Electrocardiographic and echocardiographic evidence of myocardial impairment in patients with overt hypothyroidism

Test électrocardiographique et échocardiographique de la dépréciation du myocarde chez les patients atteints d’hypothyroïdie patente

Ercan Erdogan\textsuperscript{a,\ast}, Mehmet Akkaya\textsuperscript{a}, Ahmet Bacaksiz\textsuperscript{a}, Abdurrahman Tasal\textsuperscript{a}, Muzaffer İlhan\textsuperscript{b}, Seref Kul\textsuperscript{a}, Emin Asoglu\textsuperscript{a}, Murat Turfan\textsuperscript{a}, Osman Sonmez\textsuperscript{a}, Ertugrul Tasan\textsuperscript{b}

\textsuperscript{a} Bezmialem Foundation University, Faculty of Medicine, Department of Cardiology, Vatan street, 34093 Fatih/Istanbul, Turkey
\textsuperscript{b} Bezmialem Foundation University, Faculty of Medicine, Department of Endocrinology and Metabolism, Istanbul, Turkey

Abstract

Objective. – Our aim was to evaluate cardiac function and myocardial contractility in patients with overt hypothyroidism using two-dimensional speckle tracking echocardiography (2D-STE) strain imaging and real-time three-dimensional echocardiography (RT3DE) and compare the changes at one month after starting the treatment. We also compared the P wave dispersion (Pdis) in patients with and without hypothyroidism. Subjects and methods. – Forty-one patients with overt hypothyroidism and forty age- and body mass index-matched healthy subjects underwent conventional echocardiography, RT3DE and 2D-STE for assessment of resting LV function. Electrocardiography (ECG) recordings were obtained and the P wave parameters were calculated. Measurements of RT3DE volumes and ejection fraction (EF) were performed. Global longitudinal strain (GLS) was calculated from 3 standard apical views using 2D-STE. Results. – Patients with overt hypothyroidism had significantly longer isovolumic contraction time ($P<0.001$), deceleration time ($P<0.001$) and isovolumic relaxation time ($P<0.001$). On RT3DE evaluation, none of the patients in both groups had LV systolic dysfunction with comparable LVEF and LV volumes. However, speckle tracking analysis showed that GLS was significantly reduced in the overt hypothyroidism group compared to control group ($P<0.001$). At one month follow-up after the treatment, GLS significantly improved in overt hypothyroidism group ($P<0.001$). Patients in the overt hypothyroidism group had increased Pdis compared to control group ($P=0.02$). Conclusions. – Overt hypothyroidism may be related to impairment of LV longitudinal myocardial function, and 2D-STE is useful for the detection of early impairment. Successful treatment of overt hypothyroidism has a beneficial effect on cardiac functions. In addition, overt hypothyroidism has increased risk for atrial arrhythmias due to high Pdis value.

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1. Introduction

Thyroid disease is quite common, affecting as many as 9\% to 15\% of adult female population and a smaller percentage of males [1]. Overt hypothyroidism is associated with significant cardiovascular changes including increased systemic vascular resistance (SVR), decreased cardiac contractility and accelerated atherosclerosis [2,3]. In hypothyroidism, cardiac output could decrease by 30\% to 50\% [4]. The cardiovascular changes in hypothyroidism are caused by decreased thyroid hormone action on multiple organs such as the heart, peripheral vasculature and are potentially reversible with thyroid hormone replacement [5].

Global left ventricular (LV) systolic function is most commonly assessed by LV ejection fraction (EF) using conventional echocardiography. However, this technique provides limited data because of challenges related to image quality, assumptions of LV geometry, and operator experience. Two-dimensional speckle tracking echocardiography (2D-STE) is an automated and quantitative technique for the measurement of global long-axis function from gray-scale images. Longitudinal tissue deformation is evaluated by frame-by-frame tracking of individual speckles throughout the cardiac cycle, and global longitudinal speckle strain (GLS) is calculated from the mean of 17 cardiac segments. 2D-STE is more robust than tissue Doppler-derived strain, does not have angle dependency, and is easier to calculate. The accuracy of 2D-STE has also been confirmed...
using sonomicrometry and magnetic resonance imaging (MRI) tagging as reference methods [6].

The real-time three-dimensional echocardiography (RT3DE) calculates the actual LV volume based on the actual shape, not the geometrical assumptions so that it has a good reproducible, even if in the heart cavity deformation, segmental wall motion abnormalities. RT3DE may also receive precise quantitative information, is more accurate than the two-dimensional echocardiography, and is close to the current gold standard MRI [7].

