Heart Rate Variability and Heart Rate Turbulence in Hypothyroidism before and after Treatment

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Background: Cardiac autonomic dysfunction may develop in patients with clinical or subclinical thyroid hormone deficiency. Heart rate variability (HRV) and heart rate turbulence (HRT) are used for evaluating changes in cardiac autonomic functions and also used to provide risk stratification in cardiac and noncardiac diseases. The aim of this study is to evaluate cardiac autonomic functions before and 6 months after thyroid replacement therapy in patients with thyroid hormone deficiency.

Methods: Forty hypothyroid patients (mean age 48 ± 13, four male) and 31 healthy controls (mean age 51 ± 12, three male) were included in the study. Twenty-four hour ambulatory electrocardiogram recordings were taken using Pathfinder Software Version V8.255 (Reynolds Medical). The time domain parameters of HRV analysis were performed using the Heart Rate Variability Software (version 4.2.0, Norav Medical Ltd, Israel). HRT parameters, Turbulence Onset (TO), and Turbulence Slope (TS) were calculated with HRT! View Version 0.60-0.1 software.

Results: HRV and HRT parameters were decreased in the patient group (SDNN; $P < 0.001$, SDANN; $P < 0.009$, RMSSD; $P = 0.049$, TO; $P = 0.035$, TS; $P < 0.001$). After 6 months of thyroid replacement therapy, there were no significant changes observed in either HRV or HRT.

Conclusions: Hypothyroidism may cause cardiac autonomic dysfunction. Treating hypothyroidism with L-thyroxine therapy does not effectively restore cardiac autonomic function. HRV and HRT can be used as to help monitor cardiovascular-related risk in this population.

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hypothyroidism; cardiac autonomic dysfunction; heart rate variability; heart rate turbulence

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.[1] Decreased circulating levels of thyroid hormones may cause several pathologies related to the cardiovascular system, such as decreased cardiac output, diastolic dysfunction, increased cardiovascular resistance, and cardiac electrical abnormalities (bradycardia, low voltage, and varying degrees of heart block).[2]

Heart rate variability (HRV) analysis has been used as a predictor of sudden cardiac death, as a marker of the progression of cardiovascular disease in several high-risk populations, and as a useful tool for assessing autonomic cardiac functions.[3] Clinical studies have shown that reduced HRV correlates with an increased risk of cardiac mortality.[4] Heart rate turbulence (HRT), which reflects the response of heart rate to a premature ventricular beat (PVB), has been introduced as a new, noninvasive tool for cardiac risk stratification. The disappearance of HRT indicates the loss of normal autonomic nervous regulation.[5] Several large-scale retrospective and prospective studies have unquestionably established that, beside myocardial infarction (MI), HRT is one of the strongest independent cardiac risk predictors.[6]

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Previous studies showed that HRV is reduced in both subclinical and overt hypothyroidism.[7,8] Although hypothyroidism has been associated with sympathovagal imbalance, it is unclear whether the imbalance is due to increased or decreased sympathetic or parasympathetic activity.[7–16] It is known that HRT is blunted in hyperthyroidism, but the effect of hypothyroidism on HRT is unknown.[17,18]

The aim of the study was to evaluate cardiac autonomic function using HRV and HRT measurements in patients with hypothyroidism before and 6 months after L-thyroxine ($_L$-T_4) therapy.

METHODS

Study Population

Forty hypothyroid patients (mean age 48 ± 13, four male) and 31 healthy controls (mean age 51 ± 12, three male) were included in the study. The patient group was recruited from volunteers with either subclinical or overt hypothyroidism. Subclinical hypothyroidism was defined as elevated serum thyroid stimulating hormone (TSH) levels (>5.6 μIU/mL; range, 0.27–5.6) and normal serum free thyroid hormones (fT_3 and fT_4) levels (fT_3; 2–4.4 pg/mL, fT_4; 0.93–1.7 ng/dL). Overt hypothyroidism was defined as elevated serum TSH levels (>5.6 μIU/mL; range, 0.27–5.6) and decreased fT_3 or fT_4 levels (fT_3 < 2.0 pg/mL, fT_4 < 0.93 ng/dL). The etiology of hypothyroidism was Hashimato's thyroiditis in all patients. Only patients who had stable elevated serum TSH levels for at least 3 months before enrollment were included in the study. The control group was recruited from healthy volunteers seen at the cardiology outpatient clinic who had a suitable thyroid hormone profile (normal serum TSH, fT_3, and fT_4 levels). Patients with prior MI, hemodynamically unstable valvular heart disease, congenital heart disease, atrial fibrillation, heart conduction disorders, branch block, an implanted pacemaker, hypertension, diabetes mellitus, prior cerebrovascular accident, chronic obstructive pulmonary disease, severe liver or renal insufficiency, and malignancy or patients who were on beta-blocker therapy were excluded from the study. Smokers were also excluded from both groups.

