# Clinical aspects of endogenous hypothyroidism and subclinical hyperthyroidism in patients with differentiated thyroid carcinoma

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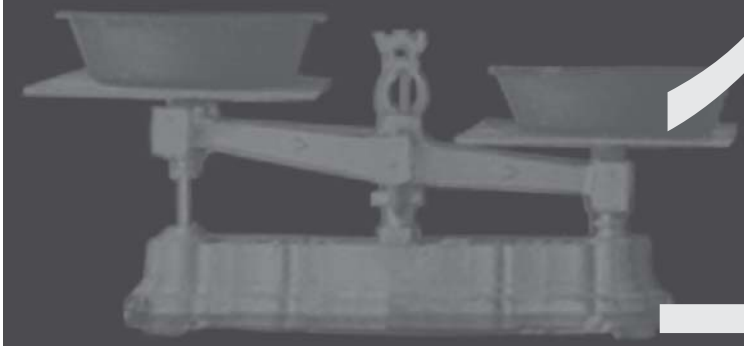

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# Short-term overt hypothyroidism induces sympathovagal imbalance in thyroidectomized differentiated thyroid carcinoma patients

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## Abstract

*Context:* Thyroid hormone impacts on the cardiovascular system. (Subclinical) Hyperthyroidism results in sympathovagal imbalance due to a decreased vagal tone. However, conflicting data have been reported on the effects of hypothyroidism on the activity of the autonomic nervous system (ANS). In hypothyroidism; both increased and decreased sympathetic activity and an increased vagal tone have been found.
*Objective:* To study the effects of acute short term overt hypothyroidism and thyroxin replacement therapy on the ANS by measuring urinary excretion of catecholamines and heart rate variability (HRV).
*Design:* Prospective study
*Setting:* University hospital
*Patients:* We studied 11 patients, previously treated by thyroidectomy for differentiated thyroid carcinoma during hypothyroidism caused by cessation of thyroxin substitution for 4 weeks and during thyroxin replacement therapy and 21 matched healthy controls.
Main outcome measures: The activity of the ANS was assessed by measuring urinary excretion of catecholamines and HRV in rest and during a challenge of the ANS by a mental stress test.
*Results:* Urinary dopamine excretion was significantly lower during hypothyroidism. Although in the patients total variability was unchanged, HRV analysis showed a significantly lower LF/HF ratio, indicating sympathovagal imbalance with sympathetic withdrawal. The mental stress test in the patients resulted in a significant increase in heart rate of 16-18%. This response was not different between the hypothyroid state and during thyroxin replacement therapy suggesting that cardiovascular reflexes in these patients remain intact.
*Conclusion:* Acute short-term overt hypothyroidism results in sympathovagal imbalance with sympathetic withdrawal with preservation of the cardiovascular reflexes to (mental) stress.

## Introduction

Changes in thyroid hormone concentrations influence the cardiovascular system. Both overt and subclinical hyperthyroidism have been associated with cardiac arrhythmias, left ventricular hypertrophy, diastolic dysfunction and increased systolic function (1-5). In addition, (subclinical) hyperthyroidism results in sympathovagal imbalance with increased sympathetic activity and a decreased vagal tone (6-12). Osman et al. found decreased vagal modulation during overt hyperthyroidism which persisted when patients became in the subclinical hyperthyroid state (13). In contrast, in hypothyroidism bradycardia, decreased cardiac output, diastolic cardiac dysfunction, mild diastolic hypertension, and increased peripheral cardiovascular resistance are observed (2;14-16). Acute short-term hypothyroidism shows similar cardiovascular abnormalities as in chronic hypothyroidism including bradycardia, diastolic dysfunction, impaired systolic function during effort and increased systemic vascular resistance (17). Although hypothyroidism has also been associated with sympathovagal imbalance (18-20), current literature shows conflicting results with either increased sympathetic activity (18), decreased sympathetic modulation (19) or an increased vagal tone in hypothyroidism (20). These differences can be due to the heterogeneity of the study populations regarding the cause and duration of hypothyroidism. Patients with differentiated thyroid carcinoma (DTC) being withdrawn from thyroxin for diagnostic purposes represent an excellent group to study the effects of acute short-term hypothyroidism on the autonomic nervous system. Only one study has documented the consequences of hypothyroidism on the autonomic nervous system in this situation. (21) In that study, however, no healthy controls were studied. In addition, the response to a challenge of the autonomic nervous system, which seems to reveal the most prominent differences in the autonomic nervous system during (subclinical) hyperthyroidism (9;11;22), was not studied in these hypothyroid patients. We therefore conducted a study on the autonomic nervous system in DTC patients during acute short-term hypothyroidism and subsequently during treatment with thyroxin, and compared these to healthy age-, gender- and BMI-matched controls. We studied urinary catecholamine excretion and heart rate variability measurements at rest and during a mental stress test (23).



