Original Research

Arterial Stiffness and Left Ventricular Diastolic Function in Subjects with Euthyroidism

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Abstract

Objective: Previous literature has suggested that the cardiovascular risk factors associated with subclinical hypothyroidism (SCH) may be found in subjects with euthyroidism, but research relating to increased arterial stiffness (AS) and left ventricular (LV) diastolic dysfunction, which have been proven to exist in patients with SCH, is limited in patients with euthyroidism. The aim of this study was to investigate this. Methods: A total of 249 participants with euthyroidism were divided into two groups based on their thyroid-stimulating hormone (TSH) levels: Group A (TSH level ranging from 0.49 to 2.5 mIU/L, n = 170) and Group B (TSH level ranging from 2.5 to 4.91 mIU/L, n = 79). The Cardiovascular Profiling System through brachial-ankle pulse wave velocity (baPWV) was used to assess AS, and the LV function was evaluated using Color-Doppler-Echocardiography. The Student’s unpaired t-test and Pearson’s χ² test were conducted to compare the clinical parameters. Spearman’s correlation analysis and multiple logistic regression analysis were used to analyze the association between thyroid function, baPWV, and LV diastolic function parameters. Results: Significant differences existed between the two groups in free triiodothyronine (FT3) values and systolic blood pressure (BP) (p < 0.05). When compared with Group A, the baPWV was higher, the A wave increased, and the E/A ratio was lower in Group B (p < 0.01). The multiple logistic regression analysis showed that FT3 was associated with a higher baPWV (p < 0.001). The E/A ratio was directly correlated with TSH, FT3, and baPWV (p < 0.05), and diastolic BP was significantly directly correlated with the E/A ratio (p < 0.05). Thyroperoxidase antibody was not a significant variable in the regression analysis (p > 0.05). Conclusions: An association was found between thyroid function, baPWV, and the E/A ratio in subjects with euthyroidism. Further study is needed to confirm these conclusions.

Keywords: thyroid-stimulating hormone; brachial-ankle pulse wave velocity; arterial stiffness; left ventricular diastolic function; thyroperoxidase antibody

1. Introduction

Thyroid dysfunction presents as one of the most frequently occurring endocrine diseases [1]. It has been reported that the prevalence of subclinical hypothyroidism (SCH) ranges from 0.4%–20% [2,3]. Previous studies have suggested that SCH may worsen many risk factors for cardiovascular disease (CVD), including hypertension, atherosclerosis, dyslipidemia, and abnormal endothelial function, and even result in CVD directly, such as pericarditis [4,5].

Arterial stiffness (AS) appears to be an important risk factor for atherosclerosis and hypertension, as well as in the process of left ventricular (LV) diastolic dysfunction (DD) [6,7]. A growing number of studies have indicated that patients with SCH exhibit increased AS and impaired LV diastolic function when compared with people with euthyroidism [8,9].

As noted by the National Health and Nutrition Examination Survey III from the United States of America (USA), the thyroid-stimulating hormone (TSH) upper reference limits may be skewed by thyroperoxidase antibody (TPO-Ab)-negative individuals with occult autoimmune thyroid dysfunction [10]. This may signify that some people with mild hypothyroidism, including SCH, were not identified and were treated as if they had normal thyroid function. Therefore, people with TSH levels close to the upper limit may suffer from similar adverse effects as people with SCH.

The literature revealed that decreased endothelium-dependent vasodilatation (a sign of endothelial dysfunction), increased blood pressure (BP), and dyslipidemia were observed in people with high–normal TSH levels [11–13]. However, AS and LV DD in patients with high–normal TSH levels have not yet been adequately studied. Pulse wave velocity (PWV) is an index measuring AS by measuring the speed of a pulse wave along an artery. A higher PWV indicates increased stiffness in the arterial wall. Lambrinoudaki et al. [14] reported that a high–normal TSH level is associated with increased PWV, but the study subjects were all healthy postmenopausal women. Sandra et al. [15] suggested that cardiac diastolic abnormalities occur in patients with autoimmune thyroiditis when their serum TSH levels are still within the normal range, but the sample size was small (n = 45).

