis, and indicating a direct impact of this disorder on arterial stiffening [6,7,16,28,29]. Akgul et al., concluded that heart rate variability is significantly reduced than contols in Hashimoto's thyroiditis patients as a result of cardiac autonomic dysfunction even at the euthyroid stage. Therefore, probable mechanisms that may explain cardiac autonomic and functional changes in eHT are probably releated with autoimmunity [6]. However, the molecular, physiological and clinical evidence is still controversial [2,17,18,28,29].

Additionally, a comprehensive literature review dealing with the underlying pathophysiologic mechanism leading to the cardiovascular effects of eHT have not yet been fully understood. Some mechanisms have been reported previously in patients with Hashimoto thyroiditis causing the cardiovascular system involvement. First, the greater numbers of the patients of eHT are in slow progressive thyroid dysfunction. At the end, it is widely acknowledged that patients with eHT will progress mostly to hypothyroidism. Thus, insidious progression to thyroid dysfunction in Hashimoto's thyroiditis may be itself responsible for cardiovascular adverse effects even in subjects with normal serum thyroid hormone levels [7,28,29]. Second, the spectrum of clinical signs may change during the course of the disease. Therefore, the patients with eHT may be hypothyroid or hyperthyroid at baseline or at any time during the course of the disease [24]. So, LV and RV functional changes might be because of previous hypothyroidism or a hyperthyroid phase. In the present study, we have showed that Hashimoto's thyroiditis is associated with subclinical LV systolic and diastolic dysfunction even if patients are euthyroid. Conventional echocardiography does not exclude subclinical left ventricular wall motion abnormalities in patients with eHT. The myocardial dysfunction could be identified as a reduction of LV global and circumferential strain and strain rate and TDI

derived Tei index. Just as, we showed that children with eHT had a significantly lower left ventricular strain and strain rate values, as well as decreased IVS and LV Tei index values compared to controls. Third, autoimmunity associated with Hashimoto's thyroiditis could be the respondent for cardiovascular influence, rather than the effects of secreted hormones. Autoimmunity induced endothelial dysfunction and inflammation may have an important role in the pathogenesis of cardiovascular conditions seen in these patients, such as hypertension, atherosclerosis and myocardial dysfunction [6,10,28,29]. In Hashimoto's thyroiditis, it has been reported that goiter may be present either due to lymphocytic infiltration of thyroid gland or increased TSH levels caused by hypothyroidism. However, there is a controversy regarding role of antibodies in the development of goiter [30]. In our study, no significant correlation was detected between serum level of thyroid antibodies and thyroid volume. In addition, there was no significant correlation was detected between thyroid volume and STE parameters. In these patients, there is typical heterogeneous hypoechogenic parenchyma on thyroid sonography. In our cases, serum TSH levels were within normal range. In fact, it may be more relevant to evaluate relationship of serum antibody level with heterogeneity of thyroid gland parenchyma rather than volume. Besides, we found correlation between serum thyroid antibody levels and STE paramaters, in our study. Subclinical systolic and diastolic dysfunction of left ventricle appeared to be significantly related to TPO-Ab and Tg-Ab levels. So, autoimmunity associated with Hashimoto's thyroiditis rather than secreted hormones could be responsible for cardiovascular effects.

Study limitations

Our study has several limitations. Firstly, the relatively small number of patients could be a limitation of our study. Secondly, we didn't investigate the effect of thyroid replacement therapy on LV and RV functions in eHT patients. Further clinical researches are needed with larger patient groups to investigate the mechanisms on myocardial dysfunction with normal LV ejection fraction and to demonstrate the long-term effects of this therapy on cardiac functions in eHT patients.

Conclusion

In this study, we demonstrated that STE is useful in the early detection of myocardial dysfunction in patients with eHT. Impairment of global LV myocardial function is present in children with Hashimoto's thyroiditis who are euthyroid and conventional echocardiography is inadequate to determine these changes. It is important to increase the data available in this field. Inparticular, such prospective data should be increased, and there is a need for additional prospective data related to cardiac function in eHT patients. Therefore, subclinical myocardial dysfunction in the early disease process may be considered as an indication for initiation of medical treatment, even in euthyroid patients.

