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Imbalance of cardiac autonomic nervous activity and increase of ventricular repolarization dynamicity induced by thyroid hormones in hyperthyroidism

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ABSTRACT

Objective: To investigate the effects of thyroid hormones on cardiac autonomic nervous activity and ventricular repolarization dynamicity in hyperthyroidism.

Methods: 57 consecutive patients first diagnosed of hyperthyroidism (HT group) and 55 age and sex-matched healthy volunteers (Control group) from March 2012 to March 2013 in our center were enrolled. All subjects underwent standard 12-lead ECG and 24 h Holter recording at baseline. For the HT group, free triiodothyronine (FT_3), free thyroxine (FT_4) and thyroid stimulating hormone (TSH) were monitored, and after they returned to normal all the examinations were redone. Heart rate variability (HRV) was assessed to determine the cardiac autonomic nervous activity. QTe/RR slope (QT end) and QTp/RR slope (QT apex) were calculated to evaluate the ventricular repolarization dynamicity.

Results: The HT patients before treatment had significantly higher LF/HF, QTe/RR slope and QTp/RR slope, and larger QT dispersion than the controls and after treatment ($P < 0.05$ for all). Correlation analyses revealed that FT_3 was positively correlated with QTe/RR and QTp/RR slopes (r = 0.689 and 0.665 respectively, $P < 0.001$ for both), and similarly in FT_4 (r = 0.665 and 0.668 respectively, $P < 0.001$ for both). While TSH was negatively correlated with QTe/RR and QTp/RR slopes (r = −0.660 and −0.680 respectively, $P < 0.001$ for both). FT_3 and FT_4 levels were independent predictors of QTe/RR slopes ($P < 0.001$, $\beta = 0.007$; $P = 0.017$, $\beta = 0.001$, respectively) and QTp/RR slopes ($P < 0.001$, $\beta = 0.008$; $P = 0.002$, $\beta = 0.001$, respectively).

Conclusions: High-level thyroid hormones induce the cardiac sympathetic overactivity and increases ventricular repolarization dynamicity, and the impact can be attenuated after euthyroidism restored.

1. Introduction

Cardiovascular system is one of the most important targets of thyroid hormones (Jabbar et al., 2017). Thyroid hormones exert similar effects as catecholamine does on the cardiac conduction system causing an increase in heart rate and altered heart rate variability (HRV) (Grais and Sowers, 2014; Kaminski et al., 2012). Previous researches have shown that excessively enhanced sympathetic tone influences ventricular repolarization dynamicity in healthy men and patients with cardiovascular diseases (Xhaët et al., 2008; Cygankiewicz et al., 2008). To investigate the impact of thyroid hormones on cardiac autonomic tone and ventricular repolarization dynamicity, we recruited 57 hyperthyroid patients with hyperthyroidism, as well as 55 healthy subjects in this study. We investigated the variations of HRV and ventricular repolarization dynamicity in hyperthyroid patients before and after treatment.

Abbreviations: FT_3, free triiodothyronine; FT_4, free thyroxine; HF, high-frequency; HRV, heart rate variability; HT, hyperthyroidism; LF, low-frequency; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; pNN50, percent of successive RR interval differences > 50 ms for each 5 min interval; QTe, the onset of QRS complex to the end of T wave; QTp, the onset of QRS complex to the peak of T wave; RMSSD, root mean square of successive difference of RR intervals; SDANN, standard deviation of 5 min mean values of RR intervals; SDNN, standard deviation of all RR intervals; TP, total power; TSH, thyroid stimulating hormone

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2. Methods

2.1. Study population

We consecutively enrolled 57 patients who were first diagnosed of hyperthyroidism (HT group, 35 females; mean age 35 ± 13 years) in the Department of Endocrinology, and 55 age and sex-matched healthy volunteers (Control group, 28 females; mean age 36 ± 12 years) from the physical examination center in our hospital from March 2012 to March 2013. The exclusion criteria of the HT group included severe infiltrative exophthalmos, thyroid crisis, white blood cells $< 3 \times 10^9$/L or neutrophils $< 1.5 \times 10^9$/L, thyroid cancer, nodular goiter, pre-existing hyperthyroid heart disease and other major complications, long-term use of antiarrhythmic drugs, cardiovascular diseases, diabetes mellitus, hypertension, with > 10% non-sinus rhythm in 24 h ambulatory ECG recording, 24 h ambulatory ECG recording time < 1400 min, unwilling or unable to undergo the required examinations. The Control group meets the criteria of without cardiovascular diseases, hyperthyroidism or other diseases; with normal physical examination results, normal ECG and echocardiography, and normal blood routine, liver function, renal function, plasma lipids level and plasma glucose level.

The study was approved by the Ethics Review Board of Renmin Hospital of Wuhan University, and all study participants have signed informed consent for the study.

