Abstract

Objective: The aim of the present study was to evaluate the effect of clinical hypothyroidism on cardiovascular autonomic function and ventricular repolarization.

Design and methods: We studied 31 patients (22 females and 9 males; mean age 53.6 ± 11.8 years) with overt hypothyroidism (TSH = 56.2 ± 14.7 μU/ml, low free thyroxine (T4), free tri-iodothyronine (T3)) and 31 euthyroid controls, to investigate the dispersion of the QT interval in electrocardiogram (ECG) (an index of inhomogeneity of repolarization) and heart rate variability (HRV; a measure of cardiac autonomic modulation). The hypothyroid patients and controls underwent a full medical examination, standard 12-lead ECG, and 24-h ambulatory ECG monitoring. The hypothyroid patients were re-examined after 6 months of treatment with L-T4.

Results: Patients with hypothyroidism showed higher QT dispersion and lower HRV measures than controls (P < 0.01 or P < 0.001). In hypothyroid patients, standard deviation of all R–R intervals was inversely related (by simple regression) to serum (log)TSH levels (r = −0.47, P = 0.008), while QT dispersion (r = 0.50, P = 0.004) and QTc dispersion (r = 0.46, P = 0.008) were directly related to (log)TSH. Parameters of HRV improved after 6 months of L-T4 treatment, with the correction of hypothyroidism, becoming comparable with those of the control subjects, whereas the QT and QTc dispersion results were found to be only partially restored, remaining higher than the controls.

Conclusions: The results of the study demonstrate that hypothyroidism is associated with a decreased sympatho-vagal modulation of the heart rate and with an increased inhomogeneity of ventricular recovery times. The assessment of HRV and QT dispersion in patients with overt hypothyroidism may represent a useful tool in monitoring the cardiovascular risks.

Introduction

The cardiovascular system is one of the most important targets of thyroid hormones (1, 2) and is very sensitive to a minimal decrease of circulating thyroid hormones (2).

It has long been recognized that hypothyroidism may cause cardiac pathologies, such as impaired cardiac contractility, decreased cardiac output, increased systemic vascular resistance, and cardiac electrical abnormalities (3, 4). Electrocardiographic changes such as bradycardia, low voltage, and varying degrees of heart block are commonly recognized in hypothyroid patients (1).

The cardiac effects of hypothyroidism depend on the severity and duration of the disease and can range from subtle abnormalities to overt and easily recognizable manifestations (1). If undiagnosed or improperly treated, hypothyroidism status is associated with changes in autonomic regulation of cardiovascular system and in ventricular repolarization. These changes, characterized by an inhomogeneity of ventricular repolarization and a cardiovascular autonomic dysfunction, have been linked to the occurrence of malignant ventricular arrhythmias and sudden cardiac death (5–9). However, sustained or life-threatening ventricular ectopy is rarely seen in hypothyroid patients (1, 10).

The aim of the study was to evaluate in patients with overt hypothyroidism the dispersion of QT interval, i.e., an index of inhomogeneity of ventricular repolarization and heart rate variability (HRV), i.e., a measure of cardiac autonomic modulation before treatment and after 6 months of the l-thyroxine (l-T4) replacement.

Materials and methods

Study population

We studied 31 patients (22 females and 9 males; mean age 53.6 ± 11.8 years; body surface area 1.78 ± 0.18 m²) with clinical hypothyroidism, as judged by elevated serum thyroid-stimulating hormone (TSH) levels (56.2 ± 14.7 μU/ml; normal range 0.35–4.9 μU/ml) and low levels
of the free thyroid hormones (FT$_4$ < 0.68 ± 0.12 pmol/l and free tri-iodothyronine (FT$_3$) < 1.84 ± 0.25 pmol/l; normal ranges 7.2–19.3 and 3.7–8.6 pmol/l respectively).

The etiology of hypothyroidism was Hashimoto’s thyroiditis (all the patients had positive antithyroid peroxidase antibodies (AbTPO > 100 UI/ml; median AbTPO titer = 347 UI/ml; Table 1).

All the subjects were found to be free from cardiovascular disease or any other major medical disorders, after assessing their medical history, physical examination, basal and stress electrocardiography, blood chemistry, hematology, and urine analysis.

Major criteria for inclusion of subjects in the trial were as follows: body mass index lower than 30 kg/m$^2$, diastolic arterial blood pressure lower than 90 mmHg, and systolic arterial blood pressure lower than 140 mmHg. Subjects were excluded if the physical examination revealed any abnormalities, or in presence of smoking habits, diabetes mellitus, or if they had received any drug treatment within the previous 3 months.