Ethics

Ethics Committe Approval

All procedures performed in study involving the patients were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was started after the approval of the Ethics Committee of University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (number of ethical approval: 2016/071).

Informed Consent: Written informed consent was obtained from parents of all patients included in the study.

Peer-review: Externally peer reviewed.

Authorship contributions

Consept: Emine Azak, I.Ilker Cetin, S. Ahmet Ucakturk. Design: Emine Azak, I.Ilker Cetin, S. Ahmet Ucakturk. Data collection and Processing: Emine Azak, Eda Mengen, Utku Pamuk. Analysis and Interpretation: Emine Azak, I.Ilker Cetin, S. Ahmet Ucakturk. Literature Research: Emine Azak, Eda Mengen, H.Alper Gursu. Writing: Emine Azak, I.Ilker Cetin.

Founding source

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Conflict of interest

No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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Figure Legends
Figure 1**:** Myocardial strain and strain rate values

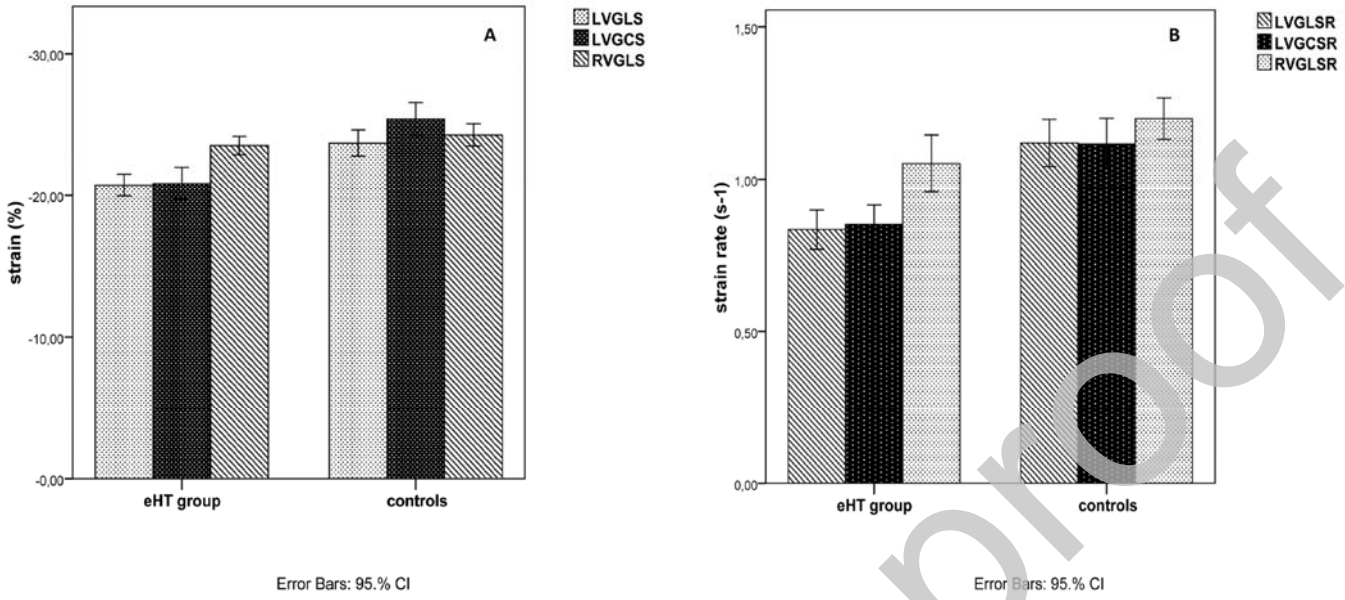

Figure A; LVGLS: Left ventricle global longitudinal strain; LVGCS: Left ventricle global circumferential strain; RVGLS: Right ventricle global longitudinal strain. Figure B; LVGLSR: Left ventricle global longitudinal strain rate; LVGCSR: Left ventricle global circumferential strain rate; RVGLSR: Right ventricle global longitudinal strain; RVGLSR: Right ventricle global longitudinal strain rate.

