Altered cardiovascular vagal responses in nonelderly female patients with subclinical hyperthyroidism and no apparent cardiovascular disease

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Introduction

Subclinical hyperthyroidism can be defined as a serum thyrotropin (TSH) level below the lower limit of the reference range with normal thyroid hormone levels (free thyroxine (free T4) and triiodothyronine (T3). Euthyroid sick syndrome, central hypothyroidism, pregnancy, advanced age and the use of drugs that could suppress TSH must be excluded.1-4

There is not enough evidence to support the need for immediate treatment in all patients who present with these laboratory changes, although there are many studies suggesting an increased cardiovascular morbidity and mortality in some patients. In patients over 60 years old there is increased risk of atrial fibrillation,5,6 and increased mortality from cardiovascular causes within 5 years (not sustained in the 10-year analysis).7 In middle-aged and elderly patients with suppressed postradioiodine TSH levels after treatment of hyperthyroidism, mortality does not seem to be increased.8 Nevertheless, when symptomatic young, middle-aged and elderly patients have been grouped together, some morphological and functional cardiac alterations have been described, such as increased left ventricular mass index (without hypertrophy),9 increased interventricular septum and left ventricular posterior wall thickness and decreased diastolic function;10-14 increased mean heart rate (HR) and increased frequency of atrial extra-systoles; decreased exercise performance;13,15 increased intimal carotid thickness16 and sympathovagal imbalance.17-20 A study with asymptomatic patients showed only increased left ventricular mass and a higher mean HR,21 and another one with nonelderly patients showed no exercise performance impairment.22

Autonomic nervous system dysfunction plays an important role in the susceptibility to cardiac arrhythmias.23 Classically, the adrenergic tone is enhanced in hyperthyroidism,24 and catecholamine levels may be normal or increased.25,26 There is a sympathovagal imbalance at rest, with a decreased vagal tone.26

Cardiovascular autonomic disturbance is a mortality predictor in postacute myocardial infarction patients27,28 and in diabetes mellitus.28 To assess its role in the mortality rate of subclinical hyperthyroid patients, it would be necessary to perform long-term studies. There is no information on the influence of this dysfunction in nonelderly patients with no cardiac disease.

Summary

Objective Subclinical hyperthyroidism (SH) has been associated with exercise intolerance, changes in cardiac morphology, atrial arrhythmias and sympathovagal imbalance. The aim of this study was to evaluate the vagal reserve and modulation by a sympathetic stimulus in nonelderly patients with SH without cardiovascular problems.

Design We carried out a cross-sectional study, comparing data of the heart rate variability (HRV) of SH patients and healthy controls at rest and after vagal and sympathetic stimulation.

Patients We studied 16 female patients with at least 6 months of SH and 16 healthy female controls with the same median age (40 vs. 34-5 years).

Measurements We used the tilt test, with electrocardiographic record at rest, during the respiratory sinus arrhythmia (RSA) manoeuvre and after tilting, in order to analyse HRV in the frequency domain (%high frequency (HF) and low/high frequency ratio (LF/HF)) using Biopotentials Captation System software.

Results The median TSH level was 0·03 mU/l in patients and 1·37 mU/l in controls. The median free T4 was 1·37 ng/dl in patients and 1·20 ng/dl in controls. Patients demonstrated a significantly smaller difference between %HF during the RSA and %HF at rest than controls (median –7·5 vs. 36·6, P < 0·001). There was a lower difference between LF/HF ratio after tilting and LF/HF ratio at rest in patients than in controls (1·5 vs. 5·3, P = 0·005).

Conclusion Subclinical hyperthyroidism affects cardiovascular autonomic balance in otherwise apparently healthy nonelderly females by blunting vagal responses.

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Heart rate variability (HRV) has been established as a reliable and reproducible marker of cardiovascular autonomic function. We chose HRV to assess cardiovascular autonomic system function (vagal reserve and sympathovagal balance after a sympathetic stimulus) in a sample of subclinical hyperthyroid patients without previous cardiovascular disease.