Subjects with high–normal TSH levels frequently progress to hypothyroidism later in life [16], and an evaluation of AS in this group was warranted. As a result, the
present study was conducted to confirm the hypothesis that AS might be greater in people with high–normal TSH levels when compared with people with normal TSH levels, using a simple measurement, i.e., brachial-ankle PWV (baPWV) in a larger sample size. Indices indicating the LV diastolic function were analyzed.

2. Materials and Methods

2.1 Study Participants

This retrospective study was conducted to examine the AS and the LV diastolic function in subjects with euthyroidism. The participants were collected by searching the computerized database of patients hospitalized in the Department of Endocrinology and Metabolism at our hospital from December 2015 to November 2021. A total of 425 participants who underwent a measurement for AS were included for eligibility assessment. The district in which the study was conducted is not an iodine-deficient district.

The following exclusion criteria were used: (1) incomplete personal medical and drug treatment history (missing vital data); (2) thyroid function not within the normal range or a history of thyroid disease or therapy; (3) the use of drugs known to affect thyroid function, e.g., metformin [17], glucocorticoids, dopamine agonists, rexinoids, carbamazepine, and metyrapone [18]; (4) a previous history of serious cardiovascular events, e.g., ischemic heart disease or heart failure, stroke, or chronic obstructive peripheral arteriopathy (ankle–brachial index <0.9 or detected by Doppler ultrasonography); (5) other serious chronic diseases, a recent history of acute illness, malignant disease, or severely impaired renal function, i.e., estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²; (6) drug or alcohol abuse.

A total of 249 subjects with euthyroidism were included in the final analysis. To evaluate the AS and LV functions in relation to the TSH level, all patients were grouped according to their serum TSH level into the normal TSH group (Group A, 0.49 mIU/L ≤ TSH ≤ 2.5 mIU/L) and the high–normal TSH group (Group B, 2.5 mIU/L < TSH ≤ 4.91 mIU/L). The cutoff point was set according to studies researching subjects with euthyroidism [14,17].

The study was conducted in accordance with the declaration of Helsinki and approved by our hospital ethical committee.

2.2 Clinical Measurements and Biochemical Analysis

The anthropometric indices (body weight and height) were measured by professional investigators using a standard protocol. Height was assessed to the nearest 1 cm and body weight with light clothing to the nearest 0.1 kg. The body mass index (BMI) was calculated as the body weight (kg) divided by the square of the body height (m). Office BP was measured on the right arm using an automatic BP monitor (J30 [±3 mmHg], Omron Healthcare Co., Ltd., Kyoto, Japan) after a minimum of 5 min of rest in a sitting position. The sociodemographic characteristics, including age, gender, smoking status, individual history of disease (CVD, stroke, hypertension, dyslipidemia, type 2 diabetes, and thyroid disorders), and detailed drug treatment were collected from participants’ medical records.

The venous blood samples were collected between 6 AM and 8 AM after fasting for at least 10 h for the measurement of thyroid function, serum lipid profile, and renal function parameters. Serum concentrations of TSH (normal range: 0.49–4.91 mIU/L), free triiodothyronine (FT3) (normal range: 2.38–6.47 pmol/L), free thyroxine (FT4) (normal range: 7.64–16.03 pmol/L), and TPO-Ab (normal range: 0–9 IU/mL) were measured using an automatic analyzer and the chemiluminescence method (UniCel Dxs 800 Access Immunoassay System, Beckman Coulter, FUL, CA, USA) using reagents from Beckman Coulter. The serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, triglyceride, and uric acid (UA) were measured using colorimetry methods; creatinine (Cr) was measured using the picric acid method; and fasting blood glucose was measured using the hexose kinase method. These measurements were performed on an automated instrument (cobas® 5000; Roche Diagnostics GmbH, Mannheim, Germany) using reagents from Roche Diagnostics. The intra- and inter-assay coefficients of variation were below 5% for the above parameters.

2.3 Arterial Wall Stiffness and Left Ventricular Function Assessment

The Cardiovascular Profiling System Colin BP-203RPE III (Omron Healthcare Co., Ltd., Dalian, China) operated by well-trained observers was used to assess AS noninvasively after rest for at least 10 min in a lying position in the Endocrinology and Metabolism Department ward. Indices reflecting AS were evaluated through the baPWV (normal range <14 m/s), which expresses the speed of a pulse wave traveling between the brachial and the ankle arteries and increases with increased stiffness of the arterial wall.