Figure 2**:** Two dimensional strain and strain rate analysis through STE imaging of eHT
(A: strain analysis, B: strain rate analysis)

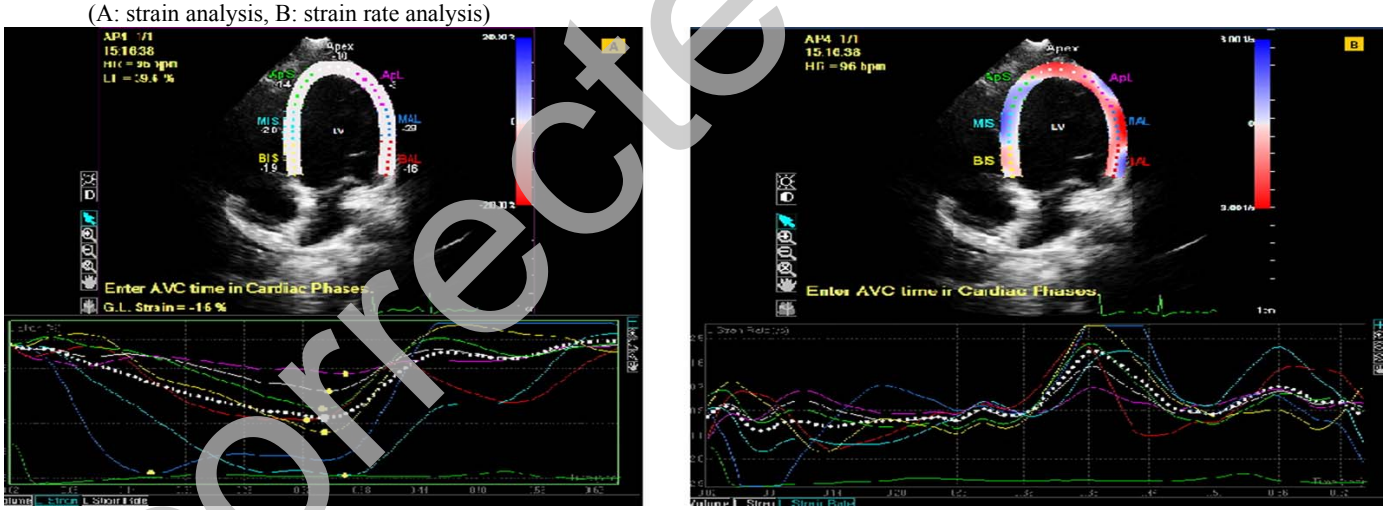

Figure 3: The correlation between myocardial strain and Tg-Ab levels

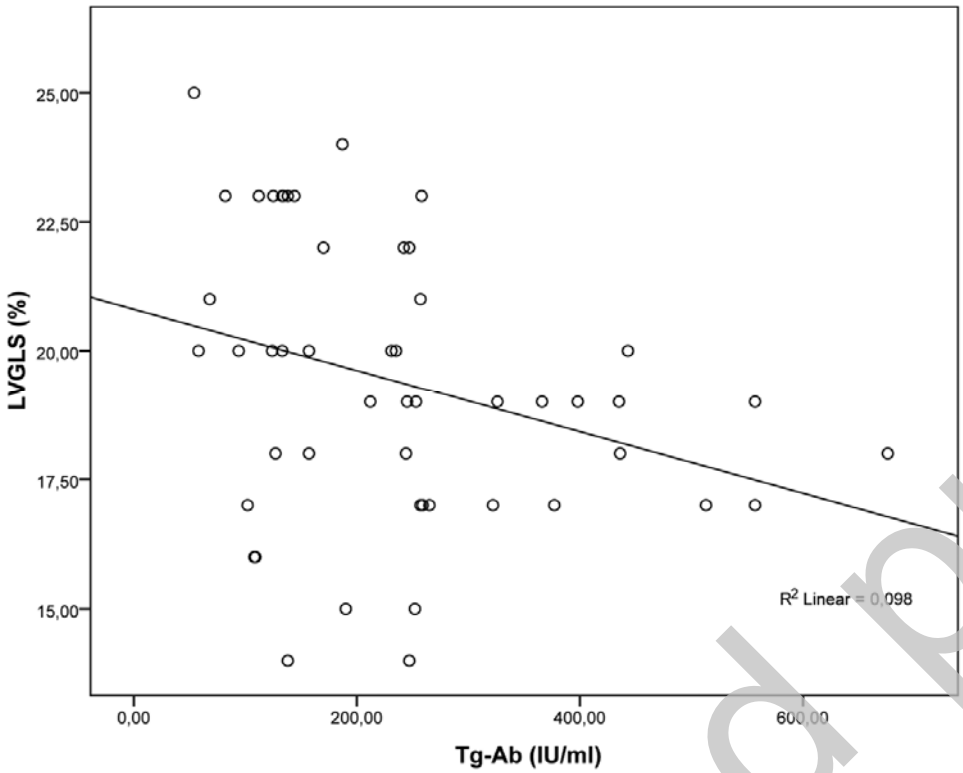

Figure 4: The correlation between myocardial strain and TPO-Ab levels

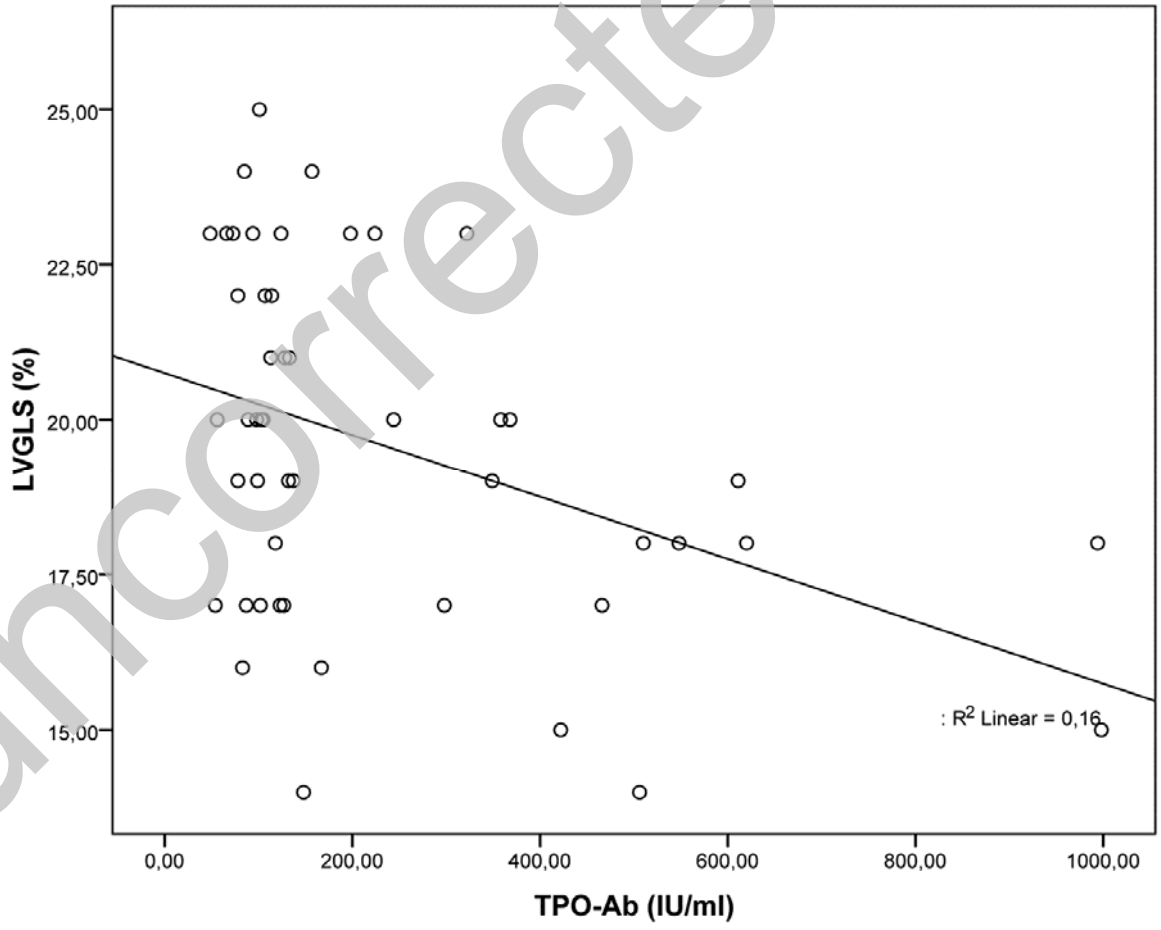

Table 1: Demographic, laboratory variables, tyroid volume and conventional echocardiographic findings in study groups

	eHTgroup	Controls	P value
***Age, years**	12.5 ± 3.2	12.8 ± 3.1	0.74
Female/male	37/13	22/13	0.45
