Effect of thyrotropin suppressive therapy on heart rate variability and QT dispersion in patients with differentiated thyroid cancer

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Abstract
The effects of thyrotropin (TSH) suppressive therapy on autonomic regulation and ventricular repolarization in patients with differentiated thyroid cancer (DTC) have not been elucidated. The aim of present study was to evaluate variation in heart rate variability (HRV) and QT dispersion after TSH suppressive therapy in patients with DTC.

Cases, defined as 271 patients with DTC within 1 year of exogenous levothyroxine, and all patients underwent a full history, physical examination, including standard 12 lead electrocardiogram (ECG), and 24 h ambulatory ECG monitoring (Holter) with normal free thyroxine (FT4) and free triiodothyronine (FT3) with levothyroxine. To evaluate effects of TSH suppressive therapy on HRV and QT dispersion, patients were divided into three groups according to different levels of TSH: TSH < 0.1 mIU/L group and 0.1 ≤ TSH < 0.5 mIU/L group were as TSH suppression groups, and 0.5 ≤ TSH < 2.0 mIU/L group was as TSH replacement group.

Comparing with 0.5 ≤ TSH < 2.0 mIU/L group, significant changes in both time and frequency domain of HRV and QT dispersion were observed in TSH < 0.1 mIU/L group (P < .001: SDNN, SDANN, LF/HF, QTd, and QTcd; P < .05: rMSSD) and 0.1 ≤ TSH < 0.5 mIU/L group (P < .001: SDNN, HF, LF/HF, QTd, and QTcd), and especially were more pronounced in TSH < 0.1 mIU/L group. Moreover, we found that TSH level was proportional to SDNN (β = 15.829, P < .001), but inversely proportional to LF/HF (β = -0.671, P < .001), QTd (β = -16.674, P < .001) and QTcd (β = -18.314, P < .001) in DTC patients with exogenous levothyroxine.

Compared with euthyroid state, patients with suppressed serum TSH have increased sympathetic activity in the presence of diminished vagal tone, ultimately showed sympathovagal imbalance and with an increased inhomogeneity of ventricular recovery times. These findings revealed that TSH suppression therapy had a significant impact on cardiovascular system and had certain guiding role in the treatment and management of patients with DTC.

Abbreviations: DTC = differentiated thyroid cancer, FT4 = free thyroxine, FT3 = free triiodothyronine, HF = high frequency power, HRV = heart rate variability, LF = low frequency power, LF/HF = ratio between the powers in the LF and HF bands, pNN50% = percent of successive N–N differences > 50 ms for each 5 min interval, QTd = QTc dispersion, QTd = QT dispersion, rMSSD = root mean square successive difference of NNs, SDANN = standard deviation of 5 min mean values of NNs, SDNN = standard deviation of NNs, TSH = thyrotropin.

Keywords: Differentiated thyroid cancer, TSH suppressive therapy, Heart rate variability, QT dispersion

1. Introduction

Patients with differentiated thyroid cancer (DTC) are routinely given a larger dose levothyroxine in TSH suppressive therapy through inhibiting pituitary TSH secretion. It is useful to prevent the recurrence, metastasis of TSH-dependent tumors and reduce tumor-related mortality.[1] Therefore, TSH suppression therapy is associated with a reduced mortality risk in patients with DTC.[2]