The aim of this study is to investigate the changes in cardiac functions and myocardial contractility of patients with hypothyroidism using 2D-STE before and at one month after treatment.

2. Materials and methods

2.1. Patient selection

We performed a prospective study between March 2012 and August 2012 including 41 newly diagnosed patients with hypothyroidism who were untreated and 40 healthy individuals matched by age, body mass index (BMI), heart rate and blood pressure during the same time period. All patients underwent physical examination, chest X-ray, 12-lead electrocardiography (ECG) and transthoracic echocardiographic evaluation. Patients with any cardiovascular disorder including hypertension, diabetes mellitus, coronary artery disease, cardiac failure, moderate to severe valvular heart disease, cardiomyopathy, rhythm disturbances, pulmonary, hematological, hepatic and/or renal diseases, use of oral contraceptives or other hormonal therapy within the prior 3 months, pregnancy or breast-feeding, hyperprolactinemia, smoking, chronic alcohol consumption, or previous use of antithyroid agents were excluded.

Subjects were informed regarding the purpose of the study and provided written informed consent. Investigations were in accordance with the Declaration of Helsinki and were approved by the local ethics committee.

2.2. Biochemistry

Thyroid hormone measurements were assessed by an Advia Centaur system (Siemens Health Care) using immunochemiluminescence assay method. Hypothyroidism was defined as free tetraiodothyronine (fT4) levels < 11.5 μIU/mL or free triiodothyronine (fT3) levels < 3.5 pmol/L, and thyroid stimulating hormone (TSH) levels > 5.5 μIU/mL.

2.3. Electrocardiography

Twelve-lead ECG of all patients was recorded in the supine position (Montara Instrument EU 250 Electrocardiograph, Milwaukee, WI, USA). ECG recordings were obtained at a paper speed of 50 mm/s and 10 mm/mV amplitude. The beginning of the P wave was defined as the point where the first atrial deflection crossed the isoelectric line and the end of the P wave was defined as point where the atrial deflection returned the isoelectric line. The P wave durations (Pmax, Pmin) were calculated in all 12-leads of ECG. The difference between Pmax and Pmin was defined as P wave dispersion (Pdis) [8]. The measurements of the P wave duration were performed manually by the use of a magnifying glass by two blinded cardiologists without knowledge of the clinical status of the patients. In all patients, derivations were excluded if the beginning or the ending of the P wave could not be clearly identified. Intraobserver and interobserver mean percent mistake (absolute difference between two observations divided by the mean and expressed in percent) for Pmax and Pmin measurements were determined in 50 randomly selected study applicant (25 patients/25 controls) and were <5% for Pmax and <5% for Pmin.

2.4. Conventional echocardiography

Conventional echocardiography was performed on the subjects at rest in the left lateral decubitus position by 2 professional cardiologists who were blinded to the clinical data with a commercially available system (Philips iE33, Bothell, WA, USA) equipped with a broadband SS-1 transducer (frequency transmitted: 1.7 MHz; received: 3.4 MHz). Complete 2D, color, pulsed and continuous-wave Doppler examinations were performed according to standard techniques. Parasternal long-axis views were used to derive the M-Mode measurements of left atrial diameter (LA), LV end-diastolic septal (LVsw) and posterior wall thickness (LVpw), and LV end-diastolic (LVEDD) and end-systolic (LVEDS) dimensions. LV mass (LVM) was calculated from 2D echocardiographic measurements by using Devereux formula: LVM = 1.04 × [(LVsw + LVpw + LVEDD)² – (LVEDD)²] – 13.6 and was indexed to body surface area [9]. Left ventricular hypertrophy (LVH) was defined as LVM index >131 g/m² in males and >100 g/m² in females [10]. LV fractional shortening (FS) was calculated as [(LVEDD – LVEDS)/LVEDD]. LV ejection fraction (LVEF) was calculated from LV volumes by the RT3DE. BMI and body surface area were calculated according to standard formulas. Pulsed Doppler profiles of mitral inflow and LV outflow were obtained successively from the apical view, and heart rate was unchanged during the pulsed Doppler recording. From the LV inflow pattern (measured at the tips of the mitral valve), the E/A ratio was measured. All echocardiographic measurements used in the analysis were averaged from 3 heart beats.

