Research Article

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Reversible autonomic dysfunction in hyperthyroid patients affects gastric myoelectrical activity and emptying

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The autonomic nervous system (ANS) function in hyperthyroidism has been so far investigated mainly from the cardiovascular point of view. The aim of this study is to show that the ANS dysfunction in hyperthyroidism is also expressed in gastric myoelectrical activity disturbances and gastric emptying disorders and to search for a correlation between the severity of clinical manifestation and free thyroid hormone levels and the degree of the ANS dysfunction. The analyzed group included 50 recently diagnosed patients with hyperthyroidism who were examined twice: before and after 3 months of thyrostatic treatment. Results were compared with those of a sex-, age- and BMI-matched control group of 50 healthy volunteers. The study included: heart rate variability analysis in time and frequency domain, at rest and during a deep-breathing test, surface electrogastrography in preprandial and postprandial periods measured simultaneously with the ultrasound assessment of gastric emptying time by Bolondi method. In patients with hyperthyroidism in comparison with the control group, the following significant differences were observed: a sharp reduction of the high-frequency component and a decrease of heart rate variability, a high incidence of dysrhythmia with dominant bradyarrhythmia, and a delay of gastric emptying. The degree of disorders related to the degree of clinical manifestation of hyperthyroidism's symptoms and free triiodothyronine serum concentration both. All the disorders were functional and disappeared in a stable euthyroidism. To conclude, the ANS dysfunction in hyperthyroidism results not only in withdrawal of vagal inhibitory effect on sinoatrial node, but in impaired mutual neuro-hormonal regulation (decrease of vagal influence) of gastric myoelectrical activity followed by delay of gastric emptying.

Key words: heart rate variability, hyperthyroidism, autonomic dysfunction, gastric emptying, electrogastrography.

Thyroid hormone excess results in dysfunction of many organs and systems of the body. Most patients with thyroid hormone excess have cardiovascular symptoms related to thyrotoxicosis. Most of the symptoms, like tachycardia or increased cardiac output, can be relieved by ß-blocking agents, suggesting increased adrenergic activity in hyperthyroid subjects [1]. Many studies, however, question that hypothesis. Production, release, degradation, and plasma concentrations of catecholamines were reported to be normal or even decreased in hyperthyroidism [2,3]. The well-known increase of heart rate in thyrotoxicosis may be caused not only by increase of intrinsic sinoatrial node activity but also by modulatory influences of the autonomic nervous system (ANS), among which decrease of physiological vagal inhibition of sinoatrial node seems to be essential [4–6]. This interpretation is supported by several findings: impaired central effect of low-dose atropine in subjects with hyperthyroidism [7], reduced capacity of vagal inhibition after selective pharmacologic blockade [8], and depression of the capacity for vagal withdrawal during exercise in the same subject group [9].

Besides the heart, vagal nerves also innervate the alimentary tract and take part in regulation of gastrointestinal motility and secretion. Therefore, the hypothesis of vagal withdrawal in thyrotoxicosis should also find confirmation in studies concerning, for instance, gastric myoelectrical activity and motility. Unfortunately, reports on this kind of research have been very limited [10].

Decrease of gastric secretion is well known in hyperthyroidism [11], but no evidence of either gastric myoelectrical disturbances or gastric emptying disorders has been reported. This is a result of a relative absence of gastric disturbance manifestations among patients with hyperthyroidism as the cardiovascular symptoms take the lead [12]. The aims of this study are: (1) to show that the ANS dysfunction in hyperthyroidism affects not only the cardiovascular system but is also expressed in gastric myoelectrical activity disturbances and gastric emptying disorders; and (2) to correlate the severity of clinical manifestation and free thyroid hormone levels with the degree of the ANS dysfunction.

Patients and methods

The study was performed in a group of 50 patients with newly diagnosed and untreated hyperthyroidism, reporting to the Provincial Endocrinologic Outpatient Clinic (in Krakow, 1998). The inclusion criteria were: age 18–65 y, good

general health with no chronic diseases, newly diagnosed hyperthyroidism, no history of surgical treatment, and willingness to provide signed consent. Smokers and pregnant and lactating women were excluded from the study. All the patients received "Information for a research participant," describing in detail the study procedures. Informed consent was obtained from all subjects, and the study was approved by the Ethical Committee of Jagiellonian University College of Medicine (Krakow).

The group examined comprised 45 (90%) females and 5 (10%) males. Multinodular toxic goiter was diagnosed in 35 (70%) patients (32 female, 2 male); Graves' disease was diagnosed in 15 (30%) patients (12 female, 3 male). The mean age was 39.6 (± 11.7 y), and the mean body mass index (BMI) was 23.72 (± 4.96)

In all cases the diagnosis of hyperthyroidism was confirmed by increased serum concentrations of thyroid hormones (free thyroxine and/or free triiodothyronine [FT_3]) and suppressed thyroid-stimulating hormone serum concentrations. After the patients received pharmacologic treatment (thiamazole, propranolol) lasting approximately 3 months and reached a stable, euthyroid state (confirmed by serum hormone concentrations), they were re-examined.

