The concentration of blood pressure regulating hormones in premenopausal women with isolated systolic hypertension related to hyperthyroidism

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Abstract

OBJECTIVE: The aim of the study was to establish the concentration of blood pressure regulating hormones in premenopausal women with isolated systolic hypertension (ISH) related to hyperthyroidism (HT).

MATERIAL AND METHODS: 61 females with HT were enrolled in the study, including 28 with ISH (Group A), 33 with normal arterial blood pressure (Group B) and 34 healthy individuals (Group C). It was determined – plasma renin activity (PRA), plasma concentration of arginine vasopressin (AVP), atrial natriuretic hormone (ANH) and aldosterone (Aldo). PRA and Aldo tests were performed twice, firstly under basal conditions and then after a 3-day low-sodium diet. In hyperthyroid patients tests were repeated during thyreostatic treatment. Patients with sodium-sensitivity of blood pressure were selected. Cardiac index (CI) and total peripheral resistance index (TPRI) were calculated.

RESULTS: In ISH patients the basal PRA was lower than in patients of Groups B and C. The highest poststimulatory PRA was observed in patients of Group B. ANH concentration was higher in both HT groups compared to the Group C. AVP concentration in ISH patients was higher than in Group C. In HT patients blood pressure correlated with basal PRA, CI and TPRI. Sodium sensitivity of blood pressure was observed more frequently in patients from Group A.

CONCLUSIONS: In women, ISH in HT is the consequence of the increased cardiac output and the decreased peripheral vascular resistance. ISH related to HT results in the reduction in basal PRA probably as the result of intensified cardiac ejection function. ISH in hyperthyroid patients shows a higher sodium-sensitivity.

ORIGINAL ARTICLE

INTRODUCTION

Cardiovascular symptoms predominate in the clinical picture of hyperthyroidism (HT). These symptoms are defined as hyperkinetic circulation and include tachycardia, increased volume and rate of tissue perfusion of circulating blood and increase in cardiac output (CO) (Biondi *et al.* 2002; Klein & Danzi 2007; Palmieri *et al.* 2004). The consequence of the above abnormalities are the changes in arterial blood pressure, which are mainly based on pulse pressure increase since systolic blood pressure (SBP) generally increases and diastolic blood pressure (DBP) decreases. 20–30% of hyperthyroid patients present secondary hypertension (Prisant *et al.* 2006). It usually fulfills the criteria of isolated *s*ystolic hypertension (ISH), which as it is accepted is related to the increased CO and decreased total peripheral vascular resistance. The mechanisms responsible for regulation of volemia and vascular resistance in case of the excess of thyroid hormones have not been fully understood. It is known that HT results in increased activity of the sympathetic system (Levey & Klein 1990) and the changes in the concentration of circulating hormones which regulate volemia and blood pressure such as components of the renin-angiotensin-aldosterone (RAA) system (Asmah *et al.* 1997; Hauger-Klevene *et al.* 1972; Marcisz *et al.* 2003; Marcisz *et al.* 2011), atrial natriuretic hormone (ANH) (Kohno *et al.* 1987; Parlapiano *et al.* 1998; Rolandi *et al.* 1992; Rundle *et al.* 1990; Shigematsu *et al.* 1989; Tajiri *et al.* 1990; Woolf & Moult 1987) and arginine vasopressin (AVP) (Arnaout *et al.* 1992; Marcisz *et al.* 2001). There is no consistency in the obtained results from medical literature regarding the diversity or the direction of changes in the concentration of these hormones in HT. In these studies ISH related to HT was not taken into consideration.

It was clearly proven that hormones regulating circulating blood volume take part both in mechanisms of arterial blood pressure compensation and the induction of arterial hypertension. However, the significance of these hormones in blood pressure regulation in HT is not fully understood. The studies regarding the evaluation of these hormones' concentration in circulating blood in hyperthyroid patients with accompanying secondary ISH have not been conducted.

The aim of the study was to determine blood concentration of blood pressure regulating hormones in premenopausal females with ISH related to HT.