Before inclusion in the study, a blood sample for the determination of TSH, fT_3, and fT_4 levels was obtained 8 hours after an overnight fast. Patients were studied at baseline and 180 days after starting hormone replacement treatment with substitutive doses of L-thyroxine ($_L$-T_4; 1–1.5 μg/kg per day).

The present study was a single center study. All examinations were performed by the cardiology clinic. All subjects gave their informed consent prior to inclusion in the study. The study protocol was approved by the ethics committee at our institution.

Heart Rate Variability Analysis

Twenty-four hour Holter recordings taken from the patient and control groups were downloaded onto a computer and analyzed with a Holter program (Reynolds Medical Pathfinder Software, Version V8.255, Hedford, UK). All recordings were also examined visually and artifacts were deleted manually. All of the recordings had at least 22 hours of data once the artifacts were deleted. The HRV parameters were calculated by a computer and statistically analyzed. The time-domain HRV parameters used in this study were chosen according to the guidelines of the European Society of Cardiology and North American Society of Pacemaker and Electrophysiology,[19] and included mean RR intervals (RR), SDNN, standard deviation of the mean of normal RR intervals at each 5 minute segment (SDANN), and root mean squared differences of successive RR intervals (RMSSD). Frequency-domain parameters of HRV were not performed on our 24-hour Holter data due to problems of nonstationarity.[19]

All of the subjects recorded under fairly similar conditions and in a fairly similar environment. The patients and the control subjects were asked not to take tea, coffee, chocolate, or alcohol containing substances for at least 8 hours before and during the entire Holter recording. They were asked not to do extraordinary behavior or activity and try to spend an ordinary day as usual. No subject was invoked in competitive sporting activities. After 6 months, identical assessments were performed for the patient group.

Heart Rate Turbulence Analysis

HRT parameters, turbulence onset (TO), and turbulence slope (TS) were calculated automatically by a computer program (HRT View, Version 0.60-0.1 Software Programme, Munich, Germany). Abnormal data found between 5 sinus beats before and 15 sinus beats after a PVB as well as

visually seen artifacts that the program accepted as a normal PVB were excluded from analysis. TO, an indicator of early sinus acceleration after PVB, was defined as the difference between the mean duration of the first two sinus beats following a PVB and the mean duration of the last two sinus beats preceding a PVB, divided by the mean duration of the last two sinus beats preceding the PVB.[20] TS is an indicator of late sinus deceleration after PVB and is defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent RR intervals within the first 20 sinus rhythm intervals after PVB.[21] A TO $\geq$ 0% and a TS $\leq$ 2.5 msec/RR were considered abnormal.

Assays

Serum TSH, fT_3, and fT_4 were measured by an electrochemiluminescence immunologic test (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). Normally distributed continuous data were expressed as mean $\pm$ standard deviation (SD); nonnormally distributed continuous variables were presented as median [interquartile range]. Categorical data were expressed as percentages. Normally distributed independent variables in the patient and control groups were evaluated by Student's *t*-test, whereas nonnormally distributed independent variables were evaluated by the Mann-Whitney U Test. Dependent variables before and after $_L$-T_4 therapy were analyzed using the Paired sample *t*-test. Spearman's correlation test was used for correlation analysis. P values below 0.05 were considered statistically significant.

RESULTS

Clinical Characteristics

There were no significant differences between the patient and control groups with regard to age, sex, body mass index, waist circumference, systolic and diastolic blood pressures, fasting blood glucose, lipid profile, erythrocyte sedimentation rate, serum creatinine, high sensitivity C-reactive protein (hs-CRP), and hemoglobin levels (Table 1). The patient group had higher TSH levels and lower fT_3 and fT_4 levels (Table 1).

Unfortunately, 12 patients discontinued the study without any reasonable excuse during follow-up. The remaining 28 patients' data were used in order to evaluate the effects of $_L$-T_4 therapy. After 6 months treatment with $_L$-T_4, TSH, fT_3, and fT_4 returned to within the normal range in all patients (TSH; 4.1 [2.6–5.6] μIU/mL, fT_3; 3.0 $\pm$ 0.6 pg/mL, and fT_4; 1.2 $\pm$ 0.2 ng/dL, $P < 0.001$ for TSH, $P < 0.05$ for fT_3 and fT_4). All of the other parameters were not statistically different from baseline.