The control group consisted of 50 healthy sex-, age- and BMI-matched volunteers. Mean age in the control group was 37.9 (± 10.97) y; mean BMI, 24.34 (± 4.67); and mean thyroid-stimulating hormone serum concentration was 2.1 (± 1.34 mU/l).

The study was performed at the Department of Experimental Pathophysiology of Jagiellonian University (Krakow). Patients arrived at 9.00 a.m. after an 8-hr, overnight fast, and within 1 to 2 days after the diagnosis of hyperthyroidism had been made by a physician in the Provincial Endocrine Outpatient Clinic in Krakow. The appropriate pharmacologic therapy was prescribed soon after the study was completed.

Hyperthyroid patients subgroups

The routine examination included the measurement of weight, BMI, BP and pulse rate. The degree of clinical manifestation of hyperthyroidism was assessed according to the Zgliczyński scale (Table 1), and patients were placed into 3 subgroups: I° (moderate hyperthyroidism: 5–12 points), II° (moderately severe hyperthyroidism: 13–19 points), or III° (severe hyperthyroidism 20–24 points). The degree of clinical manifestation of hyperthyroidism and the categorization of patients by the Zgliczyński scale is presented in table 2.

The comparison of thyroid hormone and thyroid-stimulating hormone serum concentrations in individual subgroups of patients with hyperthyroidism is presented in table 3. Each patient was re-examined after approximately 3 months of pharmacologic therapy and after reaching stable euthyroidism. Forty-eight hours before the re-examination, the β-blocking drug was discontinued.

Heart rate variability

Heart rate variability (HRV) analysis included time and frequency domain, measured by ECG 2002 system (Proster S.A., Glinice, Poland) in the following order: (a) 10 minutes at rest in a half-seated position, and (b) 10 minutes of deep-breathing (DB) test with a frequency of 6 breaths/min (0.1Hz). To help the patients sustain the assumed respiratory frequency, the sound of the metronome (working at 0.2Hz) was used to initiate both the inspiration and expiration every 5 seconds. An independent observer was present during the DB test to monitor the respiratory frequency. Before HRV recording, an electrocardiogram was made to assess the regularity of the heart rhythm and to choose one of the precardiac leads for further HRV recording. The chosen R waves had to be positive and at least 2 times higher in amplitude than T waves (usually V4 or V5). The fast-Fourier transform analysis of 10-min recordings was used at rest and in DB test, respectively. The HRV analysis included the R-R intervals variability, standard deviation of all normal RR intervals (SDNN), high-frequency (HF: 0.15–0.45 Hz) component and low-frequency (LF: 0.05–0.15 Hz) component. The power spectral data were expressed in both absolute terms [$msec^2$] and in normalized units. The latter ones were obtained by dividing the absolute power of each spectral component by the total variance of the R-R intervals, from which the power of the continuous component was removed (here defined as the power density with a frequency below 0.05 Hz).

Table 1. Zgliczyński scale (to assess the degree of clinical manifestation of hyperthyroidism [12])

Clinical symptoms	Points
Heat intolerance	1
Heart beats	1
Thirst	1
Sleeplessness	1
Clinical signs	
Weight loss	2
Diarrhea	2
Sweats	2
Tachycardia	
90–115 beats/min	2
>115 beats/min	3
Blood pressure	
SBP > DBP + 20 mm Hg	3
SBP > DBP and < DBP + 20 mm Hg	2
Hands trembling	2
Systolic murmur over apex of the heart	2
Systolic murmur over base of the heart	1
Myasthenia	4

Number in brackets refers to reference list.
SBP = systolic blood pressure; DBP = diastolic blood pressure.

Electrogastrography

Surface electrogastrography (EGG) procedure was performed with equipment produced by Synectics Medical (Stockholm, Sweden). Gastric myoelectrical activity was recorded by EGG digitrapper and the analysis of the data was carried out using an IBM PC-compatible computer with ElectroGastroGram Software (also Synectics).

Table 2. Division of the degree of clinical manifestation of hyperthyroidism in the group studied (according to Zgliczyński scale [12])—before pharmacological treatment

	I°		II°		III°	
Type of disease	Number	%	Number	%	Number	%
Graves' disease	2	4.0	11	22.0	2	4.0
Multinodular toxic goiter	15	30.0	19	38.0	1	2.0
Total	17	34.0	30	60.0	3	6.0

Number in brackets refers to reference list.
I° = moderate hyperthyroidism (5–12 points); II° = moderately severe hyperthyroidism (13–19 points); III° = severe hyperthyroidism (20–24 points).

