Evaluation of ventricular functions using tissue Doppler echocardiography in patients with subclinical hypothyroidism

Subklinik hipotiroidizmde ventrikül fonksiyonlarının doku Doppler ekokardiyografi ile değerlendirilmesi

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ABSTRACT

Objectives: We evaluated right (RV) and left (LV) ventricle functions by tissue Doppler imaging (TDI) in patients with subclinical hypothyroidism (SH).

Study design: Twenty-seven patients (24 women, 3 men; mean age 35.4±11.4 years) with newly diagnosed SH and 22 age- and sex-matched healthy subjects (20 women, 2 men; mean age 34.8±8.6 years) were evaluated by standard echocardiography and TDI. The diagnosis of SH was based on increased serum thyrotropin (TSH) level in the presence of normal free T_3 and free T_4 levels. The following TDI-derived parameters were measured: isovolumic myocardial acceleration (IVA), peak myocardial velocity during isovolumic contraction (IVV), peak systolic velocity during ejection period (S), and diastolic indices including peak early (E') and late (A') diastolic velocities, E'/A' and E/E' ratios, and myocardial performance index.

Results: Compared to healthy controls, patients with SH had higher LV mitral A velocity (p=0.022), lower E/A ratio (p=0.021), lower E' velocity (p=0.019), and higher E/E' ratio (p=0.017), suggesting significant LV diastolic dysfunction. The patient group also had lower IVV (p=0.004) and IVA (p<0.001), and higher isovolumic contraction time (p=0.012), suggesting LV subclinical systolic dysfunction. For RV parameters, decreased E/A ratio (p=0.014) and E' velocity (p=0.028) and increased isovolumic relaxation time (p=0.003) in SH patients were consistent with RV diastolic dysfunction, whereas parameters of RV systolic function were similar in the two groups. Myocardial performance indices of both ventricles were also significantly higher in the patient group (p<0.05).

Conclusion: Our data suggest that SH is associated with biventricular systolic and diastolic dysfunction.

ÖZET

Amaç: Subklinik hipotiroidi (SH) olan hastalarda sağ ve sol ventrikül fonksiyonları doku Doppler ekokardiyografi ile değerlendirildi.

Çalışma planı: Çalışmada, SH tanısı yeni konmuş 27 hasta (24 kadın, 3 erkek; ort. yaş 35.4±11.4) ve yaş ve cinsiyet uyumlu 22 sağlıklı birey (20 kadın, 2 erkek; ort. yaş 34.8±8.6) konvansiyonel ve doku Doppler ekokardiyografi ile incelendi. Subklinik hipotiroidi, normal serbest T_3 ve T_4 düzeyleri yanında serum tirotropin (TSH) düzeyinin yüksekliği olarak tanımlandı. Doku Doppler ile incelenen parametreler şunlardı: sistolik akımlardan izovolümik miyokart hızlanması (IVA), izovolümik kontraksiyon sırasındaki zirve miyokart hızı (IVV), ejeksiyon fazı sırasındaki zirve sistolik hız (S); diyastolik parametrelerden erken (E') ve geç (A') diyastolik zirve akımlar, E'/A' ve E/E' oranları ve miyokart performans indeksi.

Bulgular: Sağlıklı kişilerle karşılaştırıldığında, SH'li grupta sol ventrikülde ciddi derecede diyastolik fonksiyon bozukluğunu gösteren veriler elde edildi: yüksek mitral A hızı (p=0.022) ve E/E' oranı (p=0.017); düşük E/A oranı (p=0.021) ve E' hızı (p=0.019). Bu grupta anlamlı derecede düşük IVV (p=0.004) ve IVA (p<0.001), artmış izovolümik kasılma zamanı (p=0.012) ise sol ventrikülde subklinik sistolik fonksiyon bozukluğuna işaret ediyordu. Sağ ventriküle ait sistolik fonksiyon parametreleri kontrol grubuyla benzer bulunurken, diyastolik fonksiyon bozukluğu, düşük E/A oranı (p=0.014) and E' hızı (p=0.028) ve artmış izovolümik gevşeme zamanı (p=0.003) ile kendini gösterdi. Miyokart performans indeksi her iki ventrikülde de kontrol grubuna göre artmış bulundu (p<0.05).

