Sympathovagal imbalance in hyperthyroidism


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Received 20 September 2000; accepted in final form 16 March 2001

Burggraaf, J., J. H. M. Tulen, S. Lalezari, R. C. Schoemaker, P. H. E. M. De Meyer, A. E. Meinders, A. F. Cohen, and H. Pijl. Sympathovagal imbalance in hyperthyroidism. Am J Physiol Endocrinol Metab 281: E190–E195, 2001.—We assessed sympathovagal balance in thyrotoxicosis. Fourteen patients with Graves’ hyperthyroidism were studied before and after 7 days of treatment with propranolol (40 mg 3 times a day) and in the euthyroid state. Data were compared with those obtained in a group of age-, sex-, and weight-matched controls. Autonomic inputs to the heart were assessed by power spectral analysis of heart rate variability. Systemic exposure to sympathetic neurohormones was estimated on the basis of 24-h urinary catecholamine excretion. The spectral power in the high-frequency domain was considerably reduced in hyperthyroid patients, indicating diminished vagal inputs to the heart. Increased heart rate and mid-frequency/high-frequency power ratio in the presence of reduced total spectral power and increased urinary catecholamine excretion strongly suggest enhanced sympathetic inputs in thyrotoxicosis. All abnormal features of autonomic balance were completely restored to normal in the euthyroid state. β-Adrenoceptor antagonism reduced heart rate in hyperthyroid patients but did not significantly affect heart rate variability or catecholamine excretion. This is in keeping with the concept of a joint disruption of sympathetic and vagal inputs to the heart underlying changes in heart rate variability. Thus thyrotoxicosis is characterized by profound sympathovagal imbalance, brought about by increased sympathetic tone and increased parasympathetic tone as opposed to increased sympathetic tone, determines autonomous imbalance associated with hyperthyroidism (9).

Power spectrum analysis (PSA) of heart rate fluctuations is a sensitive, quantitative, and noninvasive measure of sympathovagal balance in humans (1). Recent studies employing PSA confirmed the hypothesis that thyroid hormone excess is associated with a reduction of parasympathetic tone (3, 10). However, although PSA allows rather accurate quantification of vagal inputs to the heart and also measures sympathovagal balance, it is less suitable for determination of absolute sympathetic tone in recumbent subjects. It is conceivable that reduced vagal activity and increased sympathetic tone perturb the autonomic balance in hyperthyroidism.

This study was performed to further elucidate the activities of the two major components of the autonomic nervous system in hyperthyroidism. We hypothesized that autonomic imbalance in hyperthyroid patients is caused by the joint effects of reduced parasympathetic tone and increased sympathetic activity. PSA was used to determine vagal inputs to the heart in hyperthyroid patients. In addition, 24-h urinary catecholamine excretion was used to estimate systemic exposure to sympathetic neurohormones. The effect of β-adrenergic receptor blockade on sympathovagal balance was evaluated to further assess the contribution of the sympathetic nervous system. Finally, autonomic balance in response to reestablishment of euthyroidism was measured.

SUBJECTS AND METHODS

Subjects. Newly diagnosed, untreated hyperthyroid patients were recruited from the outpatient clinic of the Department of Internal Medicine of Leiden University Medical Center. The diagnosis of Graves’ disease was established on the basis of clinical, biochemical, and immunological data in all patients. Severe Graves’ ophthalmopathy, any serious concomitant disease, the use of medication (except oral contraceptives), or diet and pregnancy were exclusion criteria. The healthy control subjects, who were matched for gender, age (allowed limits ±5 yr), and body mass index (BMI; allowed

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limits \( \pm 2 \text{ kg/m}^2 \), were recruited using advertisements in local newspapers. The Ethics Committee of Leiden University Medical Center approved the study protocol, and all subjects gave written informed consent. The study was conducted according to the principles of the Helsinki Declaration.