Before the examination, the skin of the epigastrium was shaved and degreased. Two research electrodes and one reference Ag/Cl^- electrode were attached to the epigastrium in the antral projection. The EGG recording was performed in two stages: (a) after 8 hours' overnight fasting, and (b) in postprandial period after ingestion of ENRICH test meal (Liquid Nutrition with Fiber Chocolate Flavor; volume: 250 ml, 365 mmol/l, proteins: 15.4%, fat: 30.9%, carbohydrates: 53.7%, caloric content of the meal: 1075.2 kJ). Total recording time was 60 min, 30 min for each stage. The meal time was excluded from the analysis. Postprandial EGG recording was made simultaneously with the ultrasound assessment of gastric emptying time. All the artefacts and periods when the ultrasound probe was pressing the abdominal wall (approximately 2 min for each measurement of antral volume) were ignored and excluded from the analysis. In frequency EGG analysis the fast-Fourier transform was used. Both graphic EGG frequency analysis and percent activity tables were assessed. Bradyarrhythmia (0–2 cpm), normogastria (2–4 cpm), tachyarrhythmia (4–10 cpm) and total dysrhythmia (a sum of bradyarrhythmia and tachyarrhythmia) were distinguished. The amplitude of the dominant spectrum of EGG frequency and its postprandial change were also estimated.

Ultrasonography

The evaluation of gastric emptying time was performed by an experienced ultrasonographer using a high-resolution, real-time ultrasound Hitachi (Tokyo, Japan) BG:11 with a 3.5 MHz linear array transducer. Examinations were performed between 9:00 A.M. and 11:00 A.M., following an 8-hr, overnight fast, with subjects in a half-seated position. The antral volume (AV) was measured using the Bolondi method [13]. The cross-sectional diameters of the gastric antrum (antero-posterior and longitudinal) of three planes crossing pylorus (A, B), angle of the stomach (E, F) and in a half between them (C, D) were measured in each case. The distance between pylorus and angle of the stomach was measured on a transverse section plane (H). The first measurement was made before the meal, and next after the meal every 10 minutes until the postprandial AV reached the preprandial capacity. The lasting time reflected total gastric emptying time.

$$AV = 0{,}065 \cdot H \cdot (2AB + 2EF + 4CD + CB + AD + ED + CF)\ [ml]$$

Statistical analysis

Statistical analysis of the data was performed using STATISTICA software (StatSoft, Krakow, Poland). To find the differences between the analyzed variables (which could influence the results), appropriate statistical tests respecting distribution of data were used:

(1) In cases of normal distribution of the parameters, an equality of variations was found:
   (a) if no statistically significant differences between variations were found, an unpaired Student *t* test was used,
   (b) if the variations were different, the Cochran-Cox test was used.
(2) In cases when at least one parameter's distribution was different than normal, the Wilcoxon test was used.
(3) For nonparametric values (eg, sex), the χ^2 test was used.
(4) For estimation of a correlation (co-dependence) of two variables, appropriate tests based on the following coefficients were used:
   (a) Pearson (if both parameters were normally distributed),
   (b) Spearman (if at least one parameter was distributed not normally),
   (c) Cramer (if at least one value was nonparametric).

Table 3. Thyroid-stimulating hormone and thyroid hormone concentrations based on clinical manifestation of hyperthyroidism (according to Zgliczyński scale [12])

	I°		II°		III°	
	Mean	SD	Mean	SD	Mean	SD
TSH (mU/L)	0.09	0.065	<0.05	<0.0005	<0.05	<0.0005
FT_3 (pmol/L)	6.91	1.76	11.93	2.04	24.25	3.68
FT_4 (pmol/L)	24.14	2.6	26.04	1.63	49.33	10.4

Number in brackets refers to reference list.
Reference values: thyroid-stimulating hormone (TSH) = 0.47–5.01 mU/L; free triiodothyronine (FT_3) = 4.0–8.3 pmol/L; free thyroxine (FT_4) = 9.0–21.0 pmol/L.
I° = moderate hyperthyroidism; II° = moderately severe hyperthyroidism; III° = severe hyperthyroidism.

Data were expressed as the mean ± SD and p <0.05 was considered as significant.

Results

Heart rate variability analysis

In the I° group no significant differences between patients with hyperthyroidism before and after treatment and the control group were found in resting HRV analysis (p >0.1).