Before inclusion in the protocol, a blood sample for the determination of FT$_4$, FT$_3$, and TSH was obtained at 0800 h after an overnight fast.

Additionally, 31 sex- and age-matched healthy volunteers (22 females and 9 males; mean age 50.4 ± 15.3 years; body surface area 1.73 ± 0.17 m$^2$) recruited among staff and relatives of patients attending the Department of Internal Medicine were recruited to form the control group (Table 1).

Patients were studied at baseline and 180 days after starting endocrine treatment with substitutive doses of l-T$_4$ (1–1.5 μg/kg per day).

The study protocol was approved by the institutional ethics committee and all the patients gave their informed written consent to participate in the study.

**HRV analysis**

A 24-h electrocardiograph (ECG) monitoring was performed by a two-channel (leads CM$_2$ and CM$_4$) amplitude-modulated tape recorder (Diagnostic Monitoring System, Santa Ana, CA, USA). All the tapes were subsequently analyzed measuring HRV in the time and frequency domain, using a commercially available program (Diagnostic Monitoring System). The time domain analysis of HRV included the mean of all normal R–R intervals (N–N), the standard deviation of N–N (SDNN), the standard deviation of 5 min mean values of N–N (SDANN), the root mean square successive difference of N–N (rMSSD), and the percentage of successive N–N differences > 50 ms for each 5-min interval (pNN50%).

Short-term HRV was evaluated further by frequency domain analysis. Spectral measures were calculated using the fast-Fourier transform method. Results are presented as a mean value for the entire recording. Frequency domain measurements included: low-frequency power (LF: 0.04–0.15 Hz), high-frequency power (HF: 0.16–0.40 Hz), and the ratio between the powers in the LF and HF bands (LF/HF). The LF/HF ratio was used as an indirect index of sympatho-vagal balance.

**Measurement of QT interval and QT dispersion**

ECGs with a duration of 10 s were recorded with a Cardiovit CS-100 (Schiller-AG, Baar, Switzerland), using the same system at 25 mm/s paper speed and standardized to 0.1 mV/mm. QT intervals were measured manually in all the 12 leads in blinded fashion from the onset of the QRS complex to the end of the T wave as previously described (11).

When U waves were present, the QT interval was measured to the nadir of the trough between the T and U waves. If the end of the T wave could not be identified, the lead was not included. Three consecutive QT intervals were measured and averaged for each lead. A minimum of nine leads in which the QT interval could be measured was required for QT dispersion to be determined. QT dispersion was defined as the difference between the longest and shortest QT intervals. With use of Bazett’s formula, QT dispersion was corrected (QTc) for heart rate. All ECGs were analyzed twice by two observers, because of the known difficulties concerning definition of the end of the T wave. To minimize these confounding factors, two independent observers who were unaware of the clinical details performed all measurements, and intra- and interobserver variability was good. Intra- and interobserver variability for QT dispersion measurements were <5% and <6% respectively. Differences were resolved by consensus.

**Table 1** Clinical and hormonal characteristics of the patients with clinical hypothyroidism (CH) and control subjects (mean ± s.d.).

<table>
<thead>
<tr>
<th></th>
<th>CH (N=31)</th>
<th>Controls (N=31)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>53.6±11.8</td>
<td>50.4±15.3</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>9/22</td>
<td>9/22</td>
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<tr>
<td>BSA (m$^2$)</td>
<td>1.78±0.18</td>
<td>1.73±0.17</td>
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<tr>
<td>BMI (kg/m$^2$)</td>
<td>24.2±1.1</td>
<td>23.8±1.0</td>
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<tr>
<td>HR (bpm)</td>
<td>66.5±6.2</td>
<td>70.2±7.4</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>126.8±8.8</td>
<td>121.2±13.4</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.3±5.2</td>
<td>75.6±4.2</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>92±5</td>
<td>90±6</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>212.3±12.2$^*$</td>
<td>181.6±10.2</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>129.6±14.2$^*$</td>
<td>104.5±11.2</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>49.8±9.2</td>
<td>52.6±8.6</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>122.8±14.2</td>
<td>119.8±12.8</td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>56.2±14.7$^7$</td>
<td>2.6±0.5</td>
</tr>
<tr>
<td>log (μU/ml)</td>
<td>1.73±0.12$^7$</td>
<td>0.41±0.02</td>
</tr>
<tr>
<td>Free T$_4$ (pmol/l)</td>
<td>1.84±0.25$^7$</td>
<td>4.78±0.14</td>
</tr>
<tr>
<td>Free T$_3$ (pmol/l)</td>
<td>0.69±0.12$^7$</td>
<td>9.68±0.64</td>
</tr>
<tr>
<td>AbTPO (UI/ml)</td>
<td>315±635$^7$</td>
<td>12±21</td>
</tr>
</tbody>
</table>