Materials and methods
A cross-sectional study was carried out. Files of adult patients followed at our endocrine clinic for subclinical hyperthyroidism were reviewed (n = 70). We excluded those without subclinical hyperthyroidism for at least 6 months (TSH serum levels below the lower reference limit and normal free T4 and T3 serum levels), patients with any chronic illness (especially cardiovascular, including hypertensive patients, even if treated), patients taking drugs that could interfere with the thyroid status or with the cardiovascular system, and patients ≥ 60 years. The remaining 16 patients had a 24-h Holter register free from arrhythmias, a normal echocardiogram and absence of myocardial ischaemia and a normal exercise performance for age, gender and body mass index (BMI). The signals were collected and stored on a hospital bed and were monitored with disposable electrodes in 12 incursions per min (over 2 min), to provoke a vagal response. The control group comprised 16 healthy female subjects from an outpatient population with similar socioeconomic status. Patients and controls signed an informed consent, approved by the local ethics committee.

Both groups were submitted to the tilt test. The HRV was analysed in the electrocardiographic register obtained at rest and after simple manoeuvres designed to elicit sympathovagal responses. They were instructed to come in on the morning of the test after a 6-h fast and were led to an acclimatized and sound-proof room, where they laid on a hospital bed and were monitored with disposable electrodes in Frank’s orthogonal derivations. The signals were collected and stored in a personal computer.

The software used to process the data was the Biopotentials Captation System, developed by Barbosa in 1997, which allows the examiner to eliminate QRS complexes with artefacts, to measure the HRV in the time and frequency domains. The method was validated for reproducibility in the same publication and has been used in other studies.

After 5 min of rest, the patients underwent the respiratory sinus arrhythmia (RSA) manoeuvre, with a controlled respiratory rate of 12 incursions per min (over 2 min), to provoke a vagal response. They remained supine until 20th min, when the bed was tilted to 70 degrees, and a sympathetic response was expected.

The frequency domain was analysed: the parameters used were the high frequency percentage (%HF), which represents the vagal component of the cardiovascular autonomic nervous system related to total power, and the low frequency: high frequency ratio (LF/HF ratio), which represents the sympathovagal balance. The HF and LF were measured in normalized units, which represent the relative value of each power component in proportion to the total power. The vagal reserve was measured by the increment in %HF during the RSA manoeuvre compared to rest. The vagal modulation of the sympathetic component was calculated by the increment in LF/HF ratio in the first 5 min after tilt compared to rest, where the greater differences reflect the best responses. We chose not to analyse time-domain parameters because they would be less reliable and less robust if any patient developed an atrial arrhythmia during the exam (which did not happen).

Serum TSH was measured by an immunometric assay (Immulus-DPC, Los Angeles, CA), with a reference range of 0.4–4.0 mU/l and a sensitivity of 0.002 mU/l. The serum free T4 and the serum total T3 were measured by chemoluminescence (Immulus-DPC), with a reference range of 0.8–1.9 ng/dl and 86–187 ng/dl and a sensitivity of 0.15 ng/dl and 7 ng/dl, respectively.

For statistical analysis we used the Stata software (version 8.0, 2003) and CIA software. Median values with interquartile range (IQR) were reported because of the skewed distribution of data. Variables were compared by the Mann–Whitney U-test. We also presented 95% confidence intervals for the median differences.

We calculated Spearman’s rank correlation coefficients to evaluate the correlation between %HF (at rest, during the RSA manoeuvre and after orlothostatism) and the following explanatory variables: TSH level, free T4 level and time since diagnosis. We also calculated Spearman’s rank correlation coefficients to evaluate the correlation between the formerly mentioned explanatory variables and the variation (Δ = RSA manoeuvre–rest) of %HF. Finally, we evaluated the correlation between LF/HF ratio, after orlothostatism and at rest, and the same explanatory variables. A P-value < 0.05 was accepted as significant for all analyses in the study.

Results
Patients had a median age of 40 years (IQR, 34–46) and a median BMI of 26.5 kg/m² (IQR, 25–27). The median time since diagnosis was 4 years (IQR, 1.9–9.5 years). There was one smoker (who smoked 30 packs/year) and all patients had a sedentary lifestyle. There were four patients with exogenous subclinical hyperthyroidism (treated papillary thyroid carcinoma) and 12 patients with endogenous subclinical hyperthyroidism (three patients with multinodular goitres, two patients with hyperfunctioning adenomas and seven patients with diffuse goitres). The median serum TSH was 0.05 mU/l (IQR, 0.01–0.14), the median serum free T4 was 1.37 ng/dl (IQR, 1.03–1.58) and the median serum T3 was 151.5 ng/dl (IQR, 127.5–168) (Table 1). The control group had a median age of 34.5 years (IQR, 30.4–40.5) and a median BMI of 24.8 kg/m² (IQR, 21.3–29.1). There were two smokers (who smoked 20 and 27.5 packets/year, respectively) and all were sedentary. The median serum TSH was 1.37 mU/l (IQR, 1.09–2.51) and the median serum free T4 was 1.20 ng/dl (IQR, 1.13–1.33) (Table 1).