The LV function was evaluated using color Doppler echocardiography (Epiq 7c, Philips Healthcare, Bothell, WA, USA) at rest by professional medical workers. The parameters involved were as follows: (1) interventricular septum thickness (IVST, cm) and the LV posterior wall thickness (LVPWT, cm); (2) the LV end-diastolic diameter (LVEDD, cm) and the LV end-systolic diameter (cm); (3) the left atrial diameter (cm); (4) the peak early diastolic phase (cm/s) and the late diastolic phase (cm/s) mitral inflow velocities; and (5) the LV ejection fraction (%).

The LV geometry was assessed with the LV mass index (LVMI) (g/m²) (over 115 g/m² in males and over 95 g/m² in females was considered as LV hypertrophy) and the relative wall thickness (RWT) using the method described by Yoshida et al. [19]. The LV mass (normal range: male: 77.6–194.0 g; female: 57.1–157.5 g) was calculated from
Table 1. Study groups’ characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Normal TSH group (group A) (n = 170)</th>
<th>High-normal TSH group (group B) (n = 79)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, n (%)</td>
<td>105 (61.8%)</td>
<td>47 (59.5%)</td>
<td>0.732</td>
</tr>
<tr>
<td>Age, years</td>
<td>48.9 ± 11.7</td>
<td>51.8 ± 13.8</td>
<td>0.086</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>27.4 ± 4.6</td>
<td>27.5 ± 4.7</td>
<td>0.926</td>
</tr>
<tr>
<td>Resting heart rate, beats/min</td>
<td>74.4 ± 13.1</td>
<td>75.5 ± 12.2</td>
<td>0.514</td>
</tr>
<tr>
<td>Office SBP, mmHg</td>
<td>137.2 ± 16.2</td>
<td>141.8 ± 17.4</td>
<td>0.046</td>
</tr>
<tr>
<td>Office DBP, mmHg</td>
<td>83.9 ± 11.8</td>
<td>85.0 ± 13.4</td>
<td>0.505</td>
</tr>
<tr>
<td>Antihypertensive treatment, n (%)</td>
<td>151 (88.8%)</td>
<td>67 (84.8%)</td>
<td>0.372</td>
</tr>
<tr>
<td>Anti-diabetes treatment, n (%)</td>
<td>90 (52.9%)</td>
<td>48 (60.8%)</td>
<td>0.248</td>
</tr>
<tr>
<td>Statin treatment, n (%)</td>
<td>95 (55.9%)</td>
<td>42 (53.2%)</td>
<td>0.688</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td>0.334</td>
</tr>
<tr>
<td>Never</td>
<td>96 (56.5%)</td>
<td>50 (63.3%)</td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td>11 (6.5%)</td>
<td>7 (8.9%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>63 (37.1%)</td>
<td>22 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.1 ± 1.1</td>
<td>5.1 ± 1.1</td>
<td>0.590</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.2 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>0.386</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.0 ± 0.9</td>
<td>2.9 ± 0.9</td>
<td>0.546</td>
</tr>
<tr>
<td>TGs, mmol/L</td>
<td>2.0 ± 1.2</td>
<td>2.1 ± 1.2</td>
<td>0.537</td>
</tr>
<tr>
<td>Cr, umol/L</td>
<td>80.6 ± 25.7</td>
<td>81.3 ± 19.3</td>
<td>0.838</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>93.1 ± 20.7</td>
<td>87.9 ± 15.8</td>
<td>0.031</td>
</tr>
<tr>
<td>UA, umol/L</td>
<td>371.0 ± 107.9</td>
<td>367.2 ± 114.4</td>
<td>0.797</td>
</tr>
<tr>
<td>FBG, mmol/L</td>
<td>6.0 ± 1.5</td>
<td>6.1 ± 1.7</td>
<td>0.632</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>1.5 ± 0.5</td>
<td>3.4 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fT3 (pmol/L)</td>
<td>5.2 ± 0.7</td>
<td>4.3 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fT4 (pmol/L)</td>
<td>11.4 ± 1.7</td>
<td>11.1 ± 1.9</td>
<td>0.207</td>
</tr>
<tr>
<td>TPOAb (+), n (%)</td>
<td>16 (9.4%)</td>
<td>12 (15.2%)</td>
<td>0.179</td>
</tr>
</tbody>
</table>

Data with normal distribution or approximate normal distribution were expressed as mean ± standard deviation (S.D.). Categorical variables were recorded as absolute numbers with percentages.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides; Cr, creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; FBG, fasting blood glucose; TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; TPOAb, thyroperoxidase antibody.

