Abnormal cardiac contractility in long-term exogenous subclinical hyperthyroid patients as demonstrated by two-dimensional echocardiography speckle tracking imaging

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*(R M Abdulrahman and V Delgado contributed equally to this work)

Abstract

Background: Subclinical hyperthyroidism is associated with cardiovascular morbidity. Recent advances in echocardiography imaging have allowed sophisticated evaluation of myocardial tissue properties.

Objective: To investigate the myocardial effects of long-term exogenous subclinical hyperthyroidism using two-dimensional speckle tracking echocardiography imaging (2D-STE).

Design: Prospective, single-blinded, placebo-controlled randomized trial of 6 months duration with two parallel groups.

Patients and methods: Totally 25 patients with a history of differentiated thyroid carcinoma on long-term TSH-suppressive levothyroxine (L-T4) substitution were randomized to persistent TSH-suppressive L-T4 substitution (low-TSH group) or restoration of euthyroidism. Additionally 40 euthyroid controls were studied.

Results (proposal): At baseline, the group of patients showed normal left ventricular (LV) systolic function but impaired diastolic function as assessed with conventional echocardiographic parameters. Importantly, 2D-STE analysis demonstrated the presence of subclinical LV systolic and diastolic dysfunction with impaired circumferential and longitudinal strain and strain rate at the isovolumic relaxation time. After restoration of euthyroidism, a significant improvement in LV systolic and diastolic function as assessed with 2D-STE strain was observed.

Conclusion: Prolonged subclinical hyperthyroidism leads to systolic and diastolic dysfunction, which is reversible after restoration of euthyroidism. 2D-STE is a more sensitive technique to evaluate subtle changes in LV performance of these patients.

Introduction

Subclinical hyperthyroidism is a relatively common thyroid dysfunction with important cardiovascular consequences such as left ventricular (LV) diastolic dysfunction, increased LV mass, and increased risk of supraventricular arrhythmias (1–7). These cardiovascular effects can be accurately evaluated in exogenous subclinical hyperthyroidism, where the duration and development of thyroid dysfunction are well controlled, and different strategies to restore euthyroidism can be performed in a randomized fashion. We recently performed a prospective, randomized, placebo-controlled study in patients treated with total thyroidectomy for differentiated thyroid carcinoma, and demonstrated that 10-year thyroid hormone excess was related to increased LV mass index and overt diastolic dysfunction (7). More importantly, restoration of euthyroidism resulted in normalization of diastolic function.

Recent advances in echocardiography imaging have allowed sophisticated evaluation of myocardial tissue properties that may provide novel insights into the effects of thyroid hormone on the myocardium. Particularly, two-dimensional speckle tracking echocardiography (2D-STE) imaging is a novel technology that permits the study of multidirectional active deformation of the myocardium, providing comprehensive information on myocardial function and closely reflecting myocardial contractile properties (8–10). 2D-STE imaging allows estimation of both strain (radial, longitudinal, and circumferential) and strain rate (SR). Strain measures the myocardial fiber deformation (shortening and thickening), and SR measures the velocity of deformation. The present study explores further the effects of thyroid hormone on the
myocardium with the use of 2D-STE and aimed to demonstrate whether LV mechanics, as assessed with multidirectional strain, are impaired in patients with subclinical hyperthyroidism and whether these abnormalities may be reversed after restoration of the euthyroid status. The echocardiographic data collected prospectively in the aforementioned randomized placebo-controlled study were reanalyzed in a blinded fashion with 2D-STE tracking echocardiography and compared with an expanded control group (7).