In the II° and III° groups, before treatment compared with the control group in resting HRV analysis, the significant differences (p <0.01) included: increase of the heart rate, decrease of the R-R interval, decrease of SDNN, decrease of all power spectra with dominant decrease of HF component. Parameters of HRV analysis after treatment were similar to the control group (p> 0.1). Detailed data are presented in table 4. No significant differences were found between patients with multinodular toxic goiter and patients with Graves' disease (p >0.2). No correlation was found between SDNN and average heart rate in patients with hyperthyroidism at rest (r = −0.1228; p = 0.735).

In HRV analysis during deep-breathing tests in the I° group before treatment compared with the control group, the significant (p <0.01) differences were: decrease of both the R-R interval and SDNN. Parameters of HRV analysis after treatment were similar to the control group.

In the II° and III° groups before treatment compared with the control group, both at rest and in DB test, the significant (p <0.01) differences were: decrease of the R-R interval, decrease of SDNN and decrease of all power spectra components. After the subjects had received treatment and reached a stable, euthyroid state, an increase of HF component was observed, both at rest and in DB test; LF power spectrum did not change, but was significantly lower than in the control group (p <0.05). No correlation was found between SDNN and average heart rate in patients with hyperthyroidism in DB test (r = −0.4167; p = 0.231).

Gastric myoelectrical activity

No significant relationship (p >0.2) between free serum thyroid hormone concentrations and the degree of gastric myoelectrical activity disturbances was found among patients in the I° group. However, the level of total dysrhythmia was 21.6% before the meal and 11.5% after the meal, and it was significantly higher (p <0.05) than in the control group. Detailed data are presented in table 5.

Positive correlation between FT_3 serum concentration, degree of clinical manifestation of hyperthyroidism (II° and III° on the Zgliczyński scale) and extent of gastric myoelectrical activity disturbances was evident (r = 0.8377; p <0.001). The trend is presented in Figure 1. Patients in the II° group had increased FT_3 and free thyroxine serum concentrations, and the dominant type of gastric myoelectrical disturbance was bradyarrhythmia within the preprandial period, with normal postprandial increase of slow waves'

Table 4. Results of HRV analysis in respective groups of hyperthyroid patients before and after thyrostatic treatment and in the control group

		HRV analysis			Statistical significance	
Parameters	Period–test	I° (Mean ± SD)	II° + III° (Mean ± SD)	CG (Mean ± SD)	I° vs. CG	II + III° vs. CG
R-R (msec)	HPT–BT-R	807.34 ± 89.77	674.82 ± 69.88	897.57 ± 120.86	NS	p <0.01
	HPT–BT-DB	681.32 ± 74.20	659.72 ± 77.80	872.40 ± 93.03	p <0.01	p <0.01
	EUT–AT-R	888.60 ± 87.20	1,010.40 ± 98.18	897.57 ± 120.86	NS	NS
	EUT–AT-DB	852.22 ± 89.65	1,000.16 ± 150.77	872.40 ± 93.03	NS	NS
SDNN (msec)	HPT–BT-R	63.40 ± 9.26	48.14 ± 11.80	63.28 ± 27.12	NS	p <0.01
	HPT–BT-DB	64.88 ± 10.89	22.12 ± 5.02	112.80 ± 35.96	p <0.01	p <0.001
	EUT–AT-R	41.41 ± 6.23	47.56 ± 11.26	63.28 ± 27.17	NS	NS
	EUT–AT-DB	101.23 ± 15.67	47.01 ± 6.28	112.80 ± 35.96	NS	p <0.05
LF ($msec^2$)	HPT–BT-R	411.42 ± 154.20	238.12 ± 88.98	467.71 ± 110.28	NS	p <0.01
(NU)		60.56 ± 6.87	78.29 ± 7.36	59.68 ± 7.58	NS	p <0.05
($msec^2$)	HPT–BT-DB	1,652.6 ± 254.33	532.88 ± 86.41	3,284 ± 2,022.40	NS	p <0.01
(NU)		71.47 ± 10.67	55.43 ± 7.56	72.48 ± 11.21	NS	p <0.05
($msec^2$)	EUT–AT-R	231.77 ± 69.70	248.98 ± 40.96	467.71 ± 110.28	p <0.05	p <0.05
(NU)		43.21 ± 4.78	49.34 ± 3.29	59.68 ± 5.58	p <0.05	p <0.05
($msec^2$)	EUT–AT-DB	2,414.2 ± 215.62	616.20 ± 79.49	3,284 ± 2,022.40	NS	p <0.01
(NU)		78.42 ± 7.88	68.33 ± 7.12	72.48 ± 15.21	NS	NS
HF ($msec^2$)	HPT–BT-R	355.34 ± 135.6	90.18 ± 28.98	487.28 ± 125.12	NS	p <0.001
(NU)		30.90 ± 4.20	13.60 ± 3.20	32.70 ± 5.80	NS	p <0.001
($msec^2$)	HPT–BT-DB	99.98 ± 15.89	207.76 ± 60.16	648.75 ± 668.73	NS	NS
(NU)		20.46 ± 2.56	15.21 ± 4.76	23.46 ± 11.92	NS	NS
($msec^2$)	EUT–AT-R	256.10 ± 10.22	336.56 ± 89.70	487.28 ± 125.12	p <0.05	NS
(NU)		44.56 ± 4.85	45.21 ± 6.98	32.70 ± 5.80	NS	NS
($msec^2$)	EUT–AT-DB	511.12 ± 92.56	486.62 ± 21.33	648.75 ± 668.73	NS	NS
(NU)		16.21 ± 2.54	31.22 ± 5.28	23.46 ± 13.92	NS	NS