Nevertheless, supplementation with excessive exogenous levothyroxine also suggested a synergistic effect with the sympathetic neurotransmitter, catecholamines, which may have provided a positive effect on increases expression of beta receptors in heart. This, in turn, enhances the excitability of cardiac sympathetic tone coupled with diminished cardiac parasympathetic reactivity, being an unsustainable condition, and leading to eventual sympathovagal imbalance and functional and structural changes of the heart and blood vessels through increasing the responsiveness of hearts to catecholamine stimulation.[3] In addition, it is well known that excessive thyroid hormone could increase the cardiac load and myocardial oxygen consumption (increased demand), moreover, affect the metabolism of the body. Especially, thyroid hormone also can increase sodium pump activity and Ca2+-ATPase activity in sarcoplasmic reticulum, and act on the cardiovascular system.
directly, which could be correspondingly changes in the structure and function on heart. Indeed, long-term supraphysiological thyroid hormone use is associated with hyperthyroidism and subclinical hyperthyroidism. Particularly, when serum TSH is suppressed at low levels (TSH < 0.1 mIU/L), myocardial ischemia and arrhythmia, especially atrial fibrillation would greatly increase among elderly populations. Furthermore, long-term treatment can seriously reduce the life quality of the patients and affect mental to a certain extent, which is related to the increase of cardiovascular mortality and cardiovascular hospitalization greatly increases. Thus, TSH suppression treatment for patients with DTC is still controversial. Heart rate variability (HRV), an indicator of sympathetic and parasympathetic nervous system function and balance, reflects a moderating effect of the neural and humoral factors on sinoatrial node. HRV is also regarded as a significant predictor of arrhythmia and associated sudden cardiac death recurrence. QT dispersion is an index of the transmural dispersion of repolarization, similarly, is used to predict the occurrence of cardiovascular system disease. Decreased HRV and increased QT dispersion are closely related to sympathovagal imbalance, characterized by increased sympathetic activity in the presence of diminished vagal tone. Accumulating evidences have revealed a close association between imbalance of autonomic nervous system and cardiovascular pathogenesis of patients with hyperthyroidism and hypothyroidism. However, the relationship between sympathovagal imbalance or alterations of ventricular repolarization and TSH suppressive therapy is not fully understood in patients with DTC. Therefore, the aim of this study was to investigate the changes of cardiac autonomic function and ventricular repolarization by monitoring HRV and QT dispersion in patients with TSH suppressive therapy.

2. Materials and methods

2.1. Study population

Patients with DTC who had maintained adjuvant endocrine therapy with levothyroxine after thyroidectomy with or without radioactive iodine therapy at the Department of Endocrinology of the First Hospital of Lanzhou University (Lanzhou, China) between May 1, 2017 and November 1, 2019 were enrolled in the present study. All surveys followed ethical principles according to the Helsinki Declaration and the study was approved by the Ethics Committee of the First Hospital of Lanzhou University. All their mean duration was above 1 year. The patients were divided into three groups according to the revised American Thyroid Association Management Guidelines for pathway with thyroid nodules and DTC. For the first two groups, pre-group one (TSH < 0.1 mIU/L; 79 females, 11 males; mean age 39.8 ± 8.6 years; BMI 23.5 ± 2.1 m²) and pre-group two (0.1 ≤ TSH < 0.5 mIU/L; 80 females, 11 males; mean age 40.6 ± 9.9 years; BMI 23.2 ± 2.0 m²), serum TSH is detected below the lower limit or slightly higher of the reference range (the normal reference range is 0.35–4.94 mIU/L), were defined as TSH suppression groups with normal free thyroxine (FT4) and free triiodothyronine (FT3). The last group, as the third (0.5 ≤ TSH < 2.0 mIU/L; 79 females, 11 males; mean age 38.8 ± 7.9 years; BMI 23.3 ± 2.0 m²), was defined as TSH replacement group. Two hundred seventy-one patients without any symptoms of cardiovascular disease and other major medical diseases were enrolled into this study after assessing their medical history, physical examination, basal and stress electrocardiography, blood chemistry, and hematology analysis. The main inclusion criteria were as follows:

1. Prior to surgical intervention, thyroid ultrasonography was performed and thyroid carcinoma was confirmed with fine needle aspiration biopsy (FNAB) and/or thyroid resection.
2. Patients with thyroid cancer were eligible for inclusion in the present study if they first had been treated with subtotal thyroidectomy, or hemithyroidectomy.
3. All patients were given levothyroxine for thyroid function replacement therapy or TSH suppression therapy after surgery with or without any radiotherapy within 1 year.
4. Body mass index lower than 30 kg/m², diastolic arterial blood pressure lower than 90 mmHg and systolic arterial blood pressure lower than 140 mmHg.

Exclusion criteria are as follows:

1. Subjects with any other major illness, including a history of clinically significant or uncontrolled cardiac disease were ineligible.
2. If those with incomplete demographic data about smoking, excessive alcohol drinking status, dyslipidemia, diabetes or family cancer history, were excluded.
3. In addition to an exclusion of TSH > 2.0 mIU/L, samples were excluded from this study if the participants had received any other medication within the past 3 months.