TPOAb (+) was defined as serum TPOAb higher than their upper limit of reference ranges.

the end-diastolic IVST, LVPWT, and LVEDD using the following equation:

\[
LV \text{ (g)} = 0.80 \times 1.04 \times (\text{[IVST} + \text{LVPWT} + \text{LVEDD}]^2 - [\text{LVEDD}]^2) + 0.6
\]

The LV mass was corrected for the body surface area (BSA) to obtain LVMI. The BSA was calculated from height (cm) and weight (kg) using the following equation from DuBois & DuBois [20]:

\[
\text{BSA (m}^2) = 0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}
\]

The RWT was calculated from LVPWT and LVEDD using the following equation [19]:

\[
\text{RWT} = (2 \times \text{LVPWT}) / \text{LVEDD}
\]

### 2.4 Statistical Analysis

The distribution of continuous variables was evaluated using the Shapiro–Wilk test. Data with a normal distribution or approximate normal distribution were expressed as mean and standard deviation, and other data were expressed as median and interquartile range. Categorical variables were presented as absolute numbers with percentages.

For comparing clinical characteristics, the baPWV, and the parameters of the LV function between the two groups, the Student’s unpaired t-test was performed for continuous variables and Pearson’s χ² test was used for categorical variables. For data with a non-normal distribution, a nonparametric test was conducted. Spearman’s correlation coefficient was calculated to evaluate the crude relationships between thyroid function index, baPWV, and the significantly different LV function parameters. Multiple logistic regression analysis was conducted to analyze the association between the thyroid function index, baPWV, and the significantly different LV function parameters.

We used two multivariate regression models. The first model included gender; age; BMI; resting heart rate; BP; antihypertensive, anti-diabetes, or statin treatment; and smoking status. The second model included variables that
achieved statistical significance in the first model and the other remaining variables. Due to collinearity, Cr was not included in the model with eGFR. A dummy variable was set for transforming the categorical variable smoking status, and never having smoked was identified as the control. The results of the regression analysis were represented as odds ratios with 95% confidence intervals.

A p value < 0.05 was considered statistically significant. The Statistical Package for Social Sciences version 23.0 (IBM, Armonk, NY, USA) was used for calculations and statistical analyses.

3. Results

3.1 Participants’ Characteristics

The clinical characteristics of the two groups are shown in Table 1. The gender, age, BMI, resting heart rate, diastolic BP (DBP), serum lipid profile, blood glucose, Cr, and UA were comparable between the groups (p > 0.05). No significant differences were observed regarding the proportion of patients smoking or receiving antihypertensive, anti-diabetes, or lipid-lowering therapy (p > 0.05). Significant differences were observed between the two groups in terms of the systolic BP (SBP) (p < 0.05), eGFR (p < 0.05), and fT3 values (p < 0.001), whereas no significant differences were found in the fT4 level and positive TPO-Ab (p > 0.05).

The data relating to the baPWV and LV functions are illustrated in Table 2. When compared with the normal group, the baPWV and A wave were significantly higher and the E/A ratio was lower in the high-normal–group (p < 0.01). No significant differences were found in the other LV function indices between the two groups (p > 0.05).

3.2 Association Between Thyroid Function, Arterial Stiffness, and Left Ventricular Function Parameters

The Spearman’s correlation analysis showed baPWV was negatively correlated with fT3 (r = -0.585, p < 0.001), but no significant correlation was found with TSH (r = 0.101, p = 0.111) or fT4 (r = 0.045, p = 0.477). The correlation was significant between E/A with baPWV (r = 0.555, p < 0.001), TSH (r = 0.235, p < 0.001), and fT3 (r = -0.554, p < 0.001), but not with fT4 (r = 0.030, p = 0.634), where E/A ratio >1 was represented as 0 and E/A ratio <1 was represented as 1.