None of the patients presented any sustained or nonsustained ventricular tachyarrhythmias as observed with 24-h ambulatory ECG monitoring. The amount of PVB was not significantly affected by 6 months of $_L$-T_4 therapy (before therapy 4 [3–12]; after therapy 3 [1–10], $P = 0.077$).

Heart Rate Variability and Heart Rate Turbulence Findings

All of the HRV parameters were lower in the patient group compared to the control group, but the difference in the RR interval remained insignificant (SDNN; $P < 0.001$, SDANN; $P < 0.009$, RMSSD; $P = 0.049$) (Table 2). Unfortunately, a similar difference could not be seen before and after $_L$-T_4 treatment in the patient group (Table 3).

Turbulence onset was significantly higher and TS was significantly lower in hypothyroid patients (Table 2). After 6 months of therapy, there was no significant change observed in TO, while there was an insignificant increase in TS (Table 3).

The numbers of PVBs that are suitable for HRT were not significantly different between the control and the patient group (patient group 4 [3–8]; control group 8 [4–25], $P = 0.095$). After 6 months of $_L$-T_4 therapy, the amount of PVB which are suitable for HRT was not significantly affected (before therapy 5 [3–13]; after therapy 3 [1–7], $P = 0.124$).

Correlation Analysis

TSH was negatively correlated with SDNN ($r = -0.690$, $P < 0.001$) and TS ($r = -0.324$, $P = 0.006$) and positively correlated with TO ($r = 0.321$, $P = 0.006$; Fig. 1).

DISCUSSION

The major finding of this study is that HRV and HRT are reduced in patients with hypothyroidism. Six months of thyroid replacement therapy failed

Table 1. Clinical Characteristics and Laboratory Findings of Patient and Control Groups

	Control (n = 31)	Patient (n = 40)	P value
Age (years)	51 ± 12	48 ± 13	0.211
Male	3 (10)	4 (10)	0.964
Body mass index (kg/m^2)	30 ± 4	30 ± 6	0.643
Waist circumference (cm)	99 ± 8	98 ± 11	0.701
Systolic blood pressure (mmHg)	130 ± 12	129 ± 20	0.750
Diastolic blood pressure (mmHg)	79 ± 8	82 ± 13	0.257
TSH (μIU/mL)	1.7 [1.0–2.5]	6.2 [5.7–8.0]	**<0.001**
fT_3 (pg/mL)	2.9 ± 0.4	2.6 ± 0.7	**0.044**
fT_4 (ng/dL)	1.2 ± 0.2	0.9 ± 0.3	**<0.001**
Glucose (mg/dL)	94 ± 9	92 ± 11	0.658
Cholesterol (mg/dL)	200 ± 44	205 ± 50	0.667
Triglyceride (mg/dL)	175 ± 90	147 ± 72	0.186
LDL-cholesterol (mg/dL)	126 ± 35	136 ± 42	0.297
HDL-cholesterol (mg/dL)	46 ± 11	50 ± 16	0.239
Creatinine (mg/dL)	0.7 ± 0.2	0.7 ± 0.2	0.550
Hemoglobin (gr/dL)	12.4 ± 0.6	12.8 ± 1.2	0.080
Erythrocyte sedimentation rate (mm/h)	13 ± 6	15 ± 8	0.359
hs-CRP (mg/L)	3.2 [3.1–5.5]	3.3 [3.1–5.9]	0.194

TSH = thyroid stimulating hormone; fT3 = free T3; fT4 = free T4; LDL = low-density lipoprotein; HDL = high-density lipoprotein; hs-CRP = high sensitivity C-reactive protein.
Data are shown as n (%), mean ± SD, median [interquartile range].

Table 2. HRV and HRT Parameters of Patient and Control Groups

	Control (n = 31)	Patient (n = 40)	P value
RR (msec)	808 ± 109	782 ± 77	0.240
SDNN (msec)	130 ± 27	73 ± 32	**<0.001**
SDANN (msec)	113 ± 26	95 ± 30	**0.009**
RMSSD (msec)	31 ± 12	25 ± 13	**0.049**
TO (%)	−2.980 ± 2.368	−1.717 ± 2.649	**0.035**
TS (msec/RR)	9.244 ± 5.577	5.356 ± 3.080	**<0.001**

RR = RR interval, SDNN = standard deviation of all normal RR intervals, SDANN = standard deviation of mean of normal RR intervals at each 5 minute segment, RMSSD = root mean squared differences of successive RR intervals, TO = turbulence onset, TS = turbulence slope.
Data are presented as mean ± standard deviation.

