Heart Rate Turbulence Analysis in Subclinical Hypothyroidism

Cennet Yildiz, Abdulmelik Yildiz and Fatih Tekiner

Background: Heart rate turbulence (HRT) is a baroreflex-mediated biphasic reaction of heart rate in response to premature ventricular beats. Abnormal HRT identifies patients with autonomic dysfunction or impaired baroreflex sensitivity. The aim of the present study was to demonstrate the effect of subclinical hypothyroidism (SCH) on cardiac autonomic function using HRT parameters.

Methods: The study sample consisted of 25 patients (10 men, 15 women with a mean age of 39.7 ± 15.5 years) who were diagnosed with SCH and 35 euthyroid patients (13 males, 22 females with a mean age 38.4 ± 11.7 years). All patients underwent 24 h ambulatory electrocardiography monitorization. The study calculated two HRT parameters, turbulence slope (TS) and turbulence onset (TO), and these HRT parameters were compared between the groups to examine the relationship between HRT and thyroid-stimulating hormone (TSH) levels.

Results: The characteristics of SCH patients and control cases were similar with regard to age, sex except for TSH levels. Serum TSH levels were significantly higher in SCH patients than in the controls (7.3 ± 1.8 μIU/ml vs. 2.4 ± 1.0 μIU/ml, p < 0.001). TO was significantly higher in SCH patients compared with controls (-1.51 ± 0.5 vs. -2.2 ± 1.0, p = 0.002). SCH patients had lower TS values than controls (7.6 ± 2.4 vs. 10.8 ± 3.4, p < 0.001). TO was positively correlated with serum TSH levels (r = 0.276, p = 0.033). There was also a negative correlation between TS and serum TSH levels (r = -0.437, p < 0.001).

Conclusions: The results of our study indicated that cardiac autonomic function is impaired in patients with SCH.

Key Words: Heart rate • Holter electrocardiography • Hypothyroidism

INTRODUCTION

Thyroid hormones are mandatory for various processes that are essential for human metabolism. The cardiovascular system is one of the most important targets of thyroid hormones and is very sensitive to a minimal decrease of circulating thyroid hormones. Subclinical hypothyroidism (SCH), also called mild thyroid failure, is diagnosed when peripheral thyroid hormone levels are within normal reference laboratory range but serum thyroid-stimulating hormone (TSH) levels are mildly elevated. This condition occurs in 3-8% of the general population. It is more common in women than men, and its prevalence increases with age. SCH may impair left ventricular diastolic function, alter endothelial function, increase the C-reactive protein level, and thus increase the risk of atherosclerosis. SCH is associated with impaired cardiovascular autonomic function reduced heart rate variability (HRV).

Heart rate turbulence (HRT) is a baroreflex-mediated biphasic reaction of heart rate in response to premature ventricular beats. More precisely, it describes...
the increase in heart rate for 1 or 2 beats and its subsequent decrease after a ventricular premature complex (VPC). The disappearance of HRT implies the loss of normal autonomic nervous regulation.5

Although the impairment of the cardiac autonomic activity in SCH has been clinically evaluated with HRV,4 no study related to subclinical hypothyroidism and HRT has been performed. The purpose of this study was to examine the HRT in patients with SCH.

METHODS

The study sample consisted of 25 patients with SCH and 35 euthyroid patients. Clinical information that was recorded at the time of the physical examination included previous myocardial infarction, hypercholesterolemia, diabetes mellitus, stroke, smoking status, antihypertensive drugs, and cardiac arrhythmias. The exclusion criteria were pregnancy, hepatic or renal dysfunction, hypertension, hyperlipidemia, heart failure, ischemic or valvular heart disease, atrial fibrillation, respiratory disease, pulmonary hypertension, diabetes mellitus, significant neurological or psychological disease, and malignancy. None of the subjects were receiving medications that could alter heart rate and serum thyroid hormone concentrations. The Medipol University Ethics Committee approved the study protocol and each subject provided informed consent prior to enrollment.

Serum hormone levels were measured by chemiluminescent immunometric assays using Elecsys 1010 (Roche Diagnostics), according to the manufacturer’s instructions. The thyroid function profile was determined by measuring free thyroxin (FT4), free triiodothyronine (FT3) and thyroid-stimulating hormone (TSH) levels. The reference intervals for our laboratory were: FT3, 3.1 to 6.8 pg/ml; FT4, 12 to 22 pg/ml; and TSH, 0.27 to 4.2 μIU/ml.