Patients and methods

The present study was a prospective single-blind randomized study of 6 months duration with two parallel groups. As previously described, the patient population consisted of athyreotic patients subjected to TSH-suppressive thyroxine (T₄) treatment (7). Patients had been diagnosed with differentiated thyroid carcinoma and had been initially treated with total thyroidectomy and radioiodine ablative therapy. Cure was documented by the absence of measurable serum thyroglobulin during TSH stimulation and by a negative total-body scintigraphy with 4 mCi¹³¹I. TSH-suppressive thyroxine (T₄) treatment (7). Patients had been diagnosed with differentiated thyroid carcinoma and had been initially treated with total thyroidectomy and radioiodine ablative therapy. Cure was documented by the absence of measurable serum thyroglobulin during TSH stimulation and by a negative total-body scintigraphy with 4 mCi¹³¹I. TSH-suppressive thyroxine (T₄) treatment (7). 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Longitudinal strains) and one diastolic parameter
systolic parameters (global radial, circumferential, and
LV mechanical properties were evaluated through three
the LV filling pressures. Therefore, in the present study,
a marker of global myocardial relaxation and reflects
panel D), as previously described (15). This parameter is
strain rate at the isovolumic relaxation time.

Continuous variables are presented as mean ± s.d., and
categorical variables are presented in number and
frequencies. Comparisons between patients and controls
were performed with Student’s t-test for unpaired data.
As previously described, the effects of different
conditions on echocardiographic parameters were
evaluated within and between low-TSH group and
euthyroid patients using Mann–Whitney U test and
Wilcoxon sum rank test for unpaired and paired data
respectively. To evaluate the relationship between free
T₄ and TSH levels and the various echocardiographic
parameters, univariate regression analysis was performed.
All statistical analyses were performed with SPSS
software (version 16.0, SPSS Inc., Chicago, IL, USA).
A P value < 0.05 was considered statistically significant.

Results
Out of an initial cohort of 33 patients, 25 patients were
included in the present study (7). Thirteen patients
continued TSH-suppressive therapy (low-TSH group,
target TSH level < 0.4 mU/l), whereas in the remaining
12 patients, the euthyroid status was restored
(euthyroid group). At baseline, weight ((73.2 ± 15.9
(low-TSH group) vs 74.0 ± 9.5 kg (euthyroid group),
P = 0.881)), systolic blood pressure (135 ± 23 vs
134 ± 14 mmHg, P = 0.920), diastolic blood pressure
(81 ± 10 vs 83 ± 5 mmHg, P = 0.728), heart rate
(71 ± 7 vs 68 ± 7 bpm, P = 0.452), T₄ dose (166 ± 34
vs 185 ± 40 μg, P = 0.200), TSH (0.054 (< 0.005–
0.339) vs 0.038 (< 0.005–0.302) mU/l, P = 0.617),
and free T₃ (21.7 ± 5.8 vs 22.6 ± 4.0 pmol/l, P = 0.637)
were not different between the low-TSH group and
the euthyroid group. After 6 months, T₄ dose (177 ± 33
vs 129 ± 37 μg, P ≤ 0.001), TSH concentrations (0.015
(< 0.005–0.347) vs 2.66 (0.218–6.090) mU/l, P = 0.001)
and free T₃ (23.1 ± 1.2 vs 18.5 ± 1.1 pmol/l,
P < 0.001) differed significantly between the low-TSH
group and the euthyroid group.