## Materials and methods

*Subjects*

Patients were recruited from the outpatient clinic of the Department of Endocrinology of Leiden University Medical Centre, which is a tertiary referral centre for differentiated thyroid carcinoma. Patients were included who had been diagnosed with DTC and had received initial therapy consisting of total-thyroidectomy and radio iodine ablation therapy. Additional therapies were allowed, as long as they resulted in cure. Cure was documented by the absence of measurable serum thyroglobulin (Tg) during TSH stimulation as well as by a negative total-body scintigraphy with 4 mCi 131-I.

Patients who had cardiovascular diseases, diabetes mellitus, other endocrine diseases or had a BMI >35 kg/mm2 were excluded. Patients who used any drug known to influence the heart rate variability were also excluded. The local ethics committees approved the study and written informed consent was obtained from all subjects.

*Study design*

Eleven consecutive patients with DTC undergoing TSH stimulated I-131 scan were asked to participate in the study. Four weeks after thyroxin withdrawal and 8 weeks after restarting thyroxin replacement, patients were admitted to the clinical research unit. For each patient, two healthy age-, gender- and BMI-matched controls were included. Subjects handed in the urine collected over the previous 48 hours. Subjects were asked to follow a diet free of potential catecholamine stimulating food or medication (excluding coffee, alcohol, bananas, nuts and paracetamol) from two days before and during urine collection. All subjects fasted from the preceding evening (18.00 hr) until the end of the study. On the study day, at 08.00 hr, height (meters [m]), weight (kilograms [kg]) and BMI (weight [kg]/height2 [m]) were measured. Plasma samples were collected for measurement of FT4, TSH and FT3. Plasma samples were handled immediately and stored at –20o C in Sarstedt tubes.

*Heart rate variability*

At least 30 minutes after blood sampling, a continuous ECG registration was made while the subject was in supine position for at least 15 min. The measurements consisted of a 1-lead electrocardiogram (ECG) registration (recording 600 subsequent beats). The subjects were instructed to relax, to breathe regularly, not to speak and to stay awake. The ECG signal was sampled at a rate of 500 Hz, digitized using a customized laboratory interface (model 1401, Cambridge Electronic Design, Cambridge, UK), and analyzed with software supplied with the interface. Each registration was screened for artefacts and subsequently analyzed for HRV parameters in the time domain: mean RR-interval (RR-int), the coefficient of variation (CV) of the successive RR-intervals (reflecting total variability), and the standard deviation of differences between adjacent R-R intervals (SDSD) reflecting “beat-to-beat” variability) as previously described (6) and according to the applicable guidelines (24). The registrations were also analyzed with HRV Analysis Software 1.1 for windows developed by The Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland. The software is distributed free of charge upon request (http://venda.uku.fi/research/biosignal), and conforms with the same guidelines (27). The power spectra were analyzed for the Low Frequency (LF) and high frequency (HF) components and are expressed as normalized units. Upon completion of the recording at rest, another 5-min recording was started during which the patients were subjected to a mental stress test (23). During this test the subjects had to perform a standardized arithmetic test with which they had been familiarized before. The registration made during this test was used to determine the percentage increase in heart rate from baseline. This test was not performed in the healthy controls as the increase in heart rate reported in the literature in healthy subjects is always between 15 and 25% (25-28) and this is also the case in our experience (data on file at CHDR).