All the participants underwent a 24-hour Holter recording to assess HRT parameters. Then, HRT parameters were calculated using an algorithm adapted from the web page popularizing the non-commercial use of HRT (http://www.h-r-t.org). Two numerical descriptors were estimated: turbulence onset (TO) reflecting the initial phase of sinus rhythm acceleration, and turbulence slope (TS) describing the deceleration phase. HRT onset was defined as the difference between the mean of the first two sinus rhythm R-wave to the next R-wave (RR intervals) following the compensatory pause after a VPC, and the mean of the last two sinus rhythm RR intervals preceding the VPC, expressed as a percentage of the former. It is calculated using the equation: TO = ((RR1 interval + RR2 interval) – (RR-2 interval + RR-1 interval)) / (RR-2 interval + RR-1 interval) * 100, with RR-2 interval and RR-1 interval being the first two normal intervals preceding the VPC and RR1 interval and RR2 interval the first two normal intervals following the VPC. Positive values for TO indicate deceleration, whereas negative values indicate acceleration of the sinus rhythm.

The HRT slope was defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus rhythm RR intervals within the first 20 sinus rhythm intervals after VPC, expressed as millisecond (ms) per beat. TS was calculated based on the averaged tachogram. Filtering algorithms were used to eliminate inappropriate RR intervals and VPCs. The HRT onset or slope was defined as abnormal if the onset was ≥ 0%, or the slope was ≤ 2.5 ms/beat.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are expressed as percentages. Statistical analyses were performed by using SPSS packed programme (version 20 software, SPSS Inc., Chicago, Illinois, USA). Mean values for subclinical hypothyroid and control patients were compared using the two-sample t-test. Fisher’s exact test was used to compare categorical variables between groups. The correlations between the observed variables were examined by use of the Pearson’s correlation test. A p value < 0.05 was considered statistically significant.

RESULTS

Table 1 shows the clinical characteristics of the study groups. There were no statistically significant differences between the two groups with respect to age, gender, smoking, blood pressure, and heart rate. The mean patient ages were 39.7 ± 15.5 years for the subclinical hypothyroid group, and 38.4 ± 11.7 for the con-
trol group. We also did not find any statistical differences between the subclinical hypothyroid and control groups in terms of means of left ventricular ejection fraction and VPCs. Serum TSH levels were significantly higher in SCH patients than in the controls.

Table 2 summarizes HRT parameters between the subclinical hypothyroid and the control groups. TO was significantly higher in SCH patients as compared with the controls, and SCH patients had lower TS values than controls. TO was positively correlated with serum TSH levels ($r = 0.276$, $p = 0.033$). There was a negative correlation between TS and serum TSH levels ($r = -0.437$, $p < 0.001$). The correlation between TO and TSH, and the correlation between TS and TSH was shown in Figure 1 and Figure 2, respectively.

**DISCUSSION**

To the best of our knowledge, this study was the first to explore HRT parameters in patients with subclinical hypothyroidism. Altered sympatovagal balance, as shown by disturbed heart rate turbulence, was observed in these patients and this alteration was found to be correlated with serum TSH levels.

The heart is highly innervated by vagal and sympathetic fibers and is very sensitive to autonomic influences. The autonomic nervous system responds to all changes sensed by baroreceptors and chemoreceptors to maintain cardiovascular homeostasis. HRT is a baroreflex-mediated biphasic reaction of heart rate in response to VPCs and is an important parameter for evaluating cardiac autonomic functions. In earlier studies, HRT has been shown to be an independent and powerful predictor of mortality, with a greater predictive

### Table 1. Clinical characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>SCH (n = 25)</th>
<th>Control (n = 35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, uears</td>
<td>39.7 ± 15.5</td>
<td>38.4 ± 11.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Male N, (%)</td>
<td>10 (40)</td>
<td>13 (37.1)</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>15 (60)</td>
<td>22 (62.9)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>5 (20)</td>
<td>7 (20)</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>64.6 ± 2.7</td>
<td>63.9 ± 2.5</td>
<td>0.45</td>
</tr>
<tr>
<td>TSH, μIU/ml</td>
<td>7.3 ± 1.8</td>
<td>2.4 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FT3, pg/ml</td>
<td>4.3 ± 1.1</td>
<td>4.4 ± 1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>FT4, pg/ml</td>
<td>15.0 ± 1.8</td>
<td>16.0 ± 2.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>114.6 ± 15.4</td>
<td>114.4 ± 18.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>66.6 ± 8.9</td>
<td>64.8 ± 10.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean HR</td>
<td>73.4 ± 8.9</td>
<td>77.5 ± 8.4</td>
<td>0.08</td>
</tr>
<tr>
<td>VPC</td>
<td>330.4 ± 219.4</td>
<td>267.8 ± 226.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

BP, blood pressure; FT3, free triiodothyronine; FT4, free thyroxin; HR, heart rate; SCH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; VPC, ventricular premature complex.