Table 3. HRV and HRT Parameters of Patients before and after $_L$-T_4 therapy

	Before (n = 28)	After (n = 28)	P value
RR (msec)	790 ± 81	788 ± 91	0.925
SDNN (msec)	65 ± 23	67 ± 42	0.840
SDANN (msec)	98 ± 29	100 ± 28	0.657
RMSSD (msec)	28 ± 14	28 ± 17	0.890
TO (%)	−1.511 ± 2.519	−1.770 ± 2.402	0.703
TS (msec/RR)	5.094 ± 3.064	6.941 ± 3.967	0.075

RR = RR interval, SDNN = standard deviation of all normal RR intervals, SDANN = standard deviation of mean of normal RR intervals at each 5 minute segment, RMSSD = root mean squared differences of successive RR intervals, TO = turbulence onset, TS = turbulence slope.

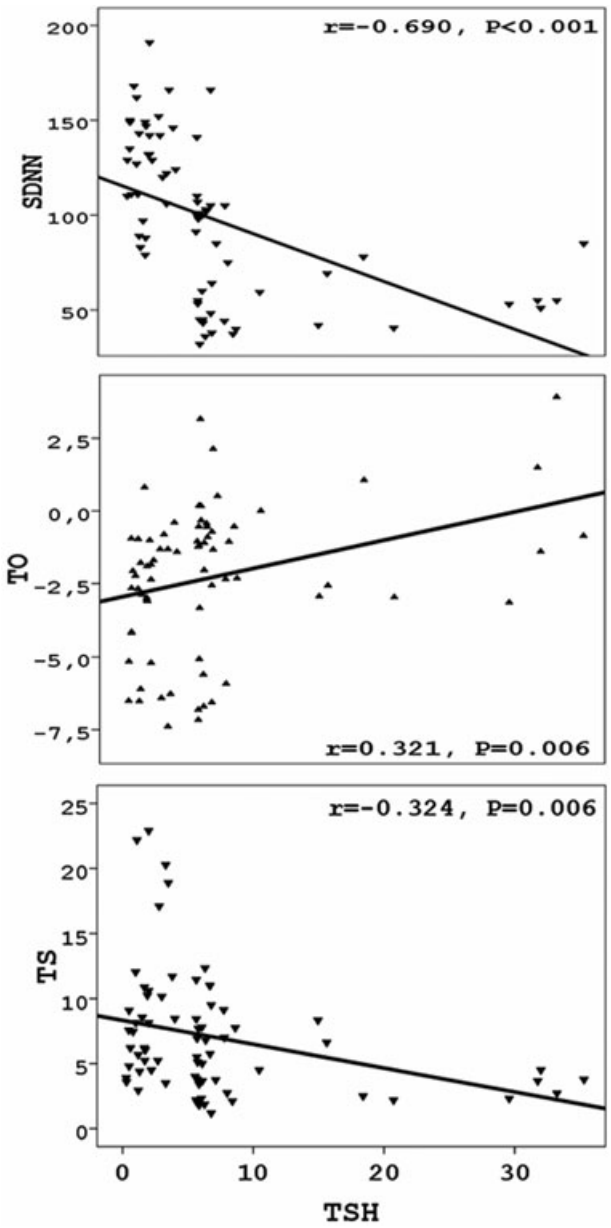

Figure 1. Relationship between TSH and SDNN, TO and TS.

to improve these indirect indices of cardiac autonomic dysfunction.

The heart is richly innervated by afferent and efferent vagal and sympathetic fibers and is thus susceptible to autonomic influences.[22] The fact that changes in efferent autonomic traffic are largely under baroreceptor control explains why baroreceptor function is correlated with cardiac arrhythmias.[23] Baroreceptor reflex sensitivity (BRS), HRV, and HRT provide different information about cardiac autonomic function, and they are predictors of mortality in heart diseases.[24] Moreover, the moderate correlation between BRS and HRV ($r = 0.63$) suggests that the two measures explore different functions of autonomic control.[25]

HRT is an indirect cardiac autonomic function test that estimates the heart rate fluctuations resulting from the stimulation of the baroreceptor arc after a single PVB. HRT is strongly correlated with spontaneous BRS, and it may be used instead of BRS.[26] The European Society of Cardiology considers HRT a marker of vagal activity and an independent indicator of total mortality.[27] It is known that TO and TS values have strong correlations with some of the HRV parameters including SDNN and RMSSD.[28]

There are several studies in the current literature evaluating HRV in hypothyroidism. Nearly all of the studies showed reduced HRV in both subclinical and overt hypothyroidism.[7–16] These studies concluded that a sympathovagal imbalance was present by showing either increased sympathetic activity,[9] decreased sympathetic modulation,[7,8,14,15] increased vagal tone[10] or decreased vagal tone.[12,13] There is only one study that found no change in HRV in subclinical hypothyroid patients.[29] In our study, HRV was found to be reduced in subclinical and overt hypothyroid patients. Our findings are consistent with prior studies.