The results of the association between the thyroid function and the baPWV assessed by multiple logistic regression analysis are represented in Table 3. The association between the fT3 and baPWV values was significant after adjustment for the variables in models 1 and 2 (p < 0.001), but no significant association was found between the TSH and baPWV values after adjustment (p > 0.05). Additionally, the DBP and SBP were not significantly associated with the baPWV in the analysis, and TPO-Ab and the eGFR were not significant variables in the models (p > 0.05). Significant association between age and the baPWV was found (EXP(B) = 1.043, p = 0.034), but the association between smoking and the baPWV did not reach significance (EXP(B) = 1.414, p = 0.079).

The multiple logistic regression analysis was conducted to further assess the association between the baPWV and the E/A ratio, excluding the thyroid function parameters (see Table 4). The results showed a significant association between the baPWV and the E/A ratio in both models (p < 0.01) and an association between the DBP and the E/A ratio in model 2 (p < 0.05). We then conducted the regression analysis again, including the thyroid function parameters (see Table 5). The analysis showed no significant association between the baPWV and the E/A ratio (p > 0.05) and a significant association between fT3, TSH, and the E/A ratio, and an association between the DBP and the E/A ratio (p < 0.05). Also, TPO-Ab was not found to be a significant variable in the analysis (p > 0.05). The association between age and the E/A ratio was significant (EXP(B) = 1.085, p < 0.001). No significant association was found between gender and the E/A ratio (EXP(B) = 0.573, p = 0.206, where male was represented as 1 and female was represented as 0.

4. Discussion

The main finding of the current study is that, when compared with the normal group, the baPWV was higher
Table 3. Multiple logistic regression analysis with baPWV as dependent variable (n = 249).

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>EXP(B)</th>
<th>95% CI of EXP(B)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV (left)</td>
<td>-0.103</td>
<td>0.902</td>
<td>0.596 1.364</td>
<td>0.624</td>
</tr>
<tr>
<td>baPWV (right)</td>
<td>-0.329</td>
<td>0.720</td>
<td>0.450 1.152</td>
<td>0.170</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV (left)</td>
<td>-0.171</td>
<td>0.843</td>
<td>0.567 1.252</td>
<td>0.397</td>
</tr>
<tr>
<td>baPWV (right)</td>
<td>-0.307</td>
<td>0.736</td>
<td>0.474 1.143</td>
<td>0.173</td>
</tr>
<tr>
<td>FT3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV (left)</td>
<td>-1.986</td>
<td>0.137</td>
<td>0.065 0.288</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>baPWV (right)</td>
<td>-1.927</td>
<td>0.146</td>
<td>0.066 0.323</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV (left)</td>
<td>-1.900</td>
<td>0.150</td>
<td>0.074 0.303</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>baPWV (right)</td>
<td>-1.888</td>
<td>0.151</td>
<td>0.071 0.322</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV (left)</td>
<td>-0.069</td>
<td>0.933</td>
<td>0.731 1.192</td>
<td>0.580</td>
</tr>
<tr>
<td>baPWV (right)</td>
<td>0.067</td>
<td>1.069</td>
<td>0.820 1.395</td>
<td>0.621</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV (left)</td>
<td>-0.031</td>
<td>0.969</td>
<td>0.769 1.222</td>
<td>0.791</td>
</tr>
<tr>
<td>baPWV (right)</td>
<td>0.118</td>
<td>1.125</td>
<td>0.880 1.440</td>
<td>0.348</td>
</tr>
</tbody>
</table>

BaPWV < 18 m/s, represented as 0, baPWV > 18 m/s, represented as 1.

TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; baPWV, brachial-ankle pulse wave velocity.

Multivariable model 1 was adjusted for sex, age, BMI, resting heart rate, BP, antihypertensive/anti-diabetes/statin treatment and smoking situation;
Multivariable model 2 was further adjusted for variables reaching statistical significance in the first model and all the rest variables.

and the E/A ratio was lower in the high–normal group. We also provided evidence of the association between the thyroid function, increased AS, and LV DD in subjects with euthyroidism after adjustment for confounders.

The PWV is a critical index for evaluating AS and is widely used for the noninvasive assessment of early atherosclerosis [8], and baPWV could reflect the comprehensive PWV of the thoracic aorta, abdominal aorta, and part of the lower extremity arteries. In recent years, the concept of vascular failure was put forward by Japanese researchers [21]. Regarded as a new physiological diagnostic criterion for vascular failure, the optimal cutoff value of baPWV for predicting CVD was suggested to be 18 m/s [22].