MATERIAL AND METHODS

Subjects

Ninety-five premenopausal females aged 18–50 years, including 61 patients with HT and 34 healthy controls (Group C) were enrolled in the study. HT patients were divided into two groups i.e. Group A (28 patients with ISH) and Group B (33 patients with normal blood pressure). The mean age of Group A was 34.0 ± 8.4 (x ± SD). In 22 cases HT was caused by Graves-Basedow disease and in 6 cases it was caused by a nodular goiter. Group B included persons with normal arterial blood pressure aged 32.3 ± 7.3. Twenty-five of them were diagnosed with Graves-Basedow disease and 8 patients were diagnosed with nodular goiter. Group C included 34 females with mean age of 30.9 ± 7.9 years. HT diagnosis was made on the bases of physical examination and medical history with the calculation of Crooks' index (Crooks *et al.* 1960), determination of free triiodothyronine (fT3) and free thyroxine (fT4) in blood serum. The restoration of thyreometabolic state was determined on the basis of the regression of clinical symptoms of thyroid dysfunction and obtaining normalization of the concentration of thyroid hormones and TSH in blood serum. The criterion for the diagnosis of ISH (Whitworth & Chalmers 2004) related to HT included SBP ≥ 140 mm Hg, its normalization during the restoration of euthyroid state and DBP < 90 mm Hg.

The following patients were excluded from the study – pregnant females, patients with circulatory and respiratory insufficiency and arrhythmias (except for sinus tachycardia), patients with kidney, liver and organic heart diseases and patients with acute inflammation and metabolic and endocrine system diseases. Patients had not taken any medication at least two weeks prior the investigation.

The study protocol was approved by the Bioethical Committee of the Medical University of Silesia in Katowice.

Study protocol

In the investigated patients the series of hormonal tests were performed. The tests in hyperthyroid patient group were repeated during treatment, firstly at the time of the predicted normalization of thyroid hormone concentration in blood serum (i.e. after 14 days of using a thyreostatic medication – short-term treatment). Then tests were repeated at the time of the restoration of euthyroid state (mean time – 7 months after thyreostatic administration – long-term treatment). All patients were treated with Thiamazol (Polfa, Poland) with the daily dose of 45–50 mg, at least for 2 weeks. Then the dose was reduced to 5–10 mg/daily as the maintenance treatment. Each time before the tests all patients were measured and for each patient BMI was calculated in accordance with the following formula – BMI = body mass[kg]/height^2 [m^2].

The preprandial measurements of heart rate (HR) and arterial blood pressure were performed in the early hours after a 20-minute rest in the sitting position. The measurements were repeated twice over a few minutes' period. On the bases of such measurements, the mean value was calculated. Pulse pressure was calculated as the difference between SBP and DBP and mean arterial pressure (MAP) in accordance with the following formula – MAP = (pulse pressure × 1/3) + DBP. Persons

with the decreased MAP by at least 5% as the result of using a low-sodium diet were classified according to Sullivan & Ratts (1988) to the group with sodium sensitivity of blood pressure. The other patients were in the sodium insensitive group.

In all investigated persons plasma renin activity (PRA), plasma concentrations of AVP and ANH, serum aldosterone (Aldo), fT3, fT4, sodium and potassium levels and hematocrit were determined. In each cycle of tests the determination of these parameters was performed twice. Firstly, it was performed under basal conditions i.e. in the lying position after a 3-day normal sodium diet which contained 120 mmol sodium and 70 mmol potassium a day and an 8-hour nocturnal bed rest. Secondly, the tests were performed after a 3-day low-sodium diet (10 mmol Na and 70 mmol K daily) and a 3-hour standing position. ANH and AVP concentrations were not determined with a low-sodium diet and standing position. Stimulants (i.e. cigarettes, alcohol, coffee and strong tea) had been avoided for at least 15 hours before the tests.

The determination of concentration of hormonal parameters was performed using a Radio Immuno Assay, with the use of ready-made sets to determine PRA, Aldo, AVP, ANH, fT3, and fT4. TSH serum concentration was determined by Immunoradiometric Assay. In each cycle of hormonal determination ultrasonocardiography (UCG) was performed determining stroke volume (SV) using the Teichholz *et al.* (1976) formula to calculate end-systolic volume and end-diastolic volume of the left ventricle, CO [(l/min) = SV × HR] and total peripheral resistance [TPR ($dyn \times s \times cm^{-5}$) = 80 × MAP/CO]. CO and TPR were shown as the parameters considering body surface – CI ($l/min/m^2$) and TPRI ($dyn \times s \times cm^{-5}/m^2$) accordingly. Arterial blood pressure was measured immediately before UCG and after its completion determining mean values of SBP, DBP and MAP. HR was measured by ECG.

Statistical analysis

All statistical calculations were performed using PC with 1.5 GHz Pentium Processor. Open Office 1.1.4 was used to prepare the spreadsheet and data base. Significance level $p(\alpha) = 0.05$ was used in statistical analysis.

The proper statistical analysis was preceded by checking the type of distribution of the analyzed variables with the use of the significance χ^2 (chi-square) test. For most parameters normal distribution or very close to normal distribution was obtained and in these cases Student's t-tests were used. In the case when the distribution differed from the normal one the Mann-Whitney U test was used for unpaired variables and Wilcoxon's test was used for paired variables.