2.5. Two-dimensional speckle tracking echocardiography

The endocardial borders were traced in the end-systolic frame of the 2D images from the 3 apical views. Speckles were tracked frame-by-frame throughout the LV wall during the cardiac cycle and basal, mid, and apical regions of interest were created. The operator manually adjusted segments that failed to be tracked. Any segments that subsequently failed to be tracked were excluded. Any view in which 2 or more segments could not be tracked was not included in the analysis, and the remaining apical views were averaged to calculate GLS; otherwise, GLS.
was calculated as the mean strain of all 17 segments. All measurements were made blinded to other results and clinical details.

2.6. Real-time three-dimensional echocardiography

Real-time 3D echocardiography images were also obtained from an apical window with the patient in the same position as 2D-STE. Full-volume images were also gathered over 4 cardiac cycles using a matrix array transducer (×4 transducer, Philips iE33, Andover, MA). Measurements of RT3DE volumes and 3D-LVEF were performed off-line.

Intra-observer variability was determined by the observer repeating the measurement of the GLS in 20 randomly selected patients ten days after the first measurement. Interobserver variability was determined by another observer measuring these variables in the same database. The intra- and inter-observer reproducibility of GLS parameter was shown to be acceptable. The intra- and inter-observer variations were 5.1% and 5.5% for GLS, respectively.

2.7. Statistical analysis

Measured values are reported as mean ± standard deviation, and statistical comparisons were performed using SPSS 15.0 statistics package (SPSS Inc, Chicago, IL, USA). Comparison of categorical and continuous variables between the two groups was performed using the χ² test and unpaired t-test, respectively. The correlation between variables (GLS, TSH, fT3, fT4) was tested using correlation analysis. Delta values is defined as difference between first month and pretreatment value. P-values of <0.05 were considered to indicate statistical significance.

3. Results

The characteristics of patients included in the study are shown in Table 1. There was no statistically significant difference between the two groups based on age, BMI and other main characteristics between the two groups. As expected, in the hypothyroidic group, fT3 and fT4 values were significantly lower (P<0.001 and P<0.001, respectively), and TSH levels were significantly higher (P<0.001), than in the control group.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypothyroid group (n=41)</th>
<th>Control group (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>43±12</td>
<td>43±7</td>
<td>0.872</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>30/11</td>
<td>30/10</td>
<td>0.853</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28±5</td>
<td>27±4</td>
<td>0.796</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>122±7</td>
<td>121±5</td>
<td>0.775</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76±4</td>
<td>75±4</td>
<td>0.477</td>
</tr>
<tr>
<td>HR (beat/min)</td>
<td>73±10</td>
<td>77±10</td>
<td>0.153</td>
</tr>
<tr>
<td>fT3 (pg/mL)</td>
<td>3.45±0.8</td>
<td>5.46±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fT4 (pg/mL)</td>
<td>10.09±2.76</td>
<td>16.19±1.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>31.55±38.63</td>
<td>2.44±0.87</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI: body mass index; DBP: diastolic blood pressure; fT3: free triiodothyronine; fT4: free tetraiodothyronine; HR: heart rate; SBP: systolic blood pressure; TSH: thyroid stimulating hormone.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypothyroid group (n=41)</th>
<th>Control group (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (cm)</td>
<td>4.7±0.3</td>
<td>4.7±0.2</td>
<td>0.258</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>2.7±0.2</td>
<td>2.6±0.2</td>
<td>0.206</td>
</tr>
<tr>
<td>LV systolic volume (cm³)</td>
<td>90.9±0.06</td>
<td>90.9±0.06</td>
<td>0.813</td>
</tr>
<tr>
<td>LV posterior wall thickness (cm)</td>
<td>19.4±0.94</td>
<td>19.4±0.92</td>
<td>0.929</td>
</tr>
<tr>
<td>3D-ESV (mL)</td>
<td>19±5</td>
<td>19±4</td>
<td>0.247</td>
</tr>
<tr>
<td>LV mass index (g/cm³)</td>
<td>104.3±14.3</td>
<td>98.5±18.2</td>
<td>0.288</td>
</tr>
<tr>
<td>E peak rate (m/s)</td>
<td>0.73±0.18</td>
<td>0.79±0.12</td>
<td>0.141</td>
</tr>
<tr>
<td>A peak rate (m/s)</td>
<td>0.65±0.13</td>
<td>0.64±0.13</td>
<td>0.809</td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>1.15±0.35</td>
<td>1.27±0.27</td>
<td>0.205</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>197±20</td>
<td>179±16</td>
<td>0.001</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>92±9</td>
<td>76±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVCT (ms)</td>
<td>84±9</td>
<td>70±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrium (cm)</td>
<td>3.67±0.3</td>
<td>3.32±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>96.19±16.31</td>
<td>93.87±13.51</td>
<td>0.488</td>
</tr>
<tr>
<td>LV mass index (g/cm³)</td>
<td>12±17</td>
<td>12±17</td>
<td>0.011</td>
</tr>
</tbody>
</table>