**Study design.** Hyperthyroid patients were studied on three occasions in this open study. The first occasion took place at the time of diagnosis. Subsequently, treatment with propranolol (\( \beta_1 \)- and \( \beta_2 \)-adrenergic receptor blockade, 40 mg orally 4 times a day) was initiated. The second occasion took place after 1 wk of propranolol treatment. Thereafter, the subjects started using thiamazol (Strumazol; 10 mg orally 3 times a day) to completely suppress thyroid function. L-Thyroxine (Thyrax; 100 \( \mu \text{g} \) starting dose, progressing to 2 \( \mu \text{g/kg} \) body wt) was added to establish clinical and biochemical euthyroidism. Propranolol treatment was continued for several weeks until most clinical symptoms had vanished. The third occasion, which was required to be \( \geq 1 \text{ mo} \) after the last dose of propranolol, took place with the subject in a stable euthyroid state. An average period of 7 mo (range: 3–10 mo) elapsed between the second and third occasions. The control subjects were studied only once.

**Procedures.** At all occasions identical studies were performed. After an overnight fast, the subjects were admitted to the clinical research unit, where they handed in the urine collected over the previous 24 h. After a brief medical history and physical examination, an intravenous cannula was inserted in a forearm vein, and blood samples to assess the thyroid hormone status were taken. Approximately 15–20 min after the cannulation, a 1-lead electrocardiogram (ECG) registration recorded 600 subsequent beats while the subject was in supine position. The subjects were instructed to relax, to breathe regularly, not to speak, and to stay awake.

**Assessment of heart rate variability.** Variations in R-R intervals present during resting conditions reflect a fine tuning of beat-to-beat control mechanisms. Fluctuations of efferent sympathetic and vagal inputs to the heart are characterized by oscillatory patterns that generate rhythmic changes of R-R interval times. PSA of heart rate fluctuations quantifies cyclical changes in heart rate, which are the result of these alterations in autonomic tone. Fluctuations of autonomic inputs in the high-frequency (HF) domain typically oscillate in the 0.15- to 0.5-Hz frequency range. The power (i.e., variance) of R-R interval length in this frequency domain is almost completely determined by vagal (parasympathetic) input. R-R interval fluctuations that occur at a lower frequency [mid-frequency (MF) domain, typically 0.07–0.14 Hz] are governed by mixed vagal-sympathetic inputs. These neural inputs are modulated by a variety of central and peripheral factors (i.e., respiratory movements, vasomotor centers, thyroid hormones) that ultimately cause changes of R-R interval length and power in associated specific frequency domains. For example, marked increase of power in the HF domain reflects strong vagal inputs to the heart. For a complete description of methods and biological significance of heart rate variability analysis, we refer the reader to Ref. 16.

In this study, ECG signals were 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 artifacts and subsequently analyzed for heart rate variability parameters in the time domain (mean, the coefficient of variation (CV), and the standard deviation (SD) of differences between subsequent R-R intervals) by use of Poincaré plots (11). The first 5-min period of the interbeat interval (IBI) time series of each registration was analyzed by PSA. The time series of IBIs were scrutinized for stationarity, artifacts, and frequency of occurrence of supraventricular extra beats by visual inspection. A linear interpolation correction procedure was applied to correct for isolated artifacts, R-wave detection errors, or isolated extra beats. If \( >5\% \) of a 5-min time segment needed correction, the segment was discarded from further analysis. The IBI time series were subjected to a discrete Fourier transform, based on nonequidistant sampling of the R-wave incidences (CARSPAN program) (14, 21), to yield power spectra of rhythmic oscillations over a frequency range of 0.02–0.50 Hz, with a resolution of 0.01 Hz. For each 5-min time segment, the power was calculated for the total band (TP: 0.02–0.50 Hz), low-frequency band (LF: 0.02–0.06 Hz), MF band (0.07–0.14 Hz), and HF band (0.15–0.50 Hz). In this study, spectral power for each selected frequency band was expressed in relative terms, i.e., as a fraction of the mean value of the considered signal (squared modulation index; MF2). If this measure is computed for the whole spectrum, it is directly comparable to the squared CV (20).