Sonuç: Bulgularımız, SH'de her iki ventrikülün sistolik ve diyastolik fonksiyonlarında bozulma olduğunu göstermektedir.

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Subclinical hypothyroidism is a common endocrine disorder characterized by normal serum free triiodothyronine and thyroxine levels and increased thyrotropin level, generally without the presence of clinical signs. In adult population, its incidence varies between 1% and 10%.[1] Especially in women above 60 years of age, its prevalence reaches 20%.[2,3] When SH is observed together with increased serum levels of autoantibodies, annual risk for progression to overt hypothyroidism is approximately 5%.[4]

In SH, thyroid hormone replacement therapy is still controversial.[5,6] Several studies have shown metabolic, neuromuscular, and neuropsychiatric deficiencies in SH patients.[7,8] In this patient group, increase in serum TSH level is accompanied by increases in serum levels of total and low-density lipoprotein cholesterol.[9] Therefore, SH may also be considered to be a risk factor for atherosclerosis.[10,11] In the Rotterdam study, a strong correlation was found between SH and atherosclerotic cardiovascular diseases in postmenopausal women, independent from conventional risk factors such as smoking, hypertension, hypercholesterolemia, and diabetes mellitus.[12] In addition, significant progression of coronary lesions was demonstrated in SH patients who did not receive thyroid hormone replacement therapy compared to SH patients under therapy.[13]

Despite having the disadvantage of load dependency, tissue Doppler imaging-derived systolic myocardial velocities are considered to be more useful parameters in evaluating longitudinal systolic functions compared to conventional echocardiography in the assessment of especially right ventricle contractile function.[14,15] In this study, we aimed to assess right and left ventricle (LV) functions in patients with SH.

PATIENTS AND METHODS

Study group

We prospectively enrolled 27 patients (24 women, 3 men; mean age 35.4±11.4 years) with newly diagnosed SH and 22 age- and sex-matched healthy subjects (20 women, 2 men; mean age 34.8±8.6 years) as controls. Subclinical hypothyroidism was diagnosed based on increased serum level of TSH in the presence of normal fT_3 and fT_4 levels. The standards of the biochemistry laboratory of our clinic for normal reference levels of the thyroid panel are as follows: TSH 0.27-4.20 mIU/ml, fT_3 1.80-4.60 pg/ml, fT_4 0.93-1.70 ng/dl. Cases with SH were defined as having a TSH level above 4.20 mIU/ml and fT_4 value within the normal range. Exclusion criteria were pregnancy, impaired liver or renal function, hypertension, heart failure, ischemic or valvular heart disease, respiratory diseases, diabetes mellitus, psychological or neurological disorders, malignancy, smoking, and use of drugs that might influence the heart rhythm or thyroid hormone levels.

Abbreviations:

ET	*Ejection time*
fT_3	*Free triiodothyronine*
fT_4	*Thyroxine*
HDL	*High-density lipoprotein*
IVA	*Myocardial acceleration during isovolumic contraction*
IVCT	*Isovolumic contraction time*
IVRT	*Isovolumic relaxation time*
IVV	*Peak myocardial velocity during isovolumic contraction*
LDL	*Low-density lipoprotein*
LV	*Left ventricle*
MPI	*Myocardial performance index*
S	*Peak velocity during systolic ejection*
RV	*Right ventricle*
SH	*Subclinical hypothyroidism*
TDI	*Tissue Doppler imaging*
TSH	*Thyrotropin*

All the patients were asymptomatic, without evidence for either systolic or diastolic heart failure and were in sinus rhythm. Findings of physical examination, medical history, and electrocardiography were found to be normal. Blood samples were collected from all patients after a fasting period of 8-12 hours. Height, weight, waist and hip circumference were also measured.

The study protocol was approved by local ethics committee of our institute and detailed written informed consent was obtained from each patient. The study was carried out in compliance with the Declaration of Helsinki.