I°, II°, and III° are classifications of hyperthyroidism in the Zgliczyński scale (moderate, moderately severe, and severe, respectively) [12]. HRV = heart rate variability; CG = control group; R-R = R-R interval; HPT = hyperthyroidism; EUT = euthyroidism; BT = before treatment; AT = after treatment; R = at rest; DB = deep-breathing test; NS = not significant; SDNN = standard deviation of all normal R-R intervals; LF = low frequency; HF = high frequency; NU = normalized units.

Table 5. Results of EGG and gastric emptying time analysis in respective groups of hyperthyroid patients before and after thyrostatic treatment and in the control group

Parameters	Period	EGG and GET analysis I° (Mean ± SD)	II° + III° (Mean ± SD)	CG (Mean ± SD)	Statistical significance I° vs. CG	II + III° vs. CG
Dysrhythmia (%)	HPT–BM	21.60 ± 11.90	55.6 ± 18.72	5.48 ± 6.83	p <0.05	p <0.001
	HPT–AM	11.50 ± 4.16	28.32 ± 7.54	2.75 ± 2.63	p <0.05	p <0.01
	EUT–BM	19.06 ± 17.65	15.12 ± 12.32	5.48 ± 6.83	NS	NS
	EUT–AM	11.69 ± 8.86	10.38 ± 5.64	2.75 ± 2.63	NS	NS
$GET_{1/2}$ (min)	HPT	40.58 ± 6.58	62.68 ± 7.97	40.2 ± 7.14	NS	p <0.01
	EUT	40.4 ± 8.56	43.76 ± 9.86	40.2 ± 7.14	NS	NS
GET (min)	HPT	71.18 ± 9.92	110.28 ± 11.5	59.8 ± 6.84	NS	p <0.01
	EUT	72.3 ± 10.3	74.6 ± 11.06	59.8 ± 6.84	NS	NS

I°, II°, and III° are classifications of hyperthyroidism on the Zgliczyński scale (moderate, moderately severe, and severe, respectively) [12]. EGG = electrogastrophy; GET = gastric emptying time; CG = control group; HPT = hyperthyroidism; EUT = euthyroidism; BM = before meal; AM = after meal; NS = not significant; $GET_{1/2}$ = half time of gastric emptying.

amplitude and bradyarrhythmia still present. In that group the preprandial decrease of slow waves (mean of 43.78% of recording) was reduced within the postprandial period (mean of 21.77% of recording). Simultaneously, the increase of postprandial physiologic rhythm of slow waves (from a mean of 36.23% of recording before the meal to a mean of 77.36% of recording after the meal) was observed. The preprandial acceleration of slow waves rhythm was significantly ($p < 0.05$) decreased after the meal (mean of 21.02% of recording before the meal to a mean of 3.37% of recording after the meal).

Patients in the III° group had significantly ($p < 0.01$) higher FT_3 and free thyroxine serum concentrations and preprandial tachyarrhythmia, which did not disappear after the meal, and the amplitude of slow waves did not increase. Among those patients the preprandial increase of slow waves (mean of 34.6% of recording before the meal) was reduced after the meal (to mean of 21% of recording). The preprandial deceleration of slow wave rhythm (mean of 20% of recording) continued after the meal (to mean of 33% of recording).

After subjects reached a stable, euthyroid state, the incidence of dysrhythmia decreased, and no statistical significance was present between the study groups and controls.

Gastric emptying

Mean time of gastric emptying was 106 ± 16.41 min in the patients with hyperthyroidism group, and it was significantly longer ($p < 0.01$) than in the euthyroid state after thyrostatic treatment (72.8 ± 10.3 min) and in the control group (59.8 ± 6.84 min). A positive correlation between the degree of clinical manifestation of hyperthyroidism (by the Zgliczyński scale), FT_3 serum concentration, and the extent of gastric emptying delay time was found ($r = 0.7376$; $p < 0.001$). The trend is presented in Figure 2. The longest gastric emptying time was found in patients with severe and moderately severe hyperthyroidism (110.28 ± 11.5 min). Among patients with moderate hyperthyroidism the gastric emptying time was only slightly prolonged (71.18 ± 9.92 min) and it was not statistically significant ($p > 0.05$). No significant differences in gastric emptying time were found in a comparison of patients with Graves' disease with patients with multinodular toxic goiter ($p > 0.2$).