A possible explanation for the elevated baPWV in the high–normal group follows. First, it is well known that dyslipidemia is an important factor leading to atherosclerosis and lipid homeostasis is influenced by thyroid hormones [23]. Previous studies have indicated correlations between TSH and dyslipidemia in subjects with euthyroidism [12].

Table 4. Multiple logistic regression analysis with E/A ratio as dependent variable (n = 249).

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>EXP(B)</th>
<th>95% CI of EXP(B)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>baPWV (average)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Model 2</td>
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<td></td>
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</tr>
<tr>
<td>DBP</td>
<td></td>
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</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
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<tr>
<td>Model 2</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

E/A ratio > 1 represented as 0, E/A ratio < 1 represented as 1.

The average level of left and right baPWV was calculated and included in the regression analysis. Thyroid function parameters were not included in the regression analysis. baPWV, brachial-ankle pulse wave velocity; DBP, diastolic blood pressure.

Multivariable model 1 was adjusted for sex, age, BMI, resting heart rate, BP, antihypertensive/anti-diabetes/statin treatment and smoking situation.
Multivariable model 2 was further adjusted for variables reaching statistical significance in the first model and all the rest variables.

Table 5. Multiple logistic regression analysis with E/A ratio as dependent variable (n = 249).

<table>
<thead>
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<th>B</th>
<th>EXP(B)</th>
<th>95% CI of EXP(B)</th>
<th>p value</th>
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<tbody>
<tr>
<td>TSH</td>
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<td>FT3</td>
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<td>Model 2</td>
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<td>baPWV (average)</td>
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<td>DBP</td>
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</tbody>
</table>

E/A ratio > 1 represented as 0, E/A ratio < 1 represented as 1.

Thyroid function parameters were included in the regression analysis. The average level of left and right baPWV was calculated and included in the regression analysis. TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; baPWV, brachial-ankle pulse wave velocity; DBP, diastolic blood pressure.

Multivariable model 1 was adjusted for sex, age, BMI, resting heart rate, BP, antihypertensive/anti-diabetes/statin treatment and smoking situation.
Multivariable model 2 was further adjusted for variables reaching statistical significance in the first model and all the rest variables.
Second, Lekakis revealed that flow-mediated vasodilata-
tion is impaired in patients with high–normal serum TSH
levels, which would influence the elastic behavior of the ar-
teries and result in increased AS [11,24]. Third, as noted in
the National Health and Nutrition Examination Survey III
[10], the prevalence of TPO-Ab increases with an increase
in the TSH level. However, even when TSH was >10
mIU/L, no thyroid autoantibodies were detected in 31% of
men and 11% of women. This means when acquiring a TSH
reference range through a large sample survey of the pop-
ulation, if thyroid dysfunction was only excluded by the
prevalence of thyroid autoantibodies, this would result in
subjects with thyroid dysfunction and negative thyroid au-
toantibodies being regarded as normal. Therefore, the TSH
upper reference limits may be skewed, and subjects with
high–normal TSH levels may exhibit a similar presentation
to patients with SCH. Therefore, it appeared reasonable that
the baPWV would be higher in subjects with high–normal
serum TSH levels.

The present research proceeded to study the indices
relating to the LV diastolic function. The PWV and AS
increase under the influence of aging, hypertension, and
atherosclerosis, which leads to an increase in the BP, pulse
pressure, and LV load with hypertrophy and LV DD [25,26].
An increase in the A wave and a decrease in E/A ratio might
reflect early LV DD [27]. Studies on the diastolic function
in patients with SCH have showed an increased A wave, re-
duced E/A ratio, and prolonged isovolumic relaxation time
when compared with healthy subjects [28,29]. The current
study showed an increased A wave and a decreased E/A
ratio in the high–normal TSH group, which is supported
by the underlying mechanism and is in accordance with the
study in patients with SCH.