*Assays*

All plasma and serum samples were measured in one batch. Serum free thyroxin (FT4) and TSH were measured with an electrochemoluminescentic immunoassay with a Modular Analytics E-170 system with an intraassay CV of 1.6-2.2 % and 1.3-5.0 % respectively (Roche, Almere, The Netherlands). Serum free thyronine (FT3) was measured with a fluorescentic polarisatic immunoassay, CV 2.5-9.0 %, on an ImX system (Abbott, Abbott Park, IL, USA). Reference values for FT4, FT3 and TSH are respectively 10-24 pmol/L, 3.9-6.7 pmol/L and 0.4-4.8 mU/L. Urinary excretion of norepineprhine, epinephrine and dopamine were determined by routine HPLC methodology.

*Statistical Analyses*

Values are expressed as mean ± SD. Data between subjects were analyzed with the paired samples t-test. Data between DTC patients and control group was analyzed with the independent t-test. Differences were considered statistically significant at P<0.05. SPSS 12.0 for windows was used for statistical analyses (SPSS. Inc., Chicago, IL, USA).

## Results

*Patient characteristics*

Eleven patients were included (4 male, 7 female). Mean age was 45.5 ± 10.0 years and BMI was 28.1 ± 4.2 kg/m2. All patients had been treated by total thyroidectomy followed by radioiodine ablation. Median (range) duration after initial therapy was 1.3 (0.6-24.3) years. Before thyroxin withdrawal the majority of patients was receiving TSH suppressive therapy (n=8). Three patients were receiving thyroxin replacement therapy, because their duration after initial therapy was more then 15 years. None of the patients had recurrent disease. Thyroid hormone levels are presented in table 1. All patients were overtly hypothyroid during the first study day, 4 weeks after withdrawal of thyroxin replacement therapy. Eight weeks after restarting thyroxin replacement therapy, six patients had thyroid parameters within the reference range, whereas 5 patients had a TSH below the reference range with normal plasma T3 and T4 levels. Mean thyroxin dose was 197 ± 42 mg/day. Diastolic blood pressures were significantly higher during the hypothyroidism state (84 ± 0 vs. 79 ± 6 mm Hg, p=0.0049), whereas systolic blood pressures were not significantly different.

Table 1. Thyroid hormone levels and urinary catcholamine excretion in 24 h urine collections

| | Overt hypothyroidism | Thyroxin replacement | P-value |
|---|---|---|---|
| TSH (Mu/L) | 142.4 ± 34.4 | 0.8 ± 1.0 | <0.001 |
| FT4 (pmol/L) | 1.4 ± 0.7 | 24.8 ± 4.06 | <0.001 |
| FT3 (pmol/L) | 0.1 ± 0.2 | 4.8 ± 0.8 | <0.001 |
| BMI (kg/m$^2$) | 28.08 ± 4.19 | 27.41 ± 4.42 | 0.004 |
| BP systolic (mm Hg) | 121 ± 6 | 123 ± 11 | 0.460 |
| BP diastolic (mmHg) | 84 ± 9 | 79 ± 6 | 0.049 |
| Norepineprhine (µmol/mmol creatinine) | 25.1 ± 10.0 | 23.6 ± 11.4 | 0.690 |
| Epinephrine (µmol/mmol creatinine) | 1.6 ± 1.2 | 2.8 ± 2.2 | 0.064 |
| Dopamine(µmol/mmol creatinine) | 97 ± 33 | 132 ± 48 | 0.016 |

*Paired samples t-test. Data are expressed as mean ± SD*

*BMI= body mass index, BP=blood pressure*

*Urinary catecholamine excretion*

Urinary catecholamine excretion (normalized for creatinine excretion) is summarized in Table 1. Urinary excretion of dopamine was significantly lower during hypothyroidism compared to thyroxin replacement (97 ± 33 vs. 132 ± 048 µmol/mmol creatinine, p=0.016). Urinary epinephrine and norepinephrine excretion rates were not significantly different.