2.2. Heart rate variability measures

Twenty-four hours ECG monitoring was performed using a two-channel (leads CM2 and CM5) amplitude modulated tape recorder (Diagnostic Monitoring System, Santa Ana, CA). The time domain analysis of HRV included NN, SDNN, SDANN, rMSSD, and pNN50%. 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: LF: 0.04 to 0.15 Hz, HF: 0.16 to 0.40 Hz and 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 Cardio-vit 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. When U waves were present, 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, and differences were resolved by consensus.
2.4. Statistical analysis

The statistical software SPSS 26.0 (IBM SPSS Statistics V26.0) was used to statistically analyze the data in this study. Numerical data is shown as the mean value plus or minus the standard deviation (mean ± SD) and compared using the one-way analysis of variance (ANOVA) among groups. Spearman’s rank correlation test was performed to assess the significance of data trends. Multivariate linear regression analysis was performed to evaluate the effects of various variables, such as age, sex, BMI, and thyroid hormone levels on HRV, QTd, and QTcd. \( P < .05 \) was considered as statistically significant difference.

3. Results

3.1. Clinical parameters and thyroid function tests

Figure 1 shows the flow chart. Divided into three different groups according to serum TSH, a total of clinical parameters and thyroid function tests were measured in 271 subjects: low TSH level \( = 90 \) subjects \((0.05 \pm 0.02 \text{ mIU/L})\), medium TSH level \( = 91 \) subjects \((0.35 \pm 0.08 \text{ mIU/L})\) and high TSH level \( = 90 \) subjects \((1.05 \pm 0.24 \text{ mIU/L})\). Pre-group one and pre-group two was defined as TSH suppression groups, the third group was defined as TSH replacement group. No differences in other parameters, including BMI, systolic blood pressure, diastolic blood pressure, levels of fasting plasma glucose, total cholesterol, triglycerides, low density lipoprotein cholesterol, and high density lipoprotein cholesterol, were observed. HR increased as the level of TSH elevated in the experiment, but did not reach statistical significance. The TSH < 0.1 mIU/L group had the highest level of FT4 \((12.85 \pm 0.58, 12.82 \pm 0.40, \text{ and } 12.81 \pm 0.37 \text{ pmol/L, respectively; } P > .05)\), compared with the other two groups. The lowest FT3 \((4.31 \pm 0.50, 4.27 \pm 0.60, \text{ and } 4.14 \pm 0.63 \text{ pmol/L, respectively; } P > .05)\) was in TSH replacement group, followed by both two TSH suppression groups. But all patients had FT3 and FT4 level within the normal range, which showed no statistical difference. The baseline clinical characteristics of the patients in the TSH suppression groups and the euthyroid group are shown in Table 1.

3.2. HRV findings

Results of HRV obtained from 24h Holter recordings are reported in Table 2. Comparing with TSH replacement group, significant changes in both the time and frequency domain measures of HRV were observed in the TSH suppression groups, and these changes were more pronounced in the TSH < 0.1 mIU/L group. Obviously, in the time domain analysis of HRV, SDNN \((122 \pm 4, 128 \pm 7, \text{ and } 138 \pm 8 \text{ ms, respectively; } P < .001)\) and SDANN \((109 \pm 13, 115 \pm 10, \text{ and } 123 \pm 16 \text{ ms, respectively; } P < .001)\) and rMSSD \((42 \pm 8, 44 \pm 9, \text{ and } 45 \pm 7 \text{ ms, respectively; } P = .04)\) decreased, while there was no significant differences in PNN50 \((19 \pm 8, 21 \pm 7, \text{ and } 21 \pm 9 \%, \text{ respectively; } P = .17)\). The frequency domain indices showed that in the TSH < 0.1 mIU/L

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Liu et al. Medicine (2020) 99:28 www.md-journal.com

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Figure 1. Flow diagram. The chart shows patient inclusion and exclusion in the study. BMI = body mass index.
group LF/HF ratio (2.8 ± 0.4, 2.5 ± 0.3, and 2.1 ± 0.2, respectively; \( P < .001 \)) was the highest, while HF (332 ± 101, 379 ± 98, and 462 ± 125 ms\(^2\), respectively; \( P < .001 \)) the lowest. No significant difference was observed in LF (907 ± 238, 917 ± 215, and 945 ± 240 ms\(^2\), respectively; \( P = .53 \)). In addition, the findings are summarized in Figure 2. It can be seen that TSH is proportional to SDNN, while inversely proportional to LF/HF, one of the frequency domain indices. Interestingly, we had no difficulty seeing that lower TSH was accompanied by an increased HR (69.9 ± 3.8, 69.8 ± 5.6, and 69.0 ± 3.8 bpm, respectively; \( P > .05 \)) even though no noticeable differences were observed in data.