Moreover, in the total group of patients with hyperthyroidism, a statistically significant ($p < 0.05$) bigger postprandial antral volume was found, which was not present in patients with euthyroidism after treatment and in the control group. In all cases the maximum capacity of antral volume was observed 10 min after the test meal, followed by an almost linear reduction of the antral volume.

Discussion

Heart rate variability analysis has become an easy and convincing diagnostic tool used to assess cardiac component of

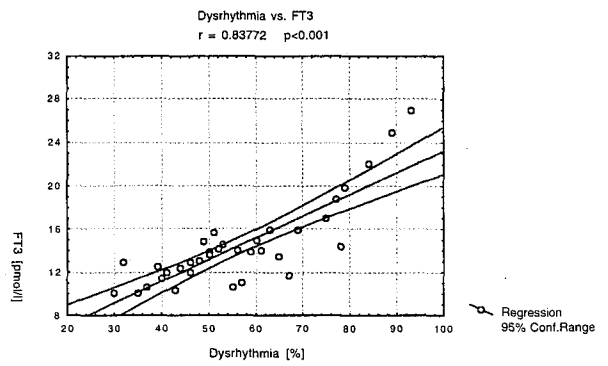

Figure 1. Correlation between dysrhythmia and free triiodothyronine (FT_3) serum concentration in patients with hyperthyroidism before treatment.

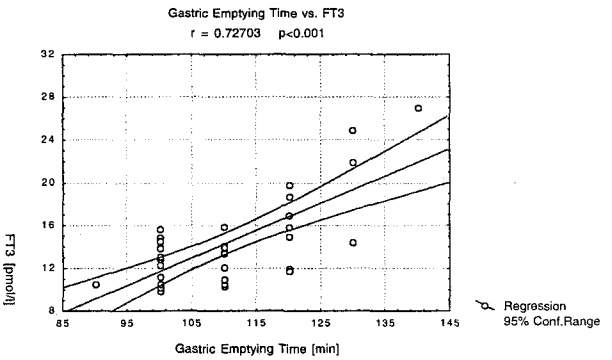

Figure 2. Correlation between gastric emptying time and free triiodothyronine (FT_3) serum concentration in patients with hyperthyroidism before treatment.

the ANS [14–19]. Diminished HRV is widely accepted as an indicator of decreased cardiac parasympathetic modulation [20–22], helpful in predicting lethal ventricular arrhythmia and risk of sudden death in patients who have had acute myocardial infarction [23]. Vagal activation prevents ventricular arrhythmia in both experimental and clinical models [24], having an effect on myocardial automaticity, refractoriness [25] and inhibition of presynaptic release of norepinephrine, and reduction of the cellular response to adrenoceptor binding [26].

Although the clinical implications of HRV have been described, the normative values of HRV are still not clarified in a large community-based population study. However, age and heart rate must be taken into account when assessing HRV. In healthy subjects there is a negative correlation between SDNN and average heart rate [22,27]. Such an observation was also confirmed in this study in the control group ($r = -0.8627$; $p < 0.05$).

In thyrotoxicosis the excess of thyroid hormones results in the development of symptoms that suggest a sympathetic activation [2,12,27]. The influence of thyroid hormones on the ANS has been the subject of study for many years. There were many doubts about the nature of that interaction until vagal withdrawal was shown to be the reason of increased heart rate and other cardiovascular symptoms of hyperthyroidism [7,8,19,28–31]. However, not all the reports support the evidence of reduced cardiac vagal modulation of the heart rate in thyrotoxicosis [32]. The present study's finding, of a decrease in vagal activity, applies only to moderately severe and severe thyrotoxicosis (on the Zgliczyński scale), and was absent in weak manifestation of hyperthyroidism. Also, the degree of vagal withdrawal was proportional to the level of FT_3 in the II° and III° groups. Reduced vagal excitability was proved in deep-breathing test. Heart rate variability during deep breathing is the most widely used cardiovascular reflex test. In healthy subjects, the length of successive individual heartbeats varies slightly, mainly with respiration. This phenomenon is known as *sinus arrhythmia,* and consists of a sinusoidal rate variation: an increase during inspiration and a decrease during expiration. Studies of different breathing frequency have established that HRV is greatest at around 6 breaths/min. The response diminishes with age, however. Control of this function of heart rate appears to be mediated by parasympathetic pathways. Cutting the vagus nerve in animals abolishes the response, and stimulating the cut end of the nerve elicits increases and decreases in variation in direct proportion to the size, frequency, and duration of the stimulus. Propranolol and other β-adrenergic blocking drugs do not affect HRV, whereas atropine abolishes the response. A transplanted human heart beats with almost no variation in rate, even with the added stimulus of deep breathing [18]. During the DB test, the increase of HRV (SDNN and LF spectrum) was very limited in the II° and III° groups of patients with hyperthyroidism, and it was inversely proportional to the degree of clinical manifestation of hyperthyroidism and the FT_3 serum concentration. After the subject had received antithyroid treatment and reached a stable, euthyroid state, the vagal modulation and its excitability were not significantly different than that of the control group. This indicates that parasympathetic dysfunction in patients with hyperthyroidism is reversible. The mechanism of vagal withdrawal in thyrotoxicosis still remains an open question. However, some investigators have found that central influence of thyroid hormones (suppression of thyroid-stimulating hormone and thyrotropin-releasing hormone) leads to the activation of inhibiting neurons in the vagal dorsal nucleus in rats [33]. Of major interest is the observation that there was no correlation between SDNN and average heart rate in patients with hyperthyroidism at rest and in DB test. Therefore, the decrease of SDNN in hyperthyroidism is a result of vagal withdrawal and is not simply derived from the increased average heart rate.