There was no statistically significant difference between median age, BMI and serum free T4 between groups. The patients had a lower median serum TSH (P < 0.001).

At rest, the median %HF in patients was 16.3% (IQR, 12.5–70.4) and in controls, 17.8% (IQR, 10.5–24.5), P = 0.42. During the RSA manoeuvre, the median %HF in patients was 7.5% (IQR, 5.2–40.8) and in controls, 51.1% (IQR, 43.0–70.2), P < 0.001. After orthostatism, the median %HF in patients was 13.2% (IQR, 5.8–40.4) and in controls it was 4.7% (IQR, 2.7–8.9), P = 0.002 (Table 2).

There was a decrease in %HF in patients after the RSA manoeuvre (median −7.5, IQR, −25.4 to −4.3) and an increase in controls (median 36.6, IQR, 20.3–48.2), P < 0.001 (Table 2).

At rest, the median LF/HF ratio was 1.3 (IQR, 0.1–3.0) in patients and 2.3 (IQR, 1.3–3.4) in controls (P = 0.1). During the RSA
There was no correlation between serum TSH, serum free T4 or time since diagnosis and the %HF (at rest, during the RSA manoeuvre or after orthostatism) or the LF/HF ratio (at rest, during the RSA manoeuvre or after orthostatism). The same applied when we tried to find a correlation between the former variables and the differences between the %HF during the RSA manoeuvre and at rest or the LF/HF ratio after orthostatism and at rest.

### Discussion

This study presents strong evidence that, even in nonelderly female patients with subclinical hyperthyroidism and no apparent heart disease or cardiac changes attributable to the subclinical hyperthyroid state, the cardiovascular vagal modulation is affected. This was demonstrated by the reduced vagal reserve after the RSA manoeuvre (paradoxical decrement in %HF in patients compared to an increment in controls) and by the blunted vagal response to a sympathetic stimulus (lower increase in the LF/HF ratio after passive orthostatism compared to the healthy controls). Patients and controls had the same vagal status at rest.

Three other studies used heart rate variability to assess cardiac autonomic function in endogenous subclinical hyperthyroid patients and found some alterations. Petretta et al. analysed the 24-h Holter register of 30 patients at the National Research Council cybernetics laboratory and found reduced time-domain parameters compared to controls and a small low frequency power in frequency domain, without difference in the LF/HF ratio. Osman et al. subjected 110 patients to a 24-h Holter register, with time-domain analysis using the Pathfinder 700 series analyser (Reynolds Medical), and found a reduction in some time-domain parameters and an altered heart rate turbulence. Only one study used approximately the same methodology as ours: Goichot et al. performed a 20-min electrocardiogram in the supine position followed by a 15-min register after standing in 12 patients and found reduced time-domain parameters and no differences between patients and controls in the frequency domain at rest (LF, HF and LF/(LF+HF)); after standing, patients had a decrease in the time-domain parameters and a predominance of the sympathetic component of the autonomic nervous system in the frequency domain caused by a reduced vagal influence (increase in LF/(LF+HF) and diminished (HF). The last response was different from our result, showing that those patients still had a physiological response to active orthostatism and the response to RSA (vagal reserve) was not evaluated. The software used for the analysis was not specified.

The three studies pointed towards vagal tone reduction at rest. The three studies pointed towards vagal tone reduction at rest.
be accurately given in the endogenous subclinical hyperthyroidism subgroup, although it is an important parameter.

Only three of our patients had responses similar to controls in the tests performed. These three patients presented no distinguishing features that might explain this normal behaviour: two had a diffuse goitre, diagnosed 4 years ago and one had a treated papillary thyroid carcinoma, diagnosed 11 years ago. This could represent milder disease, as two of them (endogenous cases) had TSH serum levels >0.1 mUI/l (of a total of six) and the other patient had a TSH serum level <0.1 mUI/l (as did nine nonresponsive patients).

Cardiovascular sympathovagal imbalance renders a worse prognosis to diabetic and postacute myocardial infarction patients. Atrial arrhythmias are more frequent in subclinical hyperthyroidism and point towards a possible early therapeutic intervention.

References


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