In two different studies by Galetta et al., it was shown that either subclinical or overt hypothyroid patients had decreased HRV.[7,8] They found that hypothyroidism was related to a state of sympathovagal imbalance. This autonomic dysfunction could be partially restored after replacement treatment with $_{L}$-T_4.[7] They also concluded that subclinical hypothyroidism was related to decreased HRV. Additionally, it was found that 6 months of $_{L}$-T_4 therapy caused an increase in HRV parameters.[8] Similar to these findings, Lakshmi et al. showed that hypothyroid patients that achieved a euthyroid state after treatment with $_{L}$-T_4 therapy had a significant increase in parasympathetic activity and improvement in sympathetic activity as measured by short-term HRV.[11] Consistent with Galetta and Lakshmi, Inukai et al. also demonstrated significant reduction in RR interval variations and improvement of these variations after treatment.[13] Contrary to these findings, there are two studies showing no improvement in HRV after $_{L}$-T_4 replacement therapy in hypothyroidism. Cacciatori

et al. found reduced HRV in seven hypothyroid patients in comparison with control subjects, but after therapy there was no improvement in reduced total HRV. They concluded that despite the $_{L}$-T_4 therapy, vagal failure of the heart still existed in this population.[9] Similar to this finding, Heemstra et al. showed that the total variability and standard deviation of the successive differences in RR intervals did not improve with $_{L}$-T_4 therapy.[15] These conflicting results may be partially explained by the differences in the patient populations (age, gender, cause, severity, and duration of hypothyroidism) and the heterogeneity of the techniques used in the various studies. In our study, none of the HRV parameters significantly improved after replacement treatment with $_{L}$-T_4. Our findings are consistent with some of the previous studies. However, it is difficult to decisively conclude whether the cardiac autonomic functions improved or not in the relatively short study period of 6 months. Longitudinal studies are needed for a stronger conclusion to be formed.

There are few studies evaluating HRT in thyroid disorders. Wutsmann et al. found decreased TS in hyperthyroid patients in comparison with post-treatment euthyroid levels.[17] Osman et al. found that HRT was impaired in patients with overt hyperthyroidism compared to healthy controls. After antithyroid treatment, TS normalized while TO remained impaired, which suggested that there were ongoing autonomic function abnormalities.[18] There is no study about HRT in hypothyroid patients. To our knowledge, our study is the first HRT study in the hypothyroid population.

The correlation between SDNN, TO, and TS with serum TSH concentration suggests that HRV and HRT may represent an early phase of autonomic dysfunction in hypothyroidism and may be a useful tool to monitor cardiovascular risk in these patients.

Despite the significant differences in TO and TS compared to controls, the mean of TO and TS values from hypothyroid patients were still within normal ranges. In the patient group, TO was abnormal in nine patients (29%) and TS was abnormal in nine patients (29%). The middle-aged population of our study may explain the relatively normal TO and TS values because it is known that TO increases and TS decreases with aging.[30]

The main limitation of our study is the small sample size. Because a small sample size results in low statistical power for equivalency testing, negative results may be simply due to chance. The lack of a reference method for studying autonomic dysfunction that could be used as a validation of the method in this study is another limitation. However, it is already known that HRV and HRT are useful tools for assessing autonomic cardiac functions.[3,5] Unfortunately, this type of data recruited from 24-hour Holter recording may not be the correct methodology for studying cardiac autonomic responses in a clinically defined group. Absence of a power spectral analysis of heart rate to a tightly controlled provocative test instead of long-term recordings obtained in circumstances that are always difficult to control is one of the other limitations of this study. Noninvasive risk predictors of arrhythmias such as HRV and HRT can cause false positive results especially in a middle-aged healthy population (1–37% for SDNN, 19% for TO, 5% for TS).[31] The false positive results of our control group are 3% for SDNN, 3% for TO, and 0% for TS. The incidence of these false positive results is lower than previous findings.

In conclusion, hypothyroidism may cause cardiac autonomic dysfunction. Restoring euthyroidism with $_{L}$-T_4 therapy does not effectively correct this dysfunction. HRV and HRT can be used as useful monitoring tools for cardiovascular-related risk in this population.

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