Echocardiographic measurements

All patients were examined in the left lateral decubitus position by M-mode, two-dimensional, Doppler and TDI echocardiography (GE Vingmed, Vivid 7, Horten, Norway) using a 2.5 MHz transducer. Left ventricular diameters and wall thicknesses were measured by M-mode echocardiography according to the recommendations of the American Society of Echocardiography.[16] Left ventricular end-diastolic and end-systolic volumes and ejection fraction were calculated using the modified Simpson's method. Right ventricular systolic diameter was measured from parasternal long-axis view by using M-mode.[17] Pulmonary artery systolic pressure was estimated by continuous-wave Doppler imaging using the Bernoulli equation.[18] Tricuspid annular plane systolic

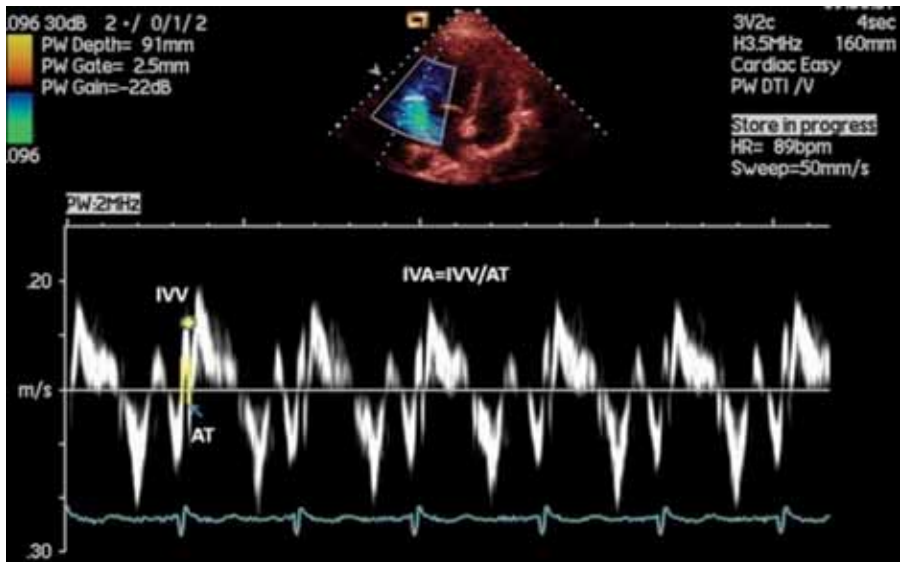

Figure 1. Peak myocardial velocity during isovolumic contraction (IVV) (m/sec), myocardial acceleration during isovolumic contraction (IVA) (m/sec^2) defined as the ratio of IVV divided by the acceleration time (AT), and peak velocity during systolic ejection (Sa) (m/sec) were measured from both mitral and tricuspid annuli.

excursion was measured by M-mode placing the cursor in apical 4-chamber view at the junction of the tricuspid valve with the right ventricular free wall. Maximum displacement during systole was evaluated.[19] End-diastolic and end-systolic areas of the RV cavity were calculated using planimetry and RV fractional shortening was calculated [(end-diastolic area –end-systolic area)/end-diastolic area) x 100)] from the apical 4-chamber view. Pulmonary flow acceleration time was measured from the period between the onset of pulmonary flow and point of peak velocity by Doppler imaging.[20] Peak early (E) and late (A) diastolic mitral and tricuspid annular velocities were also measured.

Tissue Doppler echocardiography

Guided by the two-dimensional 4-chamber view, a 5-mm sample volume was placed just apical to the medial and lateral mitral annuli and to the lateral tricuspid annulus, using pulsed-wave tissue TDI. Settings were adjusted for a frame rate between 120 and 180 Hz and a cineloop of 3 to 5 consecutive heart beats were recorded. TDI-derived systolic indices were measured from both the mitral and tricuspid annuli including peak myocardial velocity during isovolumic contraction, myocardial acceleration during isovolumic contraction, defined as the ratio of IVV divided by the acceleration time, and peak velocity during systolic ejection (S). Peak early (E') and late (A') diastolic mitral and tricuspid annular velocities were also analyzed (Fig. 1). Myocardial performance index was calculated as the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time (Fig. 2). All the measurements were calculated and averaged from three consecutive cycles.