2.2. Data collection

In all the subjects, demographic data were collected and anthropometric data including BMI, systolic and diastolic blood pressure were measured at baseline. Biochemistry assays including fasting blood glucose, total cholesterol, triglyceride, hs-CRP, and free triiodothyronine (FT_3), free thyroxine (FT_4) and thyroid stimulating hormone (TSH) levels were obtained. All the subjects underwent standard 12-lead ECG, 24 h ambulatory ECG and transthoracic echocardiography. The serum levels of the thyroid hormones were monitored in the HT group once a month after treatment begins. The treatment of the HT patients included ^{131}I radiotherapy and antithyroid drug therapy including methimazole and propylthiouracil. The data collection of the study did not interference with the patients' treatments which were decided by the endocrinologists. After the thyroid hormones levels of the HT patients come back and maintain at the normal level in 2 consecutive follow-ups, the standard 12-lead ECG and 24 h ambulatory ECG monitoring were performed again.

2.3. ECG analysis

The QTc interval and QRS interval were determined on the standard 12-lead ECG. The QTe interval was measured on the 12-lead ECG for the QT dispersion calculation, which was defined as the difference between the maximum and minimum QTe interval occurring in any of the 12 ECG leads (Pye et al., 1994). All these indices were measured independently by 2 experienced technicians who were blinded to the patients' clinical information, and corrections were made to the measurements as necessary.

2.4. Holter recordings, HRV and QT dynamicity analysis

For the 24 h ambulatory ECG recordings, the subjects were required to sleep at 10 pm the night before examination and wake up at 7 am. At follow-up, antiarrhythmic drugs were required being ceased for at least 5 half-lives before the examination. After 24 h ambulatory ECG recordings (Marquette-3000, GE Medical, USA), frequency and time domain parameters of HRV and QT dynamicity were evaluated by software (MARS 7.2, GE Medical, USA). The implications of the ECG and HRV parameters were presented in Table 1 (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Shaffer and Ginsberg, 2017). All tapes were manually edited to eliminate artifacts and premature events.

For the HRV frequency domain, the power spectral variables were determined as follows: total power (TP), high frequency (HF) component (from 0.15 to 0.40 Hz), low frequency (LF) component (from 0.04 to 0.15 Hz), and a very-low-frequency (VLF) component (below 0.04 Hz). The values of the HF and LF components were measured and expressed in normalized units (nu) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) which were calculated as follows: HFnu = HF power/TP − VLF power × 100; LFnu = LF power/TP − VLF power × 100; and ratio between LF and HF powers (LF/HF) was calculated.

For the HRV time domain we have chosen: standard deviation of all RR intervals (SDNN), standard deviation of 5 min mean values of RR intervals (SDANN), the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD), and number of pairs of adjacent RR intervals differing > 50 ms divided by the total number of all RR intervals (pNN50).

The 24 h recordings were converted into 2880 templates obtained at 30 s intervals. To assure the correct measurements of QT intervals, all recordings were checked visually accompanied with automatic measurements. For each template, average QT intervals were measured automatically. Both QTe which is from the onset of QRS complex to the end of T wave and QTp which is from the onset of QRS complex to the peak of T wave were calculated. The end of the T-wave was determined by the intersection of the tangent of the downslope of the T-wave with the isoelectric baseline, whereas the peak of the T-wave by fitting a parabola through the T-wave peak (Malik and Batchvarov, 2000). The program also automatically computed the slopes of the linear regressions of QTe and QTp values plotted against the corresponding RR interval (QTe/RR and QTp/RR). The slopes of QTe/RR and QTp/RR were calculated for the entire 24 h. QT analysis was performed when the recordings were > 20 h after manually eliminating artifacts and premature beats, and T-wave amplitude > 0.15 mV. QT dynamicity was evaluated by QTe/RR slope and QTp/RR slope (Cygankiewicz et al., 2008).

2.5. Statistical analysis

Data are presented as mean ± SD for normally distributed continuous variables, median (25th and 75th percentiles) for nonnormally distributed variables. Normally distributed continuous variables were analyzed with a *t*-test, and nonnormally distributed variables were analyzed with the Mann–Whitney *U* test. Spearman correlation analysis was performed to evaluate the association of various variables, such as age, systolic and diastolic blood pressure, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and thyroid hormone levels with QT dynamicity indices. Multivariate linear regression analysis was performed to evaluate the effects of various variables, such as age, BMI, systolic and diastolic blood pressure, LVEF, LVEDD, LF/HF, and thyroid hormone levels on QT dynamicity indices. All statistical analysis was performed using SPSS (version 22.0, SPSS, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

3. Result

3.1. Baseline characteristics and thyroid hormones profile

Baseline demographic characteristics of the study population are shown in Table 2. The history of hyperthyroidism in the HT group was (14.7 ± 21.3) months. The time interval between pre- and post-treatment assessment was (3.7 ± 0.7) months. The thyroid hormones and TSH levels pre- and post-treatment are shown in Table 3. Seven patients were lost to follow-up in the HT group after treatment. It was observed

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