**Assays.** Thyroid hormones, thyroid-stimulating hormone (TSH), and urinary creatinine concentrations were determined using standardized routine methodology. Free thyroxine (\( T_4 \)) was measured on an IMx (Abbott, Abbott Park, IL; intersay CVs: 3.8–7.1% at different levels). Total \( T_4 \) was determined on the TDx (Abbott; interassay CVs: 2.4–5.9%). Triiodothyronine (\( T_3 \)) was measured by RIABEAD of the same company (interassay CVs of 2.0–4.4%). TSH was determined with an immunofluorometric assay (Wallac, Turku, Finland, interassay CVs: 2.4–5.9%). Epinephrine (Epi), nor-epinephrine (NE), dopamine (D), and vanillylmandelic acid (VMA) were determined by routine HPLC methodology. All assays were performed at the clinical chemistry laboratories of Leiden University Medical Center.

**Statistical analysis.** The effects of different conditions on outcome variables were compared within and between patients and matched control subjects by use of paired Student’s t-tests, where matches were treated as paired data. No correction for multiple comparisons was implemented, because our primary purpose was to estimate the magnitude of the difference between the distinct thyroid states in the patients. Statistical analysis of frequency domain heart rate variability was performed on log-transformed data. All parameters are reported as means \( \pm SD \). The level of statistical significance was set at 5%, and differences are presented with the corresponding 95% confidence intervals (95% CI). For the log-transformed data, differences are presented as percentage change with the 95% CIs. The calculations were performed using SPSS for Windows (SPSS, Chicago, IL).

**RESULTS**

Fifteen hyperthyroid patients and 15 control subjects were included. The data from two subjects were not used in the analysis. One patient completed only the first occasion, and one control subject experienced a severe headache attack. Another patient withdrew from the study before the third occasion. The available data from this subject were used in the analysis. Thus the data represent 14 patients (13 F/1 M) and 14 matched controls. At inclusion, the patients were 38.9 \( \pm 9.7 \) (mean \( \pm SD \); range: 21–56 yr) old and had a BMI of 23.1 \( \pm 4.4 \) kg/m\(^2\) (range: 16.2–30.0 kg/m\(^2\)). The control subjects were 39.5 \( \pm 10.3 \) yr (range: 21–56 yr) and had a BMI of 23.7 \( \pm 4.7 \) kg/m\(^2\) (range: 14.0–
Thyroid hormone levels. Thyroid hormone levels are summarized in Table 1. TSH and free T4 (FT4) concentrations were frequently lower and higher, respectively, than the limit of detection in untreated hyperthyroid patients and propranolol-treated patients. In these cases the limit of detection for TSH or the valid upper range value for FT4 was used. FT4 concentrations were frequently lower, and FT4 concentrations were frequently higher, than the limit of detection in untreated patients and propranolol-treated patients. In these cases the limit of detection for TSH or the valid upper range value for FT4 was used. *P < 0.05; †P < 0.01.

Table 1. Serum concentrations of thyroid hormones and 95% confidence intervals of differences between disease states within patients and between patients and controls

<table>
<thead>
<tr>
<th>Hyperthyroid patients</th>
<th>TSH, mU/l</th>
<th>T3, nmol/l</th>
<th>T4, nmol/l</th>
<th>FT4, pmol/l</th>
<th>T3/T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated (1)</td>
<td>0.15 ± 0.28</td>
<td>5.27 ± 2.22</td>
<td>247.5 ± 59.1</td>
<td>64.8 ± 18.9</td>
<td>0.021 ± 0.005</td>
</tr>
<tr>
<td>β-Blocker (2)</td>
<td>0.17 ± 0.32</td>
<td>4.53 ± 2.12</td>
<td>259.6 ± 58.5</td>
<td>70.1 ± 15.8</td>
<td>0.017 ± 0.005</td>
</tr>
<tr>
<td>Euthyroid (3)</td>
<td>1.37 ± 1.91</td>
<td>1.51 ± 0.28</td>
<td>121.9 ± 27.8</td>
<td>16.9 ± 3.6</td>
<td>0.013 ± 0.002</td>
</tr>
<tr>
<td>Controls (4)</td>
<td>1.71 ± 1.52</td>
<td>1.80 ± 0.39</td>
<td>101.7 ± 16.6</td>
<td>14.3 ± 1.1</td>
<td>0.018 ± 0.003</td>
</tr>
</tbody>
</table>