It is not surprising that significant gastric myoelectrical dysrhythmia followed by delay of gastric emptying is present in thyrotoxicosis. However, it was not reported previously, since this area had not yet been investigated in detail [10,34,35]. Although not more than 15% of patients with hyperthyroidism have gastrointestinal symptoms such as diarrhea, constipation, nausea, and early satiety, the problem seems to be underestimated because these symptoms are usually overshadowed by cardiovascular manifestation of thyrotoxicosis [11,12]. To avoid an interobserver variability and to improve the reliability of ultrasonographic measurement of gastric emptying, the same experienced ultrasonographer assessed all the patients [36]. The degree of gastric dysrhythmia and delay of gastric emptying was proportional to the level of FT_3 in the II° and III° hyperthyroid groups. This may be explained by impaired mutual gastric neurohormonal co-ordination, in which vagal inhibition facilitates direct influence of thyroid hormones on smooth muscle myogenic autoregulation. Moreover, a reduced H^+ production in the stomach reported in patients with hyperthyroidism may also contribute to the delay of gastric emptying, since it was reported in healthy volunteers after intravenous injection of H_2-blockers [37]. Further investigations are required to find the exact mechanisms of gastric myoelectrical and motor disorders in thyrotoxicosis.

In conclusion, the ANS dysfunction in hyperthyroidism is completely reversible and almost never a huge clinical problem. However, in severe manifestation of thyrotoxicosis it also affects the gastrointestinal tract, resulting in significant dysrhythmia followed by a delay of gastric emptying.