The thyroid panel (fT_3, fT_4, TSH levels), serum total cholesterol and triglyceride, LDL and HDL cholesterol levels were measured from all patients. Measurements of fT_3, fT_4, TSH, antithyroid peroksidase (anti-TPO), antithyroglobuline (anti-

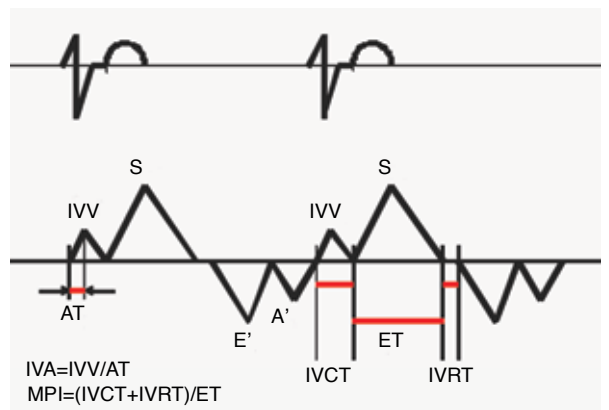

Figure 2. Myocardial performance index (MPI) was calculated as the sum of isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) divided by ejection time (ET). IVA: Myocardial acceleration during isovolumic contraction; IVV: Peak velocity during isovolumic contraction; AT: Acceleration time.

Table 1. Baseline clinical and demographic characteristics of the patients and controls

	Patient group (24 women, 3 men) (Mean±SD)	Control group (20 women, 2 men) (Mean±SD)	*p*
Age (years)	35.4±11.4	34.8±8.6	0.680
Body mass index (kg/m^2)	27.6± 5.5	26.1±3.1	0.282
Waist/hip ratio	0.80±0.07	0.82±0.07	0.239
Systolic blood pressure (mmHg)	115.7±7.39	113.0±8.0	**0.013**
Diastolic blood pressure (mmHg)	69.3±5.8	71.6±8.3	0.118
Heart rate (beats/min)	69.7±3.5	69.7±8.1	0.707
Total cholesterol (mg/dl)	188.1±38.3	167.9±21.7	**0.025**
LDL cholesterol (mg/dl)	113.4±38.6	100.6±18.9	0.135
HDL cholesterol (mg/dl)	50.1±10.7	50.1±10.1	0.983
Triglyceride (mg/dl)	106.9±55.1	85.3±38.0	0.125
Free triiodothyronine (pg/ml)	3.25±0.57	3.11±0.27	0.271
Free thyroxine (ng/dl)	1.12±0.18	1.33±0.19	**<0.001**
Thyrotropin (mIU/ml)	7.09±2.36	2.02±1.04	**<0.001**
Antithyroid peroksidase (IU/ml)	123.4±167.7	–	
Antithyroglobuline (IU/ml)	153.1±208.8	–	

TG) levels were made on an autoanalyzer (Roche Elecsys Modular Analytics E170, Roche Diagnostics GmbH, Mannheim, Germany) using the electrochemiluminescence immunoassay (ECLIA) method. Total cholesterol, triglyceride, and LDL-C were measured enzymatically and HDL-C was measured with the immunoinhibition method using the Abbott Aeroset analyzer (Abbott Diagnostics, Chicago, IL, USA).

Statistical analysis

Data were evaluated using descriptive statistics (mean, standard deviation). Qualitative data were compared using the chi-square test. Pre-treatment and post-treatment parameters were compared using the Wilcoxon signed-rank test due to the lack of parametric test conditions. Correlations were analyzed using the Spearman test. The results were considered significant when the *p* value was less than 0.05. Statistical analyses were made using the Epi Info software (version 3.5.1).

RESULTS

Table 1 summarizes the baseline clinical and demographic characteristics of the patients and the controls. The two groups were similar in terms of clinical and demographic characteristics. Compared to the control group, patients with SH showed significantly lower fT_4 and higher TSH levels (p<0.001).