95% CIs

(1) vs. (3) -0.1, -2.3* +1.6, +4.3† +70, +165† ND +0.004, +0.012†
(1) vs. (4) -0.7, -2.5* +2.2, +4.8† +112, +181† ND -0.003, +0.061
(2) vs. (3) -0.05, -2.3* +1.6, +4.3† +150, +193† ND +0.0004, +0.008*†
(3) vs. (4) -1.8, +1.0 -0.01, -0.5* +22, +39* ND -0.007, -0.0092†

Serum concentration values are means ± SD. 95% CIs, 95% confidence intervals; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; FT4, free thyroxine. (Normal values: TSH, 0.3–4.8 mU/l; T3, 1.1–3.1 nmol/l; T4, 70–160 nmol/l; FT4, 10–24 pmol/l.) ND, not done. TSH concentrations were frequently lower, and FT4 concentrations were frequently higher, than the limit of detection in untreated patients and propranolol-treated patients. In these cases the limit of detection for TSH or the valid upper range value for FT4 was used. *P < 0.05; †P < 0.01.

The patients were in a hyperdynamic circulatory state, because systolic blood pressure (16 mmHg; CI: +4, +28 mmHg), pulse pressure (11 mmHg; CI: +4, +19 mmHg), and heart rate (39 beats/min; CI: +26, +51 beats/min) were all significantly higher than values in controls.

Table 2. Urinary catecholamine excretion (normalized for creatinine) and creatinine excretion values (per 24 h) and 95% confidence intervals of differences

<table>
<thead>
<tr>
<th>Hyperthyroid patients</th>
<th>Norepinephrine, mmol/24 h</th>
<th>Dopamine, mmol/24 h</th>
<th>VMA, mmol/24 h</th>
<th>Creatinine, mmol/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated (1)</td>
<td>27.5 ± 11.1</td>
<td>0.305 ± 0.100</td>
<td>1.70 ± 0.37</td>
<td>7.30 ± 2.79</td>
</tr>
<tr>
<td>β-Blocker (2)</td>
<td>30.1 ± 10.1</td>
<td>0.314 ± 0.097</td>
<td>1.76 ± 0.40</td>
<td>7.06 ± 3.33</td>
</tr>
<tr>
<td>Euthyroid (3)</td>
<td>19.5 ± 9.5</td>
<td>0.168 ± 0.095</td>
<td>1.36 ± 0.27</td>
<td>8.60 ± 4.43</td>
</tr>
<tr>
<td>Controls (4)</td>
<td>19.0 ± 4.3</td>
<td>0.162 ± 0.043</td>
<td>1.40 ± 0.26</td>
<td>7.79 ± 2.79</td>
</tr>
</tbody>
</table>

95% CIs

(1) vs. (3) +1.3, +14.8* +0.091, +0.164‡ +0.13, +0.39‡ -4.51, +1.66
(1) vs. (4) +1.2, +15.8* +0.078, +0.208‡ +0.08, +0.52‡ -1.72, +0.64
(2) vs. (3) +5.4, +16.3‡ +0.096, +0.180‡ +0.19, +0.61‡ -4.88, +2.14
(3) vs. (4) -5.4, +7.3 -0.061, +0.083 -0.20, +0.16 -2.08, +3.72

Catecholamine and creatinine excretion values are means ± SD. VMA, vanillylmandelic acid. *P < 0.05; †P < 0.01; ‡P < 0.001.

Urinary catecholamine excretion. Urinary catecholamine excretion values are summarized in Table 2. Excretion of Epi was below the limit of detection (0.01 pmol/l) in several subjects and was therefore not analyzed. The excretions of NE, D, and VMA, normalized for creatinine excretion, were considerably increased in the hyperthyroid patients compared with controls. β-Blockade did not significantly influence urinary catecholamine excretion. Catecholamine excretion in the euthyroid state was greatly reduced and not different from excretion in control subjects.