BSA, body surface area; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; TSH, thyroid stimulating hormone; T$_3$, tri-iodothyronine; T$_4$, thyroxine; AbTPO, antithyroid peroxidase antibodies. $^*$P<0.001 and $^7$P<0.0001 versus controls.
Results

Clinical characteristics and the thyroid hormone profile of hypothyroid patients and control subjects were displayed in Table 1. As expected, patients with hypothyroidism showed higher TSH and lower FT3 and FT4 levels than controls (P<0.0001). The hypothyroid patients showed higher serum levels of total cholesterol and low density lipoprotein (LDL) cholesterol than euthyroid controls.

After 6 months treatment with L-T4, serum TSH (56.2 ± 14.7 vs 2.9 ± 0.4 μU/ml), FT3 (1.84 ± 0.25 vs 4.56 ± 0.15 pmol/l), and FT4 levels (0.68 ± 0.12 vs 9.68 ± 0.64 pmol/l) returned to within the normal range in all patients (P<0.0001 for all). At the follow-up visit, all the other parameters were not statistically different from baseline, with the exception of a significant reduction in the plasma total cholesterol (212.3 ± 12.2 vs 190.4 ± 8.2 mg/dl, P<0.05) and LDL cholesterol (129.6 ± 14.2 vs 114.6 ± 9.4 mg/dl, P<0.05) levels.

None of the patients displayed evidence of conduction abnormalities on resting ECG or presented any sustained or non-sustained ventricular tachyarrhythmias on 24-h ambulatory ECG monitoring. Eight patients had low incidence of premature beats on the 24-h ECG (as a mean, 18 ventricular and 22 supraventricular complexes per hour).

HRV findings

Hypothyroid patients showed all time domain indices, including SDNN, SDANN, rMSSD, and pNN50, significantly lower than those of the control group (P<0.01 or P<0.001; Table 2). In the frequency domain, LF amplitude and HF amplitude were lower in hypothyroid subjects than in the controls, while the LF/HF ratio was comparable (Table 2). In patients re-examined after 6 months of replacement treatment with L-T4, both time and frequency domain measures of HRV were significantly improved and comparable with controls (Table 2).
Discussion

The results of the study showed a reduction of all HRV parameters in time domain such as SDNN, rMSSD, and pNN50, markers of parasympathetic modulation, and a reduction of HF and LF components of the spectral analysis of HRV, considered respectively a marker of parasympathetic and sympathetic modulation. This confirms that hypothyroidism determines a sympatho-vagal imbalanced state, characterized by both decreased cardiovascular sympathetic and vagal modulation. This autonomic dysfunction can be partly restored after replacement treatment with L-T4.

Our findings are consistent with prior studies (12–14), who showed a decreased sympatho-vagal activity with a relatively increased sympathetic influence in hypothyroid patients. Moreover, these authors showed that in hypothyroid patients high plasma norepinephrine levels were seen and the responsiveness to endogenous catecholamines was decreased, suggesting a desensitization at the receptor and/or post-receptor level (13). This may at least partially explain the decreased basal and maximal daily heart rates seen in patients with hypothyroidism, which occurs despite elevated plasma norepinephrine levels (12) and a decreased cardiac chronotropic response to β-adrenergic stimulation (14).

Conflicting results about HRV have been reported in the literature (12, 15, 16). For example, Cacciatori et al. showed an increased sympathetic influence in hypothyroidism (12), while Xing et al. showed a higher level of vagal tone (16). These conflicting results may be partially explained by the different selection of patients (number, age, gender, type, severity, and duration of hypothyroidism) in the various studies. However, the diversity of techniques used to monitor the sympatho-vagal imbalance may also be responsible for the contradictory results obtained.

With regard to ventricular repolarization, our results showed a prolongation of the QT interval and an increased dispersion of the QT interval in hypothyroid patients, in agreement with previous observations (17, 18). The increased regional inhomogeneity of

Figure 1 QT dispersion (top) and QTc dispersion (bottom) at baseline and after L-T4 treatment in all patients with hypothyroidism.