Left ventricle

Echocardiographic and TDI findings of both ventricles are shown in Table 2. Compared to healthy controls, patients with SH exhibited several parameters suggesting significant LV diastolic dysfunction, including higher mitral A wave velocity (p=0.022), lower E/A ratio (p=0.021), lower E' velocity (p=0.019), and higher E/E' ratio (p=0.017).

In addition, patients with SH showed significantly lower IVV (p=0.004) and IVA (p<0.001), and significantly higher IVCT (p=0.012) values, suggesting LV subclinical systolic dysfunction. Left ventricular MPI, which is a sensitive indicator of both systolic and diastolic dysfunction, was also significantly higher in the patient group (p=0.004).

Right ventricle

Compared to controls, RV E/A ratio (p=0.014) and E' velocity (p=0.028) were decreased, and IVRT (p=0.003) and MPI (p=0.017) were increased in SH patients. These findings were consistent with RV diastolic dysfunction. Parameters of RV systolic function were similar in the two groups (Table 2).

Table 2. Baseline left and right ventricular echocardiography findings of the patients and controls

	Left ventricle			Right ventricle		
	Patient group (Mean±SD)	Control group (Mean±SD)	*p*	Patient group (Mean±SD)	Control group (Mean±SD)	*p*
Conventional echocardiography						
End-diastolic diameter (cm)	4.5±0.5	4.5±0.4	0.391	2.9±0.5	3.0±0.6	0.629
End-systolic diameter (cm)	2.8±0.5	2.8±0.3	0.879	1.7±0.3	1.9±0.4	0.233
Interventricular septum (cm)	1.0±0.1	1.0±0.1	0.071			
Posterior wall (cm)	0.1±0.1	0.1±0.1	0.063			
Ejection fraction (%)	70.1±6.9	67.9±6.0	0.324	68.2±9.0	70.8±8.4	0.300
Fractional shortening (%)	39.4±6.4	37.5±5.0	0.250	39.8±12.9	39.4±14.2	0.928
Tricuspid annular peak systolic excursion (cm)				1.6±0.3	1.7±0.2	0.101
Pulmonary flow acceleration time (msec)				156.3±27.2	141.6±19.6	0.051
Early diastolic transmitral flow velocity (E) (cm/sec)	0.9±0.1	0.9±0.1	0.952	0.6±0.1	0.6±0.1	0.129
Late diastolic transmitral flow velocity (A) (cm/sec)	0.8±0.2	0.7±0.1	**0.022**	0.5±0.1	0.5±0.1	0.349
E/A	1.2±0.3	1.4±0.2	**0.021**	1.2±0.2	1.4±0.2	**0.014**
Deceleration time (msec)	204.3±56.1	186.9±26.0	0.145			
Ejection time (msec)				273.7±30.6	273,.4±31.1	0.936
Isovolumic contraction time (msec)	63.9±7.8	57.0±7.1	**0.012**	68.3±11.9	64.1±11.7	0.284
Isovolumic relaxation time (msec)	91.4±19.0	84.5±11.3	**0.095**	78.7±24.3	59.9±16.9	**0.003**
Myocardial performance index	0.44±0.06	0.40±0.04	**0.004**	0.54±0.11	0.45±0.09	**0.017**
Tissue Doppler echocardiography						
Peak systolic velocity of mitral flow (S) (m/sec)	0.10±0.02	0.10±0.02	0.131	0.13±0.02	0.13±0.01	0.600
Isovolumic velocity (m/sec)	0.08±0.02	0.10±0.02	**0.004**	0.12±0.04	0.12±0.03	0.823
Isovolumic acceleration (m/sec^2)	2.35±0.34	3.71±1.06	**<0.001**	3.42±1.33	3.17±0.93	0.455
E' (cm/sec)	0.13±0.03	0.16±0.03	**0.019**	0.13±0.03	0.15±0.03	**0.028**
A' (cm/sec)	0.10±0.03	0.10±0.02	0.887	0.13±0.04	0.13±0.04	0.992
E'/A'	1.39±0.61	1.52±0.31	0.060	1.08±0.46	1.27±0.42	0.093
E/E'	6.90±1.67	5.85±1.20	**0.017**	4.98±1.66	4.4±1.33	0.185

Correlation analysis showed no correlation between the conventional and TDI echocardiographic findings and the levels of fT_3, fT_4, and TSH.