Baseline echocardiography and 2D-STE
analysis
At baseline, patients showed significantly higher values
of end-diastolic PWT and LV ESD than controls
(Table 1). However, LV mass index (LVMI) was
comparable between the two groups. In addition,
patients had significantly lower values of LV FS and
LVEF compared to the group of controls, but within
the normal range (Table 1). Regarding the diastolic
function, the group of patients showed significantly
lower values of E- and A-wave with an inverse E/A ratio
and significantly longer values of E-wave DT and IVRT,
indicating impaired LV relaxation (Table 1). There were
no differences in left atrial volume. Finally, 2D-STE
analysis demonstrated a significant impairment of LV
circumferential and longitudinal strains in the group of
patients, whereas LV radial strain was preserved
compared to the group of controls (Table 1). In addition,
the SRIVRT was significantly reduced in the group of
patients compared to the group of controls, indicating
higher LV filling pressures.
Table 1 Baseline echocardiographic characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 40)</th>
<th>Patients (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index (g/m²)</td>
<td>77.2 ± 17.2</td>
<td>86.0 ± 21.0</td>
<td>0.051</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>8.4 ± 1.0</td>
<td>9.2 ± 1.6</td>
<td>0.056</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>8.4 ± 0.9</td>
<td>9.2 ± 1.2</td>
<td>0.003</td>
</tr>
<tr>
<td>LV EDD (mm)</td>
<td>49.4 ± 4.7</td>
<td>49.2 ± 4.1</td>
<td>0.989</td>
</tr>
<tr>
<td>LV ESD (mm)</td>
<td>28.8 ± 4.5</td>
<td>31.5 ± 4.5</td>
<td>0.020</td>
</tr>
<tr>
<td>LV FS (%)</td>
<td>41.4 ± 6.1</td>
<td>36.0 ± 7.3</td>
<td>0.004</td>
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<tr>
<td>LV EF (%)</td>
<td>71.6 ± 7.1</td>
<td>64.7 ± 9.3</td>
<td>0.002</td>
</tr>
<tr>
<td>A-wave (cm/s)</td>
<td>72.9 ± 17.6</td>
<td>55.3 ± 9.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A'-wave (cm/s)</td>
<td>56.7 ± 12.6</td>
<td>63.9 ± 10.8</td>
<td>0.029</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.3 ± 0.2</td>
<td>0.87 ± 0.13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E-wave DT (ms)</td>
<td>191.1 ± 33.3</td>
<td>234 ± 34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>77.7 ± 13.3</td>
<td>121.0 ± 15.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left atrial volume (ml)</td>
<td>45.5 ± 13.7</td>
<td>50.5 ± 13.7</td>
<td>0.160</td>
</tr>
<tr>
<td>E-wave (cm/s)</td>
<td>9.2 ± 1.7</td>
<td>5.7 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A'-wave (cm/s)</td>
<td>6.5 ± 1.4</td>
<td>6.8 ± 1.4</td>
<td>0.494</td>
</tr>
<tr>
<td>E/A' ratio</td>
<td>1.4 ± 0.5</td>
<td>0.89 ± 0.35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Radial strain (%)</td>
<td>43.9 ± 17.5</td>
<td>42.3 ± 11.8</td>
<td>0.687</td>
</tr>
<tr>
<td>Circumferential strain (%)</td>
<td>−19.7 ± 2.8</td>
<td>−16.9 ± 2.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Longitudinal strain (%)</td>
<td>−19.9 ± 2.8</td>
<td>−17.7 ± 1.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SRIVRT (1/s)</td>
<td>0.39 ± 0.09</td>
<td>0.29 ± 0.08</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

DT, deceleration time; EDD, end-diastolic diameter; ESd, end-systolic diameter; FS, fractional shortening; IVRT, isovolumic relaxation time; IVST, interventricular septum thickness; LV, left ventricular; PWT, posterior wall thickness; SRIVRT, strain rate at the isovolumic relaxation time.

Low-TSH group versus euthyroid group: conventional echocardiography

At 6 months follow-up, the euthyroid group showed significant reductions in LV dimensions and improvements in LV FS and LVEF (Table 2). In addition, LV diastolic function improved significantly in the euthyroid group as indicated by a reduction in the A-wave velocity and normalization of the E/A ratio, a significant reduction in the left atrial volume, and significant decreases in E-wave DT and IVRT. In contrast, the low-TSH group exhibited a significant increase in LV dimensions (EDDs and ESDs) and a significant reduction in LV FS and LVEF (Table 2). No changes in conventional imaging-derived LV diastolic parameters were observed in the low-TSH group.

Low-TSH group versus euthyroid group: 2D-STE analysis

At baseline, both groups of patients showed comparable values of LV radial, circumferential, and longitudinal strains and comparable values of SRIVRT as measured with 2D-STE imaging (Table 3).

At 6 months follow-up, the euthyroid group showed a significant improvement in LV circumferential and longitudinal strains and in SRIVRT, whereas no changes in LV radial strain were observed (Fig. 2). In contrast, the low-TSH group did not have significant changes in multidirectional LV strain or SRIVRT (Fig. 2). There were significant differences in changes in circumferential and longitudinal strains and in SRIVRT between the two groups (Table 3).