***BMI, kg/m^2**	20.2 ± 3.1	20.4 ± 2.3	0.51
***BSA, m^2**	1.4 ± 0.3	1.3 ± 0.2	0.78
***HR, beats/min**	79 ± 13	82 ± 14	0.69
***SBP, mm Hg**	110 ± 9	106 ± 8.6	0.25
***DBP, mm Hg**	69 ± 8	66 ± 7	0.36
***fT3, pg/ml**	0.98 ± 0.5	1.1 ± 0.4	0.86
***fT4, pg/ml**	0.95 ± 0.3	1.03 ± 0.4	0.81
***TSH, mIU/l**	3.06 ± 1.3	2.6 ± 0.9	0.17
***Tg-Ab, IU/ml**	147.1 ± 192.9	2.3 ± 1.4	0.001
***TPO-Ab, IU/ml**	244 ± 279	2.6 ± 1.7	0.001
***Thyroid volume, ml**	10.1 ± 3.3	-	-
***Thyroid volume, SDS score**	**1.9 ± 1.3**	-	-
***EF, %**	68.7 ± 3.1	69 ± 2.7	0.21
***FS, %**	35.9 ± 2.6	36.6 ± 2.1	0.08
***LVDd, mm**	36.9 ± 5.9	37.3 ± 3.6	0.81
***IVSd, mm**	7.2 ± 0.8	7.4 ± 0.8	0.14
***LVPWd, mm**	7.3 ± 1.1	7.6 ± 0.8	0.49

*Values are presented as mean ± SD.
eHT: euthyroid Hashimoto's thyroiditis; BMI: body mass index; BSA: body surface area; HR: heart rate; fT3:free triiodothyronine; fT4: free thyroxine; TSH: thyroid-stimulating hormone; TPO-Ab: thyroid peroxidase antibody; Tg-Ab: thyroglobulin antibody; EF: left ventricular ejection fraction; FS: left ventricular fractional shortening; LVDd: left ventricular end-diastolic diameter; IVSd: interventricular septum diastolic thickness; LVPWd: left ventricular posterior wall diastolic thickness.