3D: three-dimensional; A: late diastolic mitral inflow velocity; DT: deceleration time; E: early diastolic mitral inflow velocity; EDV: end-diastolic volume; ESV: end-systolic volume; FS: fractional shortening; IVCT: isovolumic contraction time; IVRT: isovolumic relaxation time; LV: left ventricular; LVEDD: left ventricular ejection fraction; LVEDD: LV end-diastolic diameter; LVESD: LV end-systolic diameter; LVPW: LV posterior wall thickness; LVSVD: LV septal wall thickness; Pmax, Pmin: the P wave durations; Pmax: the difference between Pmax and Pmin.

None of the patients had a LV regional motion defect. M-mode echocardiographic findings were shown in Table 2. 3D-LVEF and FS were similar between the groups. LA diameter was significantly higher in patients with hypothyroid than the normal group (P<0.001).

Among the diastolic parameters, there was no significant difference between the groups in mitral E- and A-velocities. However, isovolumic contraction time (IVCT), deceleration time of early phase of mitral valve flow (DT), and isovolumic relaxation time (IVRT) were significantly longer in the hypothyroidic patient group (P<0.01 for all) (Table 2).

Speckle tracking analysis showed that GLS values were significantly lower in the hypothyroidic group compared to the control group. At one months follow-up after the treatment was started for hypothyroidism, the GLS values showed a significant improvement in hypothyroid patients, however, it was still lower than in control group (Table 3).

Significant correlations were showed between GLS and TSH, fT3, fT4 values (Fig. 1).
Table 3
Global longitudinal strain (GLS) was significantly reduced in the hypothyroid group compared to control group. A significant improvement was observed in GLS values after treatment in hypothyroid patients.

<table>
<thead>
<tr>
<th>Baseline Hypothyroidism (n=41)</th>
<th>Controls (n=40)</th>
<th>P-value</th>
<th>Hypothyroidism 1 month follow-up Pretreatment</th>
<th>1 month after treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS (%)</td>
<td>−14.52 ± 2.17</td>
<td>−18.04 ± 1.0</td>
<td>&lt;0.001</td>
<td>−14.52 ± 2.17</td>
<td>−15.87 ± 1.61</td>
</tr>
</tbody>
</table>

3.2. Comparison of electrocardiographic data in hypothyroid and control groups

Patients in the overt hypothyroidism group had increased Pdis compared to control group (52.02 ± 14.43 ms and 43.75 ± 18.73 ms, $P = 0.02$, respectively). $P_{max}$ was not different between the groups. There was a trend towards shortened $P_{min}$ in patients with hypothyroidism, however it did not reach statistical significance (44.17 ± 15.78 ms and 50.12 ± 14.52 ms, $P = 0.08$) (Table 2).

4. Discussion

In the present study, we found that longitudinal myocardial function detected using 2D-STE was impaired in patients with overt hypothyroidism compared to patients without hypothyroidism. Successful treatment of overt hypothyroidism had a beneficial effect on cardiac functions at short-term follow-up. We also demonstrated that patients with overt hypothyroidism had increased Pdis than non-hypothyroid patients.

The major cardiovascular effects of hypothyroidism are hypertension, bradycardia, pericardial effusion and impairment of LV function [11,12]. Schmidt and Ascheim showed that hypothyroid state alters cardiac gene expression and increases SVR, resulting in a reduction of cardiac contractility and cardiac output in hypothyroid patients [13]. Other studies have found that mucopolysaccharide accumulation, interstitial edema, and fibrosis develops in the myocardial tissue [14]. In vivo and in vitro studies showed that thyroid hormones have a strong impact on oxidative stress. Sarandol et al. found that hypothyroidism is accompanied by increased oxidative stress, due to reduced glutathione levels in the myocardial tissue causing direct myocardial damage [15]. Reduction of sarcoplasmic/endoplasmic reticulum Ca$^{2+}$-ATPase (SERCA)-2a and α-myosin heavy chain in the hypothyroid patients which may cause systolic and diastolic dysfunction [16].