### 3.3. QT dispersion

QT max interval (QTmax) (398 ± 15, 393 ± 17, and 377 ± 22 ms, respectively; \( P < .001 \)) and QTc max interval (QTcmax) (429 ± 21, 423 ± 22, and 405 ± 29 ms, respectively; \( P < .001 \)) were greater in the TSH suppression group patients than in the TSH replacement subjects, whereas QT min interval (QTmin) (343 ± 15, 347 ± 16, and 341 ± 22 ms, respectively; \( P = .06 \)) and QTc min interval (QTcmin) (370 ± 20, 374 ± 21, and 366 ± 27 ms, respectively; \( P = .06 \)) were comparable. All the suppression groups patients showed increased QT dispersion (QTd) (55 ± 5, 46 ± 7, and 36 ± 4 ms, respectively; \( P < .001 \)) and QTc dispersion (QTcd) (59 ± 6, 50 ± 7, and 39 ± 5 ms, respectively; \( P < .001 \)) respect to replacement group subjects, furthermore, QTd and QTcd were positive relation to the TSH level in Table 3. Clearly, we could find that QTd and QTcd were proportional to the serum of TSH summarized in Figure 2 on average.

### 3.4. Multivariate linear regression analysis for HRV and QT dispersion

The effects of age, BMI, serum FT3, FT4, and TSH levels on some of HRV indicators and QT dispersion were examined in a multivariate linear regression analysis in the whole patients. It

### Table 1

| Clinical parameters and thyroid function tests in three groups (mean ± SD). |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | TSH < 0.1 mIU/L | 0.1 < TSH < 0.5 mIU/L | 0.5 < TSH < 2.0 mIU/L | Euthyroid       |
| n                               | 90              | 91              | 90              |                 |
| Age (years)                     | 39.8 ± 9.6      | 40.6 ± 9.9      | 38.8 ± 7.9      |                 |
| Sex (M/F)                       | 11/80           | 11/90           | 11/79           |                 |
| BMI (kg/m\(^2\))                | 23.5 ± 2.1      | 23.2 ± 2.0      | 23.3 ± 2.0      |                 |
| SBP (mm/Hg)                     | 119.3 ± 9.7     | 119.9 ± 7.4     | 118.8 ± 9.0     |                 |
| DBP (mm/Hg)                     | 78.5 ± 4.6      | 77.8 ± 4.9      | 77.2 ± 3.7      |                 |
| HR (bpm)                        | 69.9 ± 3.8      | 69.8 ± 5.6      | 69.0 ± 3.8      |                 |
| Glucose (mg/dL)                 | 5.2 ± 0.5       | 5.2 ± 0.5       | 5.2 ± 0.4       |                 |
| LDL-cholesterol (mg/dL)         | 102.5 ± 7.1     | 102.6 ± 5.2     | 101.8 ± 6.1     |                 |
| HDL-cholesterol (mg/dL)         | 53.6 ± 5.3      | 55.3 ± 5.3      | 54.3 ± 7.6      |                 |
| Total cholesterol (mg/dL)       | 179.7 ± 15      | 180.0 ± 4.5     | 181.8 ± 8.0     |                 |
| Triglycerides (mg/dL)           | 113.4 ± 10.1    | 116.1 ± 11.5    | 115.5 ± 8.6     |                 |
| FT3 (pmol/L)                    | 4.31 ± 0.50     | 4.27 ± 0.60     | 4.14 ± 0.63     |                 |
| FT4 (pmol/L)                    | 12.85 ± 0.58    | 12.82 ± 0.40    | 12.81 ± 0.37    |                 |
| TSH (mIU/L)                     | 0.05 ± 0.02\(b\) | 0.35 ± 0.08\(b\) | 1.05 ± 0.24     |                 |

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, F = female, HR = heart rate, M = male, BP = blood pressure, TSH = thyroid stimulating hormone.

No differences were observed in BMI, blood pressure, fasting glucose, lipid profile, HR, FT3, and FT4 (\( P > .05 \)).

\( ^a \) Significantly different than the 0.5 < TSH < 2.0 group at level 0.01 by post hoc tests.