DISCUSSION

The heart is one of the major target organs of the thyroid hormones. Therefore, thyroid dysfunction has an important role in the cardiovascular system, by effecting the sarcoplasmic reticulum, contractile proteins, and myocyte cell membrane.[1-3]

Thyroid hormone deficiency alters cardiac muscle function by decreasing the activity of enzymes involved in the regulation of myocyte calcium intake and the expression of several contractile proteins. Thyroid hormone deficiency leads to a de-

crease in heart rate and impairment of myocardial contraction and relaxation.[4,5]

Many studies have demonstrated ventricular systolic and diastolic dysfunction in SH.[6-8] In addition, impairment in LV systolic functions has been reported at rest.[9-11] In our study, mitral A value was significantly higher and E/A ratio and E' values were significantly lower in SH patients compared to the control group. These parameters show LV diastolic dysfunction in SH patients. Many studies confirmed impaired LV diastolic functions in SH subjects using TDI-derived indices.[6,10,11,21] In our study, MPI, which indicates both systolic and diastolic functions, was significantly higher compared to controls. We used TDI-derived parameters such as S, IVV, and IVA to evaluate LV systolic functions. Similar to our study, Mariotti et al.[22] found impaired LV systolic functions using S and observed a significant improvement following l-T_4 substitution therapy. The main finding in our study was the ability of IVA, which is a reliable systolic parameter that is not influenced by preload and afterload changes, to show impairment in LV systolic functions. Being a noninvasive, readily applicable, and accurate measurement for the evaluation of ventricular systolic functions, IVA has received considerable attention.[20,23] In our study, we found that LV IVV and IVA values were significantly lower than those of controls. Therefore, IVA might be used for the early diagnosis of LV systolic dysfunction in patients with SH.

Despite many studies investigating LV functions in SH patients, data on RV functions are few.[9,24-26] Koşar et al.[25] found that RV systolic functions were preserved but RV diastolic functions were impaired in patients with SH. Turhan et al.[26] reported impairment in both RV systolic and diastolic functions and a significantly low IVA value in SH patients. In our study, indicators of diastolic function including RV E/A ratio and E' value were significantly low and IVRT was significantly high in SH patients, whereas the E/E' ratio was similar to that of the control group. On the other hand, RV systolic function parameters including S, IVV, and IVA did not differ from those of the control group; this might be due to the fact that our study group was younger and had newly diagnosed SH, which might be associated with less involvement of RV systolic functions. Unlike the finding of Turhan et al.,[26] RV MPI was significantly lower in our patient group.

In contrast to many studies,[9,10] we did not find any correlation between thyroid hormone levels and parameters of ventricular function, though patients with SH had subclinical LV dysfunction. This may be due to the small number of our study group.

In our study, we used TDI-derived IVA and found that LV IVA was significantly lower in patients with SH. This may be considered to be a reliable parameter for the early detection of LV systolic dysfunction in SH. We also found RV diastolic dysfunction in SH patients.

Limitations of the study

The main limitation of the study is its small size. Coronary artery disease was excluded based on history, electrocardiography, and echocardiography (wall motion abnormality), without further support by coronary angiography. Although TDI has become a widespread imaging tool for quantifying tissue velocities, it has limitations such as angle and load dependency and velocity aliasing.[17,27] Currently, strain and strain rate imaging techniques have become popular due to elicitation of quantitative information on endocardial deformation.[28-30] In our study, we did not investigate the effect of thyroid replacement therapy on LV and RV functions in SH patients. Besides its potential beneficial effects especially on symptoms and lipid profile, thyroid hormone replacement therapy may have some risks, as well, such as osteopenia and atrial fibrillation.[31] Therefore, larger controlled studies are required to demonstrate the long-term effects of this therapy on cardiac functions.

Further studies are needed with larger patient groups to investigate ventricular systolic and diastolic deformation in SH patients.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Echocardiography, Doppler; hypothyroidism/complications; ventricular dysfunction, left; ventricular dysfunction, right.

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