Table 2. Parameters of heart rate variability during hypothyroidism and thyroxin replacement therapy

| | Overt hypothyroidism (n=11) | Thyroxin replacement (n=11) | P-value |
|---|---|---|---|
| RR-interval (ms) | 1074 ± 123 | 948 ± 156 | 0.003 |
| CV (%) | 4.3 ± 2.3 | 4.4 ± 1.8 | 0.767 |
| SDSD (ms) | 40.1 ± 33.7 | 32.3 ± 19.7 | 0.159 |
| LF (nu%) | 54.7 ± 22.7 | 67.4 ± 14.5 | 0.050# |
| HF (nu%) | 45.6 ± 22.7 | 32.6 ± 14.5 | 0.081# |
| LF/HF | 2.20 ± 1.80 | 2.56 ± 1.33 | 0.041# |

*Data are expressed as mean ± SD*

*CV: coefficient of variation; SDSD: standard deviation of the successive differences in RR-intervals; LF: power in low frequency band; HF power in high frequency band; LF/HF: ratio of power in low frequency band over power in high frequency band*

*# p-value for log-transformed variables*

### *Heart rate variability*

Parameters of heart rate variability are presented in Table 2. The RR-interval was significantly prolonged during hypothyroidism compared to during thyroxin replacement (1074 ± 123 vs. 948 ± 156 ms, p=0.03). Total variability (represented by the CV) and SDSD were not significantly different between hypothyroidism and thyroxin replacement. Frequency domain analysis showed that LF tended to be lower during hypothyroidism (54.7 ± 22.7 vs. 67.4 ± 14.5 nu, p=0.050) during hypothyroidism compared to thyroxin replacement. The LF/HF power ratio was significantly lower during hypothyroidism compared to thyroxin replacement therapy (p=0.042).

### *Mental stress test*

The mental stress test produced a significant increase in heart rate of 16 ± 11% in the hypothyroid state and 18 ± 14.0% during thyroxin treatment. The response did not differ between the two conditions (p= 0.377) and has the same order of magnitude as previously reported for healthy subjects (25-28).

Table 3. Parameters of heart rate variability between patients and controls

| | Thyroxin replacement (n=11) | Control group (n=21) | P-value |
|---|---|---|---|
| RR-interval (ms) | 948 ± 156 | 863 ± 124 | 0.118 |
| CV (%) | 4.4 ± 1.8 | 3.5 ± 1.5 | 0.121 |
| SDSD (ms) | 32.3 ± 19.7 | 27.4 ± 18.6 | 0.517 |
| LF (nu%) | 67.4 ± 14.5 | 54.0 ± 22.0 | 0.037# |
| HF (nu%) | 32.6 ± 14.5 | 46.0 ± 22.0 | 0.141# |
| LF/HF | 2.56 ± 1.33 | 1.83 ± 1.69 | 0.112# |

*Data are expressed as mean ± SD*

*CV: coefficient of variation; SDSD: standard deviation of the successive differences in RR-intervals; LF: power in low frequency band; HF power in high frequency band; LF/HF: ratio of power in low frequency band over power in high frequency band*

*# p-value for log-transformed variables*

*Comparison between controls and patients*

Comparisons were made between patients on thyroxin substitution and healthy controls. The control group consisted of 8 men and 14 women. One male subject was excluded because the ECG recording had too many artefacts to be analyzed properly. Mean age was 45.5 ± 8.7 years and mean BMI was 28.3 ± 4.3 kg/m2, which was not different compared to controls. There were no differences in the RR-interval or CV between patients and controls (Table 3). The LF component was significantly higher in patients compared to controls, whereas there were no differences in LF component or the LF/HF ratio between patients and controls.