Table 2: TissueDopplerechocardiographymeasurements in studygroups

		eHTgroup	Controls	*p value
IVS	S_m, cm/s	7.8 ± 0.9	7.6 ± 0.7	0.51
	E_m, cm/s	13.6 ± 1.6	14.1 ± 2.3	0.07
A_m, cm/s		6.4 ± 0.9	6.6 ± 0.9	0.13
	IVCT, ms	56.1 ± 6.7	57.8 ± 3.3	0.07
	IVRT, ms	59.9 ± 4.2	57.9 ± 3.9	0.001
	ET, ms	253 ± 19.6	261 ± 20.3	0.10
	MPI	0.48 ± 0.05	0.41 ± 0.04	0.001
LV	S_m, cm/s	9.4 ± 1.7	8.8 ± 1.7	0.22
	E_m, cm/s	15.7 ± 1.6	16.1 ± 1.2	0.37
A_m, cm/s		7.3 ± 1.2	7.4 ± 0.8	0.33
	IVCT, ms	58.1 ± 7.1	59.7 ± 4.2	0.35
	IVRT, ms	59.8 ± 3.9	57.6 ± 2.8	0.001
	ET, ms	250 ± 24.3	274 ± 21.7	0.001
	MPI	0.49 ± 0.06	0.43 ± 0.03	0.001
RV	S_m, cm/s	10.4 ± 2.1	9.5 ± 1.4	0.06
	E_m, cm/s	14.4 ± 1.5	14.7 ± 1.1	0.29
A_m, cm/s		7.1 ± 0.9	7.4 ± 1.3	0.09
	IVCT, ms	57.1 ± 4.9	58.5 ± 3.2	0.06
	IVRT, ms	55.8 ± 8.5	57.6 ± 2.7	0.09
	ET, ms	245 ± 24.8	255 ± 16.8	0.09
	MPI	0.47 ± 0.06	0.46 ± 0.03	0.84

Valuesarepresented as mean ± SD. *p<0.05 forstatisticallysignificance.
eHT: euthyroid Hashimoto's thyroiditis; IVS: interventricularseptum; LV: leftventricle; RV: rightventricle; S_m: peaksystolicmyocardialvelocity; E_m: peakearlydiastolicmyocardialvelocity; A_m: peaklatediastolicmyocardialvelocity; ET: ejection time; IVCT: isovolumetriccontraction time; IVRT: isovolumetricrelaxation time.

Table 3: Speckle tracking echocardiography measurements in study groups

	eHT group	Controls	*p value
LVGLS, %	-20.7 ± 2.7	-24.1 ± 3.1	0.01
LVGLSR, s^{-1}	-0.8 ± 0.2	-1.1 ± 0.2	0.01
LVGCS, %	-20.8 ± 4.1	-25.4 ± 3.4	0.01
LVGCSR, s^{-1}	-0.9 ± 0.2	-1.1 ± 0.2	0.01
RVGLS, %	-23.5 ± 2.3	-24.2 ± 2.2	0.12
RVGLSR, s^{-1}	-1.1 ± 0.3	-1.2 ± 0.1	0.07

Values are presented as mean ± SD. *p<0.05 for statistically significance.
LVGLS: Left ventricle global longitudinal strain; LVGLSR: Left ventricleglobal longitudinal strain rate; LVGCS: Left ventricle global circumferential strain; LVGCSR: Left ventricle global circumferential strain rate; RVGLS: Right ventricle global longitudinal strain; RVGLSR: Right ventricle global longitudinal strain rate.

Table 4: Correlation between left ventricular STE parameters and thyroid antibody levels and volume in eHT group

	TPO-Ab	Tg-Ab	Thyroid Volume
LVGLS	r= -411; p<0.001	r= -397; p<0.001	**r= -0.09; p=0.256**
LVGLSR	r= -541; p<0.001	r= -473; p<0.001	**r= -0,59; p=0.684**
LVGCS	r= -430; p<0.001	r= -519; p<0.001	**r= -0.75; p=0.602**
LVGCSR	r= -502; p<0.001	r= -421; p<0.001	**r= -0,094; p=0.517**

(r = correlation coefficient, p= significance level (p<0.05 for statistically significance)