Relationship between TSH levels and echocardiographic parameters at follow-up

Univariate regression analysis was used to evaluate the influence of free T4 and TSH levels on different echocardiographic parameters (Table 4). Free T4 and TSH levels were not related to LV dimensions or systolic function as measured with conventional parameters. In contrast, some LV diastolic parameters as measured with transmitral pulsed-wave Doppler echocardiography (A-wave, E/A ratio, DT, and IVRT) or tissue Doppler imaging showed significant differences in the low-TSH and euthyroid groups.

Table 2 Low-TSH group versus euthyroid group: conventional echocardiography and tissue Doppler imaging.

<table>
<thead>
<tr>
<th></th>
<th>Low-TSH (n = 13)</th>
<th>Euthyroid (n = 12)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index (g/m²)</td>
<td>86.0 ± 26.0</td>
<td>89.0 ± 12.0</td>
<td>0.052</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>8.9 ± 1.9</td>
<td>9.2 ± 1.1</td>
<td>0.763</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>9.0 ± 1.2</td>
<td>8.9 ± 1.2</td>
<td>0.567</td>
</tr>
<tr>
<td>LV EDD (mm)</td>
<td>49.1 ± 4.0</td>
<td>52.1 ± 3.3</td>
<td>0.045</td>
</tr>
<tr>
<td>LV ESD (mm)</td>
<td>30.1 ± 4.0</td>
<td>34.1 ± 5.4*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV FS (%)</td>
<td>38.4 ± 7.0</td>
<td>34.8 ± 8.0*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>67.6 ± 8.6</td>
<td>62.6 ± 11.4*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E-wave (cm/s)</td>
<td>58.1 ± 7.9</td>
<td>58.9 ± 8.2</td>
<td>0.353</td>
</tr>
<tr>
<td>A-wave (cm/s)</td>
<td>66.1 ± 11.2</td>
<td>67.7 ± 12.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.91 ± 0.16</td>
<td>0.88 ± 0.12</td>
<td>0.001</td>
</tr>
<tr>
<td>E-wave DT (ms)</td>
<td>230 ± 34</td>
<td>236 ± 26</td>
<td>0.001</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>115 ± 15</td>
<td>121 ± 17</td>
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<td>Left atrial volume (ml)</td>
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<td>5.9 ± 1.8</td>
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<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/A' ratio</td>
<td>0.34 ± 0.42</td>
<td>0.97 ± 0.34</td>
<td>0.003</td>
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DT, deceleration time; EDD, end-diastolic diameter; ESd, end-systolic diameter; FS, fractional shortening; IVRT, isovolumic relaxation time; IVST, interventricular septum thickness; LV, left ventricular; PWT, posterior wall thickness; SRIVRT, strain rate at the isovolumic relaxation time.

aDifference between 6 months and baseline, euthyroid versus low-TSH group.
imaging (E'-wave) were significantly related to free T₄ and TSH levels. Finally, novel indices of LV systolic function based on 2D-STE analysis showed a borderline association with TSH levels but not with free T₄ levels.

**Discussion**

The present study provides new insights into the effects of thyroid hormone on myocardial mechanical performance assessed with 2D-STE. In patients with long-term exogenous subclinical hyperthyroidism and preserved LVEF, 2D-STE analysis demonstrated the presence of impaired LV myocardial deformation. After restoration of euthyroid status, a significant improvement in circumferential and longitudinal strains and SRIVRT was observed. Therefore, in patients with exogenous subclinical hyperthyroidism and preserved LVEF, the excess of thyroid hormone exerts a deleterious effect on myocardial function that is reversible upon restoration of euthyroid status. It remains to be determined whether these changes may be reversed or not once overt heart failure is present.

