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

Subklinik hipotiroidizmdede ventrikül fonksiyonlarının doku Doppler ekokardiyografi ile değerlendirilmesi

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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.

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

Çalışma planı: Çalışmanda, SH tanısı yeni konmuş 27 hasta (24 kadını, 3 erkeği; ort. yaş 35.4±11.4) ve yaş ve cinsiyet uyumlu 22 sağlıklı birey (20 kadını, 2 erkeği; 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), peak miyokardiyal hızları izovolümik kasılma sırasında (IVV), peak sistolik hız (S); diyastolik parametrelerden erken (E') ve geç (A') diastolik zirveler, 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 anlama 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 ventrikülde ait sistolik fonksiyon parametreleri kontrol grubuya benzer bulunurken, diyastolik fonksiyon bozukluğu, düşük E/A oranı (p=0.014) ve 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 göstermekteydi.
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 fT₃ and fT₄ 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, fT₃ 1.80-4.60 pg/ml, fT₄ 0.93-1.70 ng/dl. Cases with SH were defined as having a TSH level above 4.20 mIU/ml and fT₄ 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.

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
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.\textsuperscript{[19]} End-diastolic and end-systolic areas of the RV cavity were calculated using planimetry and RV fractional shortening was calculated \([\text{end-diastolic area} - \text{end-systolic area}] / \text{end-diastolic area} \times 100\)] 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.\textsuperscript{[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 cine loop 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 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.](image1)

![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.](image2)
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 ($p=0.013$), 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 IV A ($p<0.001$), 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).
Correlation analysis showed no correlation between the conventional and TDI echocardiographic findings and the levels of fT₃, fT₄, 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.\textsuperscript{4,5}

Many studies have demonstrated ventricular sys-
tolic and diastolic dysfunction in SH.\textsuperscript{6-8} In addi-
tion, impairment in LV systolic functions has been
reported at rest.\textsuperscript{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.\textsuperscript{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.\textsuperscript{22} found impaired LV systolic func-
tions using S and observed a significant improve-
ment following l-T\textsubscript{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 impair-
ment in LV systolic functions. Being a noninvasive,
readily applicable, and accurate measurement for the
evaluation of ventricular systolic functions, IVA has
received considerable attention.\textsuperscript{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 dys-
function in patients with SH.

Despite many studies investigating LV functions
in SH patients, data on RV functions are few.\textsuperscript{9,24-26}
Koşar et al.\textsuperscript{25} found that RV systolic functions were
preserved but RV diastolic functions were impaired
in patients with SH. Turhan et al.\textsuperscript{26} reported impair-
ment 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, where-
as the E/E’ ratio was similar to that of the control
group. On the other hand, RV systolic function pa-
rameters 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.\textsuperscript{26} RV MPI was significantly
lower in our patient group.

In contrast to many studies,\textsuperscript{9,10} we did not find any
correlation between thyroid hormone levels and pa-
rameters 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 param-
eter 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 his-
tory, electrocardiography, and echocardiography
(wall motion abnormality), without further support
by coronary angiography. Although TDI has be-
come a widespread imaging tool for quantifying tis-
sue velocities, it has limitations such as angle and
load dependency and velocity aliasing.\textsuperscript{17,27} Cur-
tently, strain and strain rate imaging techniques
have become popular due to elicitation of quantita-
tive information on endocardial deformation.\textsuperscript{28-30} In
our study, we did not investigate the effect of thy-
roid 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.\textsuperscript{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
deposition in SH patients.

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

Anahtar sözcükler: Ekokardiyografi, Doppler; hipotiroidizm/komplikasyon; ventrikül disfonksiyonu, sol; ventrikül disfonksiyonu, sağ.