Increased arterial stiffness in these patients, caused mostly by hypertension, may result in impairment of LV diastolic function [17]. The prolonged IVRT, IVCT and DT in our study and decreased E/A ratio confirm impaired diastolic function in this disease; however, none of the patients in this study had hypertension. In the setting of normal blood pressures, the myxodema of the arterial wall in untreated hypothyroid patients may be another factor leading to stiff arterial wall and impaired diastolic function [18].

Conventional echocardiography is the most common method to assess LV systolic function, however, it is not sensitive in

Fig. 1. Global longitudinal strain (ΔGLS) was negative correlated with thyroid stimulating hormone (ΔTSH) value; positive correlated with free triiodothyronine (ΔT3) and free tetraiodothyronine (ΔT4) values.
detecting early deterioration of myocardial function. We used a novel imaging modality, 2D-STE with myocardial strain analysis, which is more accurate for detecting subclinical myocardial systolic dysfunction [19,20]. In the present study we showed that, as compared to controls, patients with hypothyroidism had more impaired LV GLS. These results are consistent with a previous study reported by Tiryakioğlu et al. and suggest that patients with hypothyroidism might have impaired myocardial function despite normal LVEF [21]. In addition, we showed that the treatment of hypothyroidism resulted in an improvement in myocardial function at one month follow-up. However, despite significant improvement after hormone replacement therapy, the GLS at one month was still lower than in non-hypothyroid group. We think that the findings in our study may have 3 major implications in clinical practice. First, patients with hypothyroidism may have myocardial dysfunction although they have normal LVEF and no wall motion abnormality on conventional echocardiography or RT3DE. Second, strain echocardiography may help physicians to identify the patients at early stage of myocardial dysfunction. Since the cardiovascular deterioration caused by hypothyroidism is mostly reversible with hormone replacement, early detection of patients and initiation of hormone replacement therapy may prevent these patients from getting symptomatic heart failure. Third, the improvement of subclinical myocardial dysfunction may take longer than the improvement in thyroid function and patients who had myocardial dysfunction on strain echocardiography might need longer and more aggressive hormone replacement treatment. On the other hand, patients with early myocardial dysfunction may have underlying cardiac disease and may get consulted early with that respect as well.

Pdīs has been shown to be increased in patients with hyperthyroidism and is related to increased risk of arrhythmias, atrial fibrillation (AF) in particular [22]. However, cardiac arrhythmias are rare in the setting of hypothyroidism and there is little known about the P wave characteristics in this group. In this study, we demonstrated increased Pdīs in hypothyroid group compared to control patients. This is consistent with a recent study done by Ozturk et al. and suggests an impaired conduction abnormality in the atria [23]. The increased Pdīs might be either a result of myxedema in the atrial tissue or induced fibrosis in the cardiac tissue. Since fibrosis is irreversible, we think that the former is a more reasonable explanation. LV diastolic dysfunction might cause increased Pdīs and Gunduz et al. have shown the association between increased LV dysfunction and increased Pdīs [24]. Our results are consistent with a previous study reported by Ozturk et al. found that LA diameter and Pdīs were significantly higher in patients with overt hypothyroidism [23]. However, despite increased Pdīs, the less prevalence of atrial arrhythmias in hypothyroidism needs to be clarified.

5. Study limitations

The quality of speckle tracking depends highly on the spatial resolution of the image and on the frame rate of the cine-loop. Therefore, a number of subjects had to be excluded from the analysis because the image quality in one or more segments was insufficient for 2D-STE analysis, particularly due to the physiological growth of the myocardial chambers. Another limitation of our study is manual calculation of P wave parameters using magnifying lens instead of computer-assisted P wave calculations. Our study included a relatively small number of patients, and long-term clinical outcome data, such as cardiovascular event rates and survival assessment, were not part of the present study.

6. Conclusions

These results indicate that overt hypothyroidism may be associated with impairment of LV longitudinal myocardial function, and that 2D-STE is useful for detection of early impairment. Successful treatment for overt hypothyroidism has a beneficial effect on cardiac functions at short-term follow-up. In addition, we showed that patients with overt hypothyroidism have increased Pdīs so they have increased risk for the development of atrial arrhythmias.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References