### Table 2. Results of heart rate turbulence analyses

<table>
<thead>
<tr>
<th></th>
<th>SCH (n = 25)</th>
<th>Control(n = 35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT onset, %</td>
<td>-1.51 ± 0.5</td>
<td>-2.2 ± 1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>HRT slope, ms/beat</td>
<td>7.6 ± 2.4</td>
<td>10.8 ± 3.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations are in Table 1. HRT, heart rate turbulence.
power than HRV.\textsuperscript{5,8,9} A blunted HRT reflects cardiac autonomic dysfunction, especially reduced baroreflex sensitivity.\textsuperscript{10} HRT is quantified by TO reflecting the initial acceleration of heart rate following premature beat, with TS describing subsequent deceleration of heart rate. The concept of HRT was first introduced by Schmidt et al. as a predictor of mortality after myocardial infarction. Abnormal HRT identifies patients with autonomic dysfunction or impaired baroreflex sensitivity due to a variety of disorders, but also may reflect changes in the autonomic nervous system induced by different therapeutic modalities such as drugs, revascularization, or cardiac resynchronization therapy.\textsuperscript{8} Impaired HRT was found to have predictive value in congestive heart failure with regard to disease progression and fatal ventricular arrhythmias.\textsuperscript{11} In addition to congestive heart failure, impaired HRT may be encountered in certain conditions including metabolic syndrome,\textsuperscript{12} coronary artery disease,\textsuperscript{13} obstructive sleep apnea syndrome,\textsuperscript{14} and mitral valve prolapse\textsuperscript{15} probably due to hemodynamic changes and impaired baroregulatory mechanism associated with these conditions.

SCH is usually an asymptomatic condition and characterized by an elevated level of serum thyrotrphin, but with normal free T3 and free T4 concentrations.

There are contradictory reports about autonomic function in subclinical hypothyroidism. Sahin et al. found no difference in the time and frequency domains of HRV compared to controls in those subclinical hypothyroid patients who had TSH levels less than ten; but there was a decrease in sympathetic tone if TSH levels were greater than ten.\textsuperscript{16} Galetta et al. showed an increase in LF/HF frequency in heart rate variability reflecting higher sympathetic activity with a decrease in HRV suggesting a decrease in vagal tone in subclinical hypothyroid patients. They also found that the TSH values correlated with LF/HF ratio.\textsuperscript{4} Another study in subclinical hypothyroid patients reported a hypofunctional parasympathetic system based on the analysis of heart rate response to exercise and recovery.\textsuperscript{17} Mahajan et al. showed both sympathetic function abnormality and decreased parasympathetic function reactivity in subclinical hypothyroid and hypothyroid patients.\textsuperscript{18} Kahaly et al. reported a hypofunctional parasympathetic system by analyzing time and frequency domains of HRV.\textsuperscript{19}

In our study we found impaired HRT. The SCH group showed a positive correlation between serum TSH levels and TO. In addition, there was a negative correlation between TS and serum TSH levels. The common element of the underlying reason is primarily cardiac autonomic system dysfunction. Heart rate turbulence cannot be measured in subjects without VPCs, as a minimum of 15-20 sinus beats after each VPC and 3-5 beats before the VPC are required for accurate calculation of HRT. Thus, we had to exclude those patients who did not have any VPCs from the study. Factors known to affect autonomic nervous system are; age, gender, cigarette use, diabetes mellitus, and coronary artery disease. In this study, our selection criteria ensured that all factors affecting the cardiac autonomic function either were excluded or two groups had similar clinical and demographic data.

The small number of patients was a limitation of our study. In addition, the effects of L-thyroxine therapy on cardiac autonomic activity in patients with SCH were not investigated in the study.

In conclusion, findings of the current study have suggested that subclinical hypothyroid patients had autonomic dysfunction. Further large-scale and long-term studies should be performed to better advise early L-thyroxine treatment not only to prevent progression to overt hypothyroidism but also to improve abnormal cardiac autonomic function.

This study had no supporters.

CONFLICT OF INTEREST

None declared.

REFERENCES


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