\( ^b \) Significantly different than the 0.1 < TSH < 0.5 group at level 0.01 by post hoc tests.

### Table 2

#### The results of HRV in three groups (mean ± SD).

|                                | TSH < 0.1 mIU/L | 0.1 < TSH < 0.5 mIU/L | 0.5 < TSH < 2.0 mIU/L | P     | P for trend |
|---------------------------------|-----------------|-----------------|-----------------|-------|------------|
| SDNN (ms)                       | 122 ± 4\(b\)    | 128 ± 7\(c\)    | 138 ± 8         | <.001 | <.001      |
| SDANN (ms)                      | 109 ± 12\(c\)   | 115 ± 10        | 123 ± 16        | <.001 | .005       |
| rMSSD (ms)                      | 42 ± 5          | 44 ± 9          | 46 ± 7          | .04   | <.001      |
| PNN50(%)                        | 19 ± 8          | 21 ± 7          | 21 ± 9          | .17   | .04        |
| LF (ms\(^2\))                   | 907 ± 238       | 917 ± 215       | 945 ± 240       | .53   | .31        |
| HF (ms\(^2\))                   | 332 ± 101\(a\)  | 379 ± 98\(a\)   | 462 ± 125       | <.001 | <.001      |
| LF/HF (%)                       | 2.8 ± 0.4\(c\)  | 2.5 ± 0.3\(b\)  | 2.1 ± 0.2       | <.001 | <.001      |

Comparing with TSH replacement group, significant changes were observed on SDNN, SDANN, rMSSD, HF, and LF/HF of HRV in TSH suppression groups, and these changes were more pronounced in TSH < 0.1 mIU/L group, however, no difference was detected on PNN50 and LF/HF (\( P > .05 \)).

rMSSD = root mean square successive difference of NNs; SDNN = standard deviation of NNs.

\( ^a \) Significantly different than the 0.5 < TSH < 2.0 group at level 0.01 by post hoc tests.

\( ^b \) Significantly different than the 0.5 < TSH < 2.0 group at level 0.05 by post hoc tests.

\( ^c \) Significantly different than the 0.1 < TSH < 0.5 group at level 0.01 by post hoc tests.

\( ^d \) Significantly different than the 0.1 < TSH < 0.5 group at level 0.05 by post hoc tests.
was clear that the changes of QTd ($P < .001, \beta = -16.674$) and QTcd ($P < .001, \beta = -18.314$) caused by decreased TSH were far more significant than those due to other factors. In the multivariate regression analysis, serum TSH was one of the most important independent “predictors” of changes of QT disperse (Table 4). Additionally, using this same method of analysis, the direct effects of TSH on SDNN ($P < .001, \beta = 15.829$) and LF/HF ($P < .001, \beta = -0.671$) were showed, and FT3 ($P = .02, \beta = 1.546$) remained statistically significant in SDNN (Table 5).

4. Discussion

The measurements of HRV and QT dispersion may predict diabetes status, insulin resistance, metabolic syndrome and cardiovascular disease. HRV, recorded by 24h Holter electrocardiography, corresponds to the global variability of the heart rate, which caused by both the sympathetic and parasympathetic modulation of the heart. Lower time domain SDNN and SDANN values indicate greater sympathetic nervous system contribution to HRV as well as lower frequency domain LF values. The lower frequency domain HF values indicate less vagally mediated changes reflected on HRV as well as the lower time domain rMSSD and PNN50 values. LF/HF Indicates sympathovagal balance consistent with greater sympathetic activity. Our findings suggested that DTC patients with suppressed circulating TSH had a decreased HRV. Comparing to TSH replacement group, SDNN ($P < .001$) could be seen decreased and LF/HF ($P < .001$) increased obviously in two TSH suppressed groups in the present study. However, SDANN ($P < .001$) could be seen decreased only in the TSH < 0.1 mIU/L group. Given the functional significance of HRV, lower TSH level may have increased parasympathetic but decreased sympathetic activities. We also have provided evidence that HRV is positively correlated with TSH levels, when too low, associated with cardiovascular risk events and served as independent risk factors for cardiovascular disease. Eustatia-Rutten CF et al. showed that TSH was associated with HRV in DTC patients and were consistency with ours, and Kaminski G et al. reported HRV is a predictor of poor prognosis of myocardial infarction or cardiac failure in patients with subclinical hyperthyroidism.

