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Original article

Heart rate variability and QT dispersion in patients with subclinical hypothyroidism

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Abstract

The effect of subclinical hypothyroidism (SH) on cardiovascular autonomic function and ventricular repolarization has not been yet elucidated. The aim of the present study was to evaluate the dispersion of QT interval, i.e. an index of inhomogeneity of repolarization, and heart rate variability (HRV), i.e. a measure of cardiac autonomic modulation, in SH patients.

Methods: The study included 42 patients (29 women and 13 men; mean age 53.2 ± 14.2 years; body surface area 1.76 ± 0.14 m^2) with SH, as judged by elevated serum TSH levels (> 3.6 mIU/l; range, 3.8–12.0) and normal free thyroid hormones (FT_4 and FT_3) and 30 euthyroid volunteer. Subjects with cardiac, metabolic, neurological disease or any other systemic disease that could affect autonomic activity were excluded from the study. Patients with SH and control subjects underwent a full history, physical examination, standard 12-lead ECG, and 24-h ambulatory ECG monitoring. To evaluate the effect of treatment with L-thyroxine on QT dispersion and HRV, 15 patients with SH were randomly assigned to receive therapy with L-thyroxine. All the subjects were evaluated at enrolment and after 6 months.

Results: Patients with SH showed higher QT dispersion and lower HRV measures than healthy controls ($P < 0.01$ for all). In SH patients, the standard deviation of N–Ns (SDNN) was negatively related to TSH ($r = –0.42$, $P = 0.006$), while low frequency (LF)/high frequency (HF) ratio was positively related to TSH ($r = 0.42$, $P = 0.006$). Moreover, in SH patients both QT dispersion and QTc dispersion were positively related to TSH ($r = 0.64$ and $r = 0.63$, $P < 0.001$ for both). After 6 months, the patients treated with L-tiroxine exhibited a reduction of QT dispersion and an increase of HRV parameters.

Conclusion: The results of the present study demonstrated that SH can alter autonomic modulation of heart rate and cause increased inhomogeneity of ventricular recovery times. Accordingly, early L-thyroxine treatment may be advised not only to prevent progression to overt hypothyroidism but also to improve abnormal cardiac autonomic function and ventricular repolarization inhomogeneity.

Keywords: Subclinical hypothyroidism; Ventricular repolarization; Cardiovascular autonomic function; Heart rate variability; QT dispersion

1. Introduction

Subclinical hypothyroidism (SH) is an apparently asymptomatic condition defined by slightly increased serum thyrothrophine (TSH) concentrations, but normal serum-free T_3 (FT_3) and free T_4 (FT_4) hormone levels. Altered serum lipid levels and abnormal vascular reactivity in patients with SH may confer a higher risk for cardiovascular disease [1,2]. Moreover SH is associated with the risk of heart failure, other cardiovascular events, and death [3].

The QT interval dispersion (QTd) is an index of inhomogeneity of ventricular repolarization [4], and heart rate variability (HRV) is a measure of cardiac autonomic modulation [5]. Experimental and clinical studies have shown that increased QTd and reduced HRV have correlated with an increased risk of ventricular arrhythmias and cardiac mortality [6–8]. Although, the impairment of the cardiac autonomic activity [9] and of the alteration of ventricular repolarization [10] in overt hypothyroidism has been both clinically and experimentally well demonstrated, results of previous studies concerning

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the presence of similar alterations in SH are somewhat inconsistent and are still a matter of debate.

The aim of the present study, was to evaluate the cardiovascular autonomic function and the inhomogeneity of ventricular repolarization in SH patients and the effects of the levothyroxine (L-T4) replacement.

2. Methods

2.1. Study population

We studied 42 patients (29 women and 13 men; mean age 53.2 ± 14.2 years; body surface area 1.76 ± 0.14 m^2) with SH, as judged by elevated serum TSH levels (> 3.6 mIU/l; range, 3.8–12.0) and free thyroid hormones (FT_4 and FT_3) within the normal range.

The etiology of SH was Hashimoto's thyroiditis in all patients. Only the patients with stable elevated serum TSH and normal thyroid hormone levels for at least 3 months before enrolment in the study were included.

All the subjects were free from cardiovascular disease or other major medical disorders, as assessed by clinical 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 they had abnormal findings at physical examination, smoking habits, diabetes mellitus, or 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 08:00 h after an overnight fast.

Additionally, 30 sex- and age-matched healthy volunteers (21 women and nine men; mean age 51.4 ± 16.2 years; body surface area 1.72 ± 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).

Table 1
Clinical and hormonal characteristics of the study groups (mean ± S.D.)

	SH $N = 42$	Controls $N = 30$
Age (years)	53.2 ± 14.2	51.4 ± 16.2
Sex (M/F)	13/29	9/21
BSA (m^2)	1.76 ± 0.14	1.72 ± 0.17
BMI (kg/m^2)	23.7 ± 1.2	23.8 ± 0.9
HR (bpm)	69.4 ± 7.2	70.3 ± 6.4
SBP (mmHg)	126.0 ± 8.3	124.8 ± 9.4
DBP (mmHg)	76.7 ± 3.2	74.5 ± 3.4
Glucose (mg/dl)	90 ± 6	91 ± 4
Total cholesterol (mg/dl)	200.3 ± 16.0	184.0 ± 10.6
LDL-cholesterol (mg/dl)	118.2 ± 16.1	102.0 ± 11.0
HDL-cholesterol (mg/dl)	54.1 ± 12.6	54.2 ± 10.6
Tryglicerides (mg/dl)	118.4 ± 22	112.6 ± 20.1
TSH (mIU/l)	9.8 ± 1.7**	2.1 ± 0.4
Free T_3 (pmol/l)	4.32 ± 0.18	4.82 ± 0.16
Free T_4 (pmol/l)	9.30 ± 1.10	9.86 ± 0.74

SH: subclinical hypothyroidism; BSA: body surface area; BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure. **$P < 0.0001$ vs. controls.

Fifteen patients were randomly assigned to receive L-thyroxine (Eutirox, Bracco S.p.A., Milan, Italy) replacement therapy. These patients returned after 6 months for repeat thyroid function tests and the evaluation of all parameters.

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

2.2. HRV analysis

Twenty-four hour ECG monitoring was performed using a two-channel (leads CM_2 and CM_5) amplitude modulated tape recorder (Diagnostic Monitoring System, Santa Ana, CA). All the tapes were subsequently analyzed to measure 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–Ns (SDNN), the standard deviation of 5 min mean values of N–Ns (SDANN), the root mean square successive difference of N–Ns (rMSSD) and the percent 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 computed 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 sympathovagal balance.

2.3. 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 at 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. Because of the known difficulties concerning definition of the end of the T wave, all ECGs were analyzed twice by two observers. However, to minimize these confounding fac-