Figure 2 In hypothyroid patients, SDNN (top) was inversely related (by simple regression) to serum (log)TSH levels ($r = -0.47, P = 0.008$), while QTc dispersion (bottom) ($r = 0.46, P = 0.008$) was directly related to (log)TSH.
ventricular repolarization in patients with hypothyroidism is partially determined by fibrous ventricular wall remodeling, induced by lack of thyroid hormones (18). Other processes can contribute to an increased QT dispersion. Vascular smooth muscle cells swelling and water accumulation in the myocardial wall due to protein deposition in extracellular space could be a source of increased QT dispersion (19, 20).

Furthermore, experimental evidence suggests that thyroid hormones may selectively prevent the induction of fibrosis (21), by the inhibition of collagen type 1 synthesis (22, 23).

No study investigated contemporary HRV and QT dispersion in clinical hypothyroidism; the simultaneous evaluation of both these parameters could be of particular value owing that they are both influenced by sympatho-vagal tone and are related to each other. In fact, as shown by many studies in the literature (24–27), a significant association is present between QTc dispersion and HRV. So, the contemporary evaluation of both these parameters should strengthen the significance of the results, and could lead to a firmer conclusion. To our knowledge, our study evaluated contemporary HRV and QT dispersion in clinical hypothyroidism for the first time.

The evidence that l-T4 therapy appears to restore the vagal activity and reduces (rather than increases as generally supposed) the sympathetic drive on the heart also supports the view of an increased ratio of sympathetic to vagus nerve traffic to the heart in patients with clinical hypothyroidism.

The sympatho-vagal imbalance and the prolonged QT dispersion are considered to be a marker of electrical instability and risk factors for ventricular arrhythmias (3–5). The absence of any clinically important arrhythmias on the 24-h ECG monitoring of our patients suggests that other factors (triggers) could be required for the development of sustained or life-threatening ventricular arrhythmia. In patients with hypothyroidism, the occurrence of this arrhythmia in the presence of a prolonged QT interval has been reported in only a few reports (28–31). In most of these cases, no other predisposing factors were ascertained, and the arrhythmogenic tendency abated with l-T4 replacement. In our patients, with overt hypothyroidism the QT dispersion parameters improved partially after l-T4 treatment. In subclinical hypothyroidism, we previously reported that abnormalities of QT dispersion and sympatho-vagal balance were fully reversible after 6 months of l-T4 therapy (26). On the contrary, in clinical hypothyroidism the patients showed, after 6 months of l-T4 therapy an increased QT dispersion compared with normal controls, indicating a persistent depressed vagal modulation. This finding may be related to increased myocardial fibrosis, in fact, previous tissue characterization studies by videodensitometry documented increased intramyocardial fibrosis – only in overt but not in subclinical hypothyroid patients (18).

However, a longer period of treatment may be needed to fully reverse QT dispersion and sympatho-vagal balance. In fact, a few patients (n = 6) had TSH levels after l-T4 treatment between 3.5 and 4.5 mIU/ml, revealing that l-T4 replacement therapy in these subjects needed a further increase of the dosage.

Surely the cardiac effects of hypothyroidism depend on the severity and duration of the disease and could also be modulated by age, gender, and possibly other factors as yet unknown. The occurrence of malignant arrhythmias is higher in long standing and severe hypothyroidism, and in myxedema coma (where the mortality is more than 50% and often due to cardiac arrest). The evaluation of markers of arrhythmic risk, such as HRV and QTc dispersion (that can be easily monitored), will be helpful in evaluating the cardiac risk in these patients. The correlation of serum TSH with the parameters of HRV and QT dispersion confirms that the severity of hypothyroidism plays an important role in these factors for arrhythmic risk. Replacement with l-T4 is the definitive treatment and should be initiated promptly but cautiously to safely eliminate the arrhythmic risk.

In conclusion, patients with clinical hypothyroidism have a sympatho-vagal imbalance, and increased inhomogeneity of ventricular recovery times, both of which predispose to the potentially life-threatening arrhythmias. The assessment of HRV and QT dispersion in patients with clinical hypothyroidism may represent a useful tool in monitoring the cardiovascular risk and may bring some additional understanding to this entity, facilitating the management of the patient. An additional advantage is its easy repeatability and, therefore, it could be used to serially evaluate the adequacy and efficacy of l-T4 treatment.

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