In the present study of patients with DTC, there was no significant difference on PNN50 in three groups. PNN50 is mainly influenced by cardiac parasympathetic tone, therefore, we consider that serum TSH plays dominant roles of the sympathetic nerves not parasympathetic nerves. Besides this, maybe the results are associated with course of the disease, and we speculate the damage of vagus nerve had not been manifested in 1 year directly.

Table 3

The measurements of QT dispersion in three groups (mean ± SD).

| TSH suppression | Euthyroid |
|-----------------|----------|
| TSH < 0.1 mIU/L | 0.1 ≤ TSH < 0.5 mIU/L | 0.5 ≤ TSH < 2 mIU/L | $P$ | $P$ for trend |
| Qtmin (ms) | 343 ± 15 | 347 ± 16$^b$ | 341 ± 22 | .06 | .41 |
| Qtmax (ms) | 398 ± 15$^a$ | 393 ± 17$^a$ | 377 ± 22 | <.001 | <.001 |
| QTd (ms) | 55 ± 5$^a$ | 46 ± 7$^a$ | 36 ± 4 | <.001 | <.001 |
| QTcd (ms) | 370 ± 20 | 374 ± 21$^b$ | 366 ± 27 | .06 | .14 |
| Qtcmax (ms) | 429 ± 21$^a$ | 423 ± 22$^a$ | 405 ± 29 | <.001 | <.001 |
| QTd (ms) | 50 ± 6$^a$ | 50 ± 7$^a$ | 39 ± 5 | <.001 | <.001 |

QTd and QTcd were significant differences between TSH suppression groups and replacement group. TSH < 0.1 mIU/L and 0.1 ≤ TSH < 0.5 mIU/L group was no difference ($P > .05$).

$^a$ Significantly different than the 0.5 ≤ TSH < 2.0 group at level 0.01 by post hoc tests.

$^b$ Significantly different than the 0.5 ≤ TSH < 2.0 group at level 0.05 by post hoc tests.

$^c$ Significantly different than the 0.1 ≤ TSH < 0.5 group at level 0.01 by post hoc tests.
The QTD and QTdC are well-known electrocardiographic markers of an increase in the dispersion of ventricular repolarization. QT maximum value present in the area surrounding the lesion, a prolonged QT is considered a marker of ventricular electrical instability and a risk factor for ventricular arrhythmias and sudden death. Variations of QTd and QTCD were detected in three different TSH levels, furthermore, an inverse correlation was found between QT dispersion and TSH in patients. Our research also disclosed that QTd and QTCD prolonged in TSH <0.1mIU/L group compared with another two groups (P<.001). Previous studies discovered a statistically significant decreased HRV but increased QTd and QTCD in patients subclinical hyperthyroid and the present study was consistent with their results. Patients with DTC included in present study consisted of 33 males and 238 females within an age range from 20 to 70 years. Multivariate linear regression indicated that TSH level was a prognostic factor associated with arrhythmia and sudden death and had little correlation with the presence of age and BMI. Admittedly, there are reports indicating that increasing age is associated with decrease in HRV due to an age related decline in parasympathetic regulation. However, HRV occurring in the age range of the population that we studied is little. Thyroid cancer shows notable sex disparities, so gender was not included in final models and our results could not be influenced by bias. Previous research has been shown that the autonomic nervous system and its activity are not substantially influenced by gender. Further studies will be needed to verify above conclusions in a broader age range of patients.

Our data differed from these prior studies in that we did study all patients with homogeneity, we would like to argue that the present study was sufficiently powered for most of the parameters. We feel that our approach, in which the suppression to different TSH levels in a homogenous group of patients with exogenous subclinical hyperthyroidism was studied in a seemingly sufficiently powered retrospective experiment, is the most appropriate approach to study the effects of HRV and QT dispersion on patients.

In conclusion, the present study showed that TSH level was proportional to SDNN, but inversely proportional to LF/HF, QTd, and QTCD in DTC patients with exogenous levothyroxine. Thus, we conclude TSH may directly modulate HRV and ventricular repolarization. Moreover, the assessments of HRV and QT dispersion provide us a useful method for monitoring the cardiovascular risk and supporting the decision of treatment in patients with DTC.

Acknowledgments

We thank the patients and their families for consenting use their medical documentations and information that lead to our paper.

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