## Discussion

We investigated the impact of acute short-term hypothyroidism and restoration to subclinical hyperthyroidism on the autonomic nervous system in thyreoidectomized patients with DTC by measuring urinary catecholamine excretion and heart rate variability at rest and in response to a mental stress test.

Heart rate was significantly lower during hypothyroidism compared to thyroxin replacement therapy and controls. As expected, the RR-interval was significantly prolonged during hypothyroidism in the patients. The LF/HF power ratio, representing sympathovagal balance with lower levels suggesting sympathetic withdrawal (24), was significant lower during hypothyroidism compared to thyroxin replacement therapy, indicating sympathovagal imbalance with sympathetic withdrawal. The LF component tended to be lower during hypothyroidism compared to thyroxin replacement therapy. Although the LF component is associated with both sympathetic and vagal activity (24), other studies report that the LF component, especially when expressed in normalized units, reflects sympathetic activity (8;24;29). Our findings are consistent with some studies (19-21;30), but at odds with two other studies which reported a decreased LF/HF power ratio with an increased LF component and a decreased HF component in hypothyroid patients (18;19). We hypothesize that the discrepancies between the different studies may be explained by differences in duration, cause and severity of hypothyroidism as in these studies patients with hypothyroidism caused by Hashimoto thyreoiditis were investigated, whereas we studied thyreoidectomized patient with DTC with a controlled duration and degree of hypothyroidism. Our patients did not have any endogenous thyroid hormone production and therefore represent a unique model population to study controlled hypothyroidism.

In our study, the LF component was significant higher in patients compared to controls, whereas there were no differences in the HF component and the LF/HF power ratio between the patients compared to healthy controls. Other studies reported sympathovagal imbalance with increased sympathetic activity and a decreased vagal tone during (subclinical) hyperthyroidism characterized by an increased LF component (expressed in normalized units) and a decreased HF component resulting in an increased LF/HF power ratio (6-13),13. Possible explanations for the fact that the HRV spectrum had characteristics of hyperthyroidism despite normal mean TSH levels could be that the patients in the present study were treated for a long period (5.0 ± 7.1 years) with TSH suppressive thyroxin replacement therapy preceding the present study and it is plausible that irreversible changes or adaptation of the autonomic nervous were present. This would concur with other recent findings of our group which showed that long-term subclinical hyperthyroidism affects the autonomic nervous system and that these changes persist even after a 6 months-period of restoration to euthyroidism (31).

It has been suggested that the VLF component reflects influences on heart rate variability mediated by thermoregulatory and angiotension-mediated mechanisms (32). We noticed a substantial difference between patients and controls. In controls, the absolute VLF power (92 ± 115 ms2) was much lower than in the patients (208 ± 152 ms2 when hypothyroid and 321 ± 369 ms2 when on thyroxin replacement therapy). It may well be that this difference in the contribution of the VLF frequency band influenced our findings on the LF and HF component. We suggest that investigations in the VLF component should receive more attention in patients with thyroid disorders.

To our knowledge, this is the first report showing that the cardiovascular adaptation mediated by the autonomic nervous system during mental stress is preserved in thyreoidectomized patients irrespective of a hypothyroid state or when on thyroxin replacement. Apparently, short term thyroid hormone withdrawal is not crucial in the (short-term) reflex-mediated cardiovascular regulation as indicated by the mental stress test.

Urinary excretion of dopamine was significantly lower during hypothyroidism. This is consistent with the results reported by Guasti et al (21). There were no differences in urinary excretion rates of norepinephrine and epinephrine.

In conclusion, acute short-term hypothyroidism in thyreoidectomized DTC patients results in a sympathovagal imbalance with sympathetic withdrawal. This, however, does not compromise the ability of the cardiovascular system to react normally to a (short-term) challenge of the autonomic nervous system.

# 10 Autonomic Nervous System during hypothyroidism

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