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References

1. Keneth A, Woeber MD. Thyrotoxicosis and the heart. *N Engl J Med* 1992; 327:94–98.
2. Levey GS, Klein I. Catecholamine-thyroid hormone interaction and the cardiovascular manifestations of hyperthyroidism. *Am J Med* 1990; 88:642–646.
3. Ligget SB, Shah SD, Cryer PE. Increased fat and skeletal muscle ß-adrenergic receptors but unaltered metabolic and haemodynamic sensitivity to epinephrine *in vivo* in experimental human thyrotoxicosis. *J Clin Invest* 1989; 83:803–809.
4. Valcavi R, Menozzi C, Roti E, *et al.* Sinus node function in hyperthyroid patients. *J Clin Endocrinol Metab* 1992; 75:239–242.
5. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system: from theory to practice. *J Clin Endocrinol Metab* 1994; 78:1026–1027.
6. Girard A, Hugues FC, Le Jeunne C, *et al.* Short-term variability of blood pressure and heart rate in hyperthyroidism. *Clin Auton Res* 1998; 8:181–186.
7. Kollai B, Kollai M. Reduced cardiac vagal excitability in hyperthyroidism. *Brain Res Bul* 1988; 20:785–790.
8. Heinbach DM, Crout JR. Effect of atropine on the tachycardia of hyperthyroidism. *Arch Int Med* 1972; 129:430–432.
9. Maciel BC, Gallo L, Marin Neto JA, *et al.* Autonomic control of heart rate during dynamic exercise in human hyperthyroidism. *Clin Sci* 1988; 75:209–215.
10. Pfaffenbach B, Adamek RJ, Hagelmann D, *et al.* Effects of hyperthyroidism on antral myoelectrical activity, gastric emptying and dyspepsia in man. *Hepatogastroenterology* 1997; 44:1500–1508.
11. Laurence JM, Colum AG, Vay Liang WG. Gut-thyroid interrelationships. *Gastroenterology* 1978; 75:901–911.
12. Zgliczyński S. *Thyroid diseases.* Wrocław: Urban & Partner; 1998. pp. 152–163.
13. Bolondi L, Bortolotti M, Santi V, *et al.* Measurement of gastric emptying rate by real-time ultrasonography. *Gasroenterology* 1985; 99:752–759.
14. Amara CE, Wolfe LA. Reliability of noninvasive methods to measure cardiac autonomic function. *Can J Appl Physiol* 1998; 23:396–408.
15. Ewing DJ. Noninvasive evaluation of heart rate: the time domain. In: *Clinical Autonomic Disorders. Evaluation and Management.* Low PA, ed. Boston, Toronto, London: Little, Brown and Company; 1993. pp. 297–314.
16. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 1996; 17:354–381.
17. Hojgaard MV, Holstein-Rathlou NH, Agner E, *et al.* Dynamics of spectral components of heart rate variability during changes in autonomic balance. *Am J Physiol* 1998; 275:H213–H219.
18. Hayano J, Sakakibara Y, Yamada A *et al.* Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *Am J Cardiol* 1991; 67:199–204.
19. Pomeranz B, Macaulay RJB, Caudill MA, *et al.* Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985; 248:H151–H153.
20. Barczyński M, Thor P, Pitala A, *et al.* The heart rate variability analysis shows a reversible autonomic nervous system dysfunction in hyperthyroid patients. *Clin Auton Res* 1999; 9:49.
21. Barczyński M, Thor P, Słowiaczek M, *et al.* Autonomic dysfunction in hyperthyroid patients affects gastric myoelectrical activity and emptying. *Neurogastroenterol Mot* 2000; 12:280.
22. Low PA. The effects of aging on the autonomic nervous system. In: *Clinical autonomic disorders. Evaluation and management.* Low PA, ed. Boston, Toronto, London: Little, Brown and Company; 1993. pp. 685–699.
23. La Rovere MT, Bigger JT Jr, Marcus FI, *et al.* (for the ATRAMI Investigators). Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1988; 351:478–484.
24. De Ferrari GM, Vanoli E, Schwartz PJ. Vagal activity and ventricular fibrillation. In: *Vagal control of the heart: experimental basis and clinical implications.* Levy MN, Schwartz PJ, eds. Armonk: Futura; 1994. pp. 613–636.
25. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation* 1992; 85(Suppl I):I77–I99.
26. Levy MN. Sympathetic-parasympathetic interactions in the heart. *Circ Res* 1971; 29:437–445.
27. Tsuji H, Venditti FJ, Manders ES, *et al.* Determinants of heart rate variability. *J Am Coll Cardiol* 1996; 28:1539–1546.
28. Polikar R, Burger AG, Scherrer U, *et al.* The thyroid and the heart. *Circulation* 1993; 87:1435–1441.
29. Cacciatori V, Bellavere F, Pezzarossa A, *et al.* Power spectral analysis of heart rate in hyperthyroidism. *J Clin Endocrinol Metab* 1996; 81:2828–2835.
30. Wingate DL. Autonomic dysfunction and the gut. In: *Autonomic failure. A textbook of clinical disorders of the autonomic nervous system.* Oxford: Oxford University Press; 1993. pp. 510–527.
31. Safa-Tisseront V, Ponchon P, Laude D, *et al.* Contribution of the autonomic nervous system to blood pressure and heart rate variability changes in early experimental hyperthyroidism. *Eur J Pharmacol* 1998; 352:247–255.
32. Pitzalis MV, Mastropasqua F, Massari F, *et al.* Assessment of cardiac vagal activity in patients with hyperthyroidism. *Int J Cardiol* 1998; 64:145–151.
33. Krowicki ZK, Hornby PJ. TRH and substance P independently affect gastric motility in nucleus raphe obscurus of the rat. *Am J Physiol* 1994; 266:G870–G877.
34. Kaneko H, Sakakibara M, Mitsuma T, *et al.* Possibility of postprandial electrogastrography for evaluating vagal/nonvagal cholinergic activity in humans, through simultaneous analysis of postprandial heart rate variability and serum immunoreactive hormone levels. *Am J Gastroenterol* 1995; 90:603–609.
35. Watanabe M, Shimada Y, Sakai S, *et al.* Effects of water ingestion on gastric electrical activity and heart rate variability in healthy human subjects. *J Auton Nerv Syst* 1996; 58:44–50.
36. Irvine EJ, Tougas G, Lappalainen R, *et al.* Reliability and intraobserver variability of ultrasonographic measurement of gastric emptying rate. *Dig Dis Sci* 1993; 38:803–810.
37. Parkman HP, Urbain JL, Knight LC, *et al.* Effects of gastric acid suppressants on human gastric motility. *Gut* 1998; 42:243–250.