Heart rate variability during supine rest. An example of the R-R intervals obtained for one patient and her control subject counterpart, plotted as a Poincaré plot, is given in Fig. 1, which demonstrates the increased heart rate and reduced R-R interval variability in all frequency domains in the hypothyroid condition, the reduction of heart rate by β-adrenergic receptor blockade, and the normalization of R-R interval variability in response to treatment with thiamazol and l-thyroxine. Figure 2 shows the power spectrum in various frequency domains in the same hyperthyroid patient and in her control subject counterpart.

A summary of time-domain measures and PSA of heart rate fluctuations is given in Table 3. R-R interval
length was considerably shorter in hyperthyroid patients than in controls. The CV of R-R interval length and the SD of differences between subsequent R-R intervals were significantly smaller. Nonselective blockade of β-adrenergic receptors increased R-R interval length. It did not affect the other time-domain measures to a significant extent.

Heart rate variability was considerably reduced in both MF and HF frequency domains in hyperthyroid patients compared with control subjects. The MF-to-HF power ratio (MF/HF) was significantly increased (more than doubled) in hyperthyroid patients compared with values in the euthyroid state. The increase of the MF/HF in hyperthyroid patients vs. controls did not reach statistical significance. Although the power in both frequency domains tended to increase in response to β-adrenergic receptor blockade, the differences compared with baseline did not reach statistical significance. In the euthyroid state, all parameters were restored to values similar to those in the control subjects.

DISCUSSION

This study reveals profound changes of autonomic inputs to the heart in hyperthyroidism. The spectral power in both frequency domains was considerably reduced in hyperthyroid patients. In addition, their 24-h urinary catecholamine excretion was increased. Nonselective antagonism of β-adrenergic receptors reduced heart rate in hyperthyroid patients, but it did not significantly affect heart rate variability. Reestablishment of euthyroidism by thiamazol and L-thyroxine treatment completely restored heart rate variability power spectra and catecholamine excretion to normal.

The reduction of spectral power in the HF domain in hyperthyroid patients indicates withdrawal of vagal inputs to the heart (11, 18). This finding is in keeping with several previous observations (3, 9, 10). It is more difficult to draw definite conclusions concerning activity of the sympathetic nervous system on the basis of PSA. Although sympathetic inputs primarily affect heart rate variability in the MF domain (1, 18), MF spectral power in supine, resting subjects is also determined by vagal tone (18). However, several observations suggest that sympathetic activity was increased in our hyperthyroid patients. First, 24-h urinary D, NE, and VMA excretion was almost twice as high as that in euthyroid conditions and in normal control subjects. Urinary excretion of catecholamines and their metabolites reflects their average plasma concentrations and whole body turnover in plasma (8, 19). Second, heart rate and the MF/HF were increased and total spectral power was decreased in hyperthyroid subjects compared with values in the euthyroid state. All these features of heart rate variability are typical of enhanced sympathetic inputs to the heart (13, 18). The fact that sympathetic tone appears to be increased in hyperthyroidism is in apparent contrast to earlier studies reporting normal or even reduced sympathetic activity in hyperthyroidism (4, 6, 7, 17). However, these reports are generally based on plasma NE concentrations in single samples of venous forearm blood (4, 17) or whole body catecholamine turnover rates calculated from specific activities of radiolabeled catecholamines in venous plasma (6, 7). It is now known that catecholamine levels are more appropriately determined in arterialized blood, inasmuch as extraction from venous circulation occurs across various or-
**Fig. 2.** Power spectra of heart rate variability in the patient and the control subject whose the Poincaré plot data are shown in Fig. 1.