The effect of the thyroid gland on the cardiovascu-
lar system is primarily exerted through biologically active
T₃. The related mechanism includes two aspects: (1) the
genomic effect (increased gene expression of sarcoplasmic
reticulum calcium ATPase [SERCA] or cardiac α-myosin
heavy chain and upregulation of the potassium channel
through the thyroid hormone receptor-α); and (2) the non-
genomic effect (increased nitric oxide [NO] synthesis and
release from the endothelial cells) [30–32]. Previous stud-
ies found that reduced calcium reuptake into the sarcoplas-
mic reticulum from decreased expression of SERCA is in-
volved in LV DD in SCH [30]. A reduction in NO was
found to be associated with increased AS in SCH [32]. The
activity of type 3 deiodinase was stimulated up to five-fold
in hypertrophic ventricular tissue, which converts T₄ and
T₃ to the inactive compounds reverse-T₃ and 3',3'-T₂, re-
spectively [33]

In the present study, fT₃ was lower in the high–normal
group, and the association analysis after adjustment for con-
founders also proves the pivotal role of T₃ in cardiovascular
system dysfunction. We could also infer from our investiga-
tion that, by affecting BP, increased AS could result in LV
DD. In addition, the E/A ratio was found to be correlated
with TSH levels, which is consistent with the findings of
Sandra [15]. We speculated that some indices, such as the
E/A ratio, may also be affected by the local generation of T₃
from circulating T₄. As TSH levels were more sensitive
than T₄, the association to T₄ may be explained. Further
research is warranted.

The association between cardiovascular events, car-
diovascular mortality, and all-cause mortality with the
baPWV has been proven in several studies, even after ad-
justments for the conventional risk factors, including age,
gender, brachial SBP, history of use of antihypertensive
agents, hemoglobin A1c, BMI, TC, HDL-C, and current
smoking habits [34,35]. The result of our analysis of the
association between the baPWV and the E/A ratio without the
thyroid function index was consistent with previous studies;
however, the baPWV was not a significant variable after
the thyroid function was included in the regression analy-
sis. We are inclined to think that the effect of the thyroid
on the pathophysiological process of LV DD was stronger
in this investigation. Further studies are required.

This study had several limitations. First, it was a
single-center study, and the applicability of these results
to other centers needs to be confirmed. Causal relation-
ships could not be established due to the nature of the ob-
servational study, and the influence of unknown confound-
ing factors and potential reverse causality could not be ex-
cluded. A strictly designed prospective study may be re-
quired to verify the conclusions. Second, the blood sam-
ple were drawn between 6 AM and 8 AM after fasting
for at least 10 hours, and the intra- and inter-assay coef-
ficient variations were below 5%, but it is important to note
that the influences of diurnal variation and assay variation
could not be excluded completely. Another confounder that
could not be neglected was the state of the menopausal
stage, which was not included in the current study. Fur-
ther study is needed. Third, previous literature revealed
patients with SCH present LV DD at rest and systolic and
DD under effort [36,37]. Our investigation in subjects with
high–normal TSH levels showed LV DD at rest, but the as-
essment of systolic and diastolic function under effort is
required. Because the E/A ratio would be influenced by
many factors and might be pseudo-normal in patients with
DD, or even with severe DD, E/e’ ratio is an important in-
dicator for evaluating the type of DD and should be em-
ployed in future in the analysis of correlation between the
thyroid function, AS, and DD. Other more valuable indices
including the left atrial function and volume should also be
measured in future. Finally, replacement therapy was not
included in the current investigation. Levothyroxine ther-
apy appears to ameliorate AS and cardiac dysfunction, but
age, the presence of CVD, and the presence of autoimmune
antibodies may influence the decision to conduct replace-
ment therapy in subjects with high–normal TSH levels and
its curative effect [37,38].
5. Conclusions

In conclusion, this study may signify the association between the thyroid function, increased AS, and LV DD in subjects with euthyroidism after adjustment for confounders. It would be helpful to evaluate the benefit of replacement therapy in people with high–normal TSH levels, especially in the presence of TPO-Ab in future large, multicenter, randomized trials.

Consent for Publication

All participants signed a document of informed consent.

Availability of Data and Materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Author Contributions

Conception and design of the research—LJY, HT, YZ. Acquisition of data—LJY, XQS. Analysis and interpretation of the data—LJY, HT, YZ. Statistical analysis—LJY, XQS. Obtaining financing—None. Writing of the manuscript—LJY, HT, YZ. Critical revision of the manuscript for intellectual content—HT, YZ. All authors read and approved the final draft.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the declaration of Helsinki and approved by the Beijing Anzhen Hospital Ethical Committee (No. 2022053X). Written informed consent was obtained from all participants.

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Conflict of Interest

The authors declare no conflict of interest.

References


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