The cardiovascular effects of subclinical hyperthyroidism have been well documented, and include increased LV mass, diastolic dysfunction, and increased risk of cardiac arrhythmias (1–6, 16). However, it is important to note that previous studies included retrospective series and yielded observational and controversial results (4, 16–18). In contrast, the randomized design of the present study permitted evaluation of the direct cardiovascular effects of thyroid hormone. Patients with subclinical hyperthyroidism showed impaired diastolic function as assessed with conventional pulsed-wave Doppler echocardiography and tissue Doppler imaging (7). After restoration of euthyroid hormone levels, significant improvements in diastolic function were observed. The present study represents a step further in the characterization of LV diastolic performance by evaluating the relaxation properties of the myocardium with 2D-STE. At baseline, the overall population showed a reduced SRIVRT, a surrogate of increased LV filling pressures (15). Improvement in LV filling pattern with an increase in SRIVRT was only observed in those patients with restored euthyroidism, whereas in those patients with low-TSH levels, SRIVRT remained unchanged. The measurement of SRIVRT provides additional insight to previous findings based on tissue Doppler imaging, as this parameter may be less load-dependent and relies on active deformation of the myocardium. In addition, these changes in LV diastolic dysfunction were independent of LV mass. The present study population had an increased LV mass as compared with controls. However, most patients did not show LV hypertrophy. As previously demonstrated, thyroid hormone exerts direct effects on myocardial diastolic relaxation independent of protein synthesis and cardiac growth (1, 19). Therefore, it may reflect more the direct biochemical effects of thyroid hormone on the myocardium, which lead to activation of local signal transduction pathways rather than the effects of LV hypertrophy (1, 20). In earlier studies, more profound LV hypertrophy was found that was reversed by β-blockers (5, 21, 22) or dose reduction (23). These studies also included patients with multinodular goiter, who may have been exposed to higher levels of

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**Table 3** Low-TSH group versus euthyroid group: two-dimensional speckle tracking strain imaging.

<table>
<thead>
<tr>
<th></th>
<th>Low-TSH (n = 13)</th>
<th>Euthyroid (n = 12)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6 months</td>
<td>Baseline 6 months</td>
<td></td>
</tr>
<tr>
<td>Radial strain (%)</td>
<td>42.9 ± 10.2 39.7± 13.7</td>
<td>41.7± 13.7 42.0± 11.2</td>
<td>0.431</td>
</tr>
<tr>
<td>Circumferential strain (%)</td>
<td>−17.0± 2.8 −16.5± 1.3</td>
<td>−16.9± 1.7 −18.8± 2.3*</td>
<td>0.018</td>
</tr>
<tr>
<td>Longitudinal strain (%)</td>
<td>−17.9± 1.3 −17.5± 1.8</td>
<td>−17.5± 1.1 −19.7± 2.1*</td>
<td>0.001</td>
</tr>
<tr>
<td>SRIVRT (1/s)</td>
<td>0.29± 0.1 0.28± 0.08</td>
<td>0.29± 0.06 0.42± 0.09*</td>
<td>0.004</td>
</tr>
</tbody>
</table>

SRIVRT, strain rate at the isovolumic relaxation time. *P<0.05 versus baseline (within the groups).

*Difference between 6 months and baseline, euthyroid versus low-TSH group.
free T₄ and have subsequently shown more profound myocardial hypertrophy.

It can be hypothesized that the fact that we did not find a significant difference between patients and controls in LVMI and IVST could be explained by the fact that TSH levels were not suppressed in all patients. We therefore compared IVST and LVMI between patients with completely suppressed TSH levels at baseline and controls in LVMI and IVST could be explained by the fact that TSH levels were not suppressed in all patients.

Some limitations have to be acknowledged. First, the assessment of LV myocardial function with 2D-STE analysis after an acute change of TSH or free T₄ was not performed, and therefore the effects of these hormones at the tissue level could not be elucidated. In addition, the small study population may preclude us from observing stronger relationships between the 2D-STE-derived parameters of LV function and TSH levels.

In conclusion, patients with prolonged subclinical hyperthyroidism show subtle LV systolic and diastolic dysfunction, which is reversible after restoration of euthyroidism.

### Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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