**Table 3.** Heart rate variability parameters in the time and frequency domains

<table>
<thead>
<tr>
<th></th>
<th>Time Domain</th>
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<th>Frequency Domain</th>
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<tbody>
<tr>
<td></td>
<td>RR-int (ms)</td>
<td>CV RR-int (%)</td>
<td>SD RRdif (ms)</td>
<td>MF power (MI² × 10⁶)</td>
</tr>
<tr>
<td>Hyperthyroid patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated (1)</td>
<td>621 ± 102</td>
<td>2.86 ± 0.80</td>
<td>9 ± 3</td>
<td>159 ± 126</td>
</tr>
<tr>
<td>β-Blocker (2)</td>
<td>780 ± 130</td>
<td>3.73 ± 2.08</td>
<td>19 ± 21</td>
<td>272 ± 334</td>
</tr>
<tr>
<td>Euthyroid (3)</td>
<td>873 ± 99</td>
<td>6.37 ± 2.60</td>
<td>47 ± 30</td>
<td>1,175 ± 1,358</td>
</tr>
<tr>
<td>Controls (4)</td>
<td>936 ± 114</td>
<td>6.66 ± 3.76</td>
<td>45 ± 28</td>
<td>1,512 ± 1,949</td>
</tr>
</tbody>
</table>

95% CIs

(1) vs. (2)         -203, -114 ‡ -0.28, +2.02 -22, +1 -22, +127% -23, +248% -5, +158% -0.2, +0.4%
(1) vs. (3)         -307, -185 ‡ +1.86, +5.08 ‡ -56, -20 ‡ -155, -16% ‡ -161, -30% ‡ -144, -34% ‡ +26, +316% ‡
(1) vs. (4)         -417, -218 ‡ +1.13, +5.62 ‡ -51, -20 ‡ -164, -15% ‡ -173, -12% ‡ -151, -19% ‡ -43, +166% ‡
(2) vs. (3)         -158, -18 ‡ +0.94, +4.21 ‡ -44, -9 ‡ -151, +2% ‡ -137, -13% ‡ -124, -10% ‡ -36, +278% ‡
(3) vs. (4)         -35, +163 -1.80, +2.77 ‡ -19, +19 -105, +41% ‡ -75, +126% ‡ -65, +70% ‡ -103, +31%

Heart rate variability parameters are means ± SD. 95% CIs of differences are shown. Frequency domain parameters (analyzed after log transformation) are expressed as % change. RR-int, RR interval; CV, coefficient of variation; SD RRdif, standard deviation of difference in RR intervals; MF, mid frequency (0.07–0.14 Hz); HF, high frequency (0.15–0.50 Hz); MF/HF, ratio of mid- to high-frequency power; MI² × 10⁶, squared modulation index, times 10⁶. *P < 0.05; †P ≤ 0.01; ‡P ≤ 0.001.
gans (2, 8). Because hormone clearance critically depends on blood flow (8), this phenomenon may be of particular relevance in hyperthyroidism in view of the hyperdynamic circulatory state associated with this disease.

Although nonselective β-adrenoceptor antagonism reduced heart rate in hyperthyroid subjects, it did not fully restore heart rate to normal values. Also, it did not significantly affect heart rate fluctuations. These findings are in agreement with earlier observations indicating a lack of effect of β-blockade on heart rate variability in healthy volunteers (5, 15). Once euthyroidism was established, heart rate and heart rate variability were similar in patients and controls. These observations support the concept that sympathetic inputs alone cannot explain the cardiac symptoms in hyperthyroidism. Reduced vagal tone contributes to diminished heart rate variability and increased heart rate. In addition, thyroid hormones may have a direct chronotropic effect on the heart (16). Propranolol significantly reduced the T3 concentrations in the patients, which is a well known effect of this drug that is probably responsible for some of the clinical effects of propranolol in thyrotoxicosis (22).

In conclusion, hyperthyroidism is associated with a profoundly altered balance of the autonomous nervous system. It appears that the sympathetic component prevails over the parasympathetic as a result of enhanced sympathetic activity in the presence of diminished parasympathetic tone. The observed changes at least partly explain many of the clinical signs and symptoms of thyrotoxicosis and underscore the rationale for use of propranolol as a drug to reduce these symptoms.

REFERENCES