Parametric Student's t-test of the unpaired variables was used in order to validate the hypothesis concerning the equality of mean values in two different groups. At the first stage, the Fisher F-test was performed to check variance equality of the investigated groups. In the case of irregularity of these variances the Satterthwaite's test was used. In the remaining cases the classic Student's t-test was adopted. To test the mean values in the same group before treatment and after the restoration of euthyroid state, Student's t-test for paired variables was used. A non-parametric independence χ^2 test was used to verify whether the compared groups differed in terms of characteristic features.

Analyzing the relationship between different measurable features in the investigated group, the regression function (II type) was used. Its parameters were determined by the least sum squares method. The linear function of $y = ax + b$ was used. The *r* correlation coefficients were calculated and they were statistically verified.

Multiple regression analysis was used to determine the relationship between the chosen feature (dependent variable) and a few other parameters at the same time (independent variables). A linear multiple regression was adopted and its indices were calculated by the least sum squares method. Similarly to the linear two-dimensional regression, besides the evaluation of regression coefficients, the verification of statistical hypotheses concerning the value of these coefficients was performed.

RESULTS

It was shown that there were no significant differences between both HT groups (Groups A and B) with regard to the hyperthyroid symptom duration, Crooks' clinical index and concentration of free thyroid hormones (Table 1). In hyperthyroid patients higher pulse pressure, HR and CI and lower TPRI were observed in comparison with the control group (Table 2). Significant differences regarding HR, CI and TPRI were noted between HT groups. Higher HR and CI and lower TPRI were observed in ISH patients. After restoration of euthyreosis, pulse pressure and CI did not reach the values obtained in Group C (Table 2).

In non-treated patients with ISH basal PRA was significantly lower than in patients with normal blood pressure ($p<0.05$) and in healthy individuals ($p<0.05$) (Table 3). The highest poststimulatory PRA was observed in non-treated patients with normal blood pressure. A significant difference was observed only when compared with the control group ($p<0.05$). Aldosteronemia was comparable in all investigated groups, irrespective of the conditions in which the tests were performed. ANH plasma concentration was significantly higher in both investigated groups with non-treated HT and short-time HT treatment compared with the control group ($p<0.001$) (Table 3). AVP plasma concentration in ISH patients was significantly higher than in healthy individuals ($p<0.05$).

A low-sodium diet resulted in significantly more frequent occurrence of sodium-sensitivity of blood pressure in non-treated ISH patients (compared with the

Tab. 1. Parameters determining thyroid function and body mass index (BMI) in patients with hyperthyroidism with isolated systolic hypertension and normal blood pressure and in healthy controls (x ± SEM).

Parameter	INVESTIGATED GROUPS						
		Hyperthyroid patients					
	Controls (n = 34)	Isolated systolic hypertension (n = 28)			Normal blood pressure (n = 33)		
		Before treatment	After short-treatment	Euthyroid, after treatment	Before treatment	After short-treatment	Euthyroid, after treatment
Symptom duration (months)		4.9 ± 0.7			4.2 ± 0.4		
Treatment time			2 weeks	7.2 ± 0.3 months		2 weeks	6.8 ± 0.2 months
Crooks' index	3.5 ± 0.1	27.1 ± 0.2	16.2 ± 0.2	4.3 ± 0.1	27.4 ± 0.2	15.3 ± 0.2	3.8 ± 0.2
Serum fT3 (pmol/l)	5.4 ± 0.4	28.1 ± 2.1	7.4 ± 1.1	7.2 ± 0.7	22.7 ± 2.3	7.9 ± 1.5	7.4 ± 0.9
Serum fT4 (pmol/l)	15.3 ± 1.0	62.3 ± 7.9	17.8 ± 2.3	16.4 ± 1.7	52.9 ± 4.4	17.1 ± 2.2	15.5 ± 1.8
Serum TSH (mIU/l)	1.63 ± 0.38	0.09 ± 0.05		2.79 ± 0.71	0.08 ± 0.02		1.95 ± 0.12
BMI (kg/m^2)	23.2 ± 0.8	22.8 ± 0.6	23.2 ± 0.7	24.2 ± 0.7	21.1 ± 0.4	21.2 ± 0.4	22.7 ± 0.5

Tab. 2. Arterial blood pressure and heart rate and hemodynamic parameters in patients with hyperthyroidism with isolated systolic hypertension and normal arterial blood pressure and in healthy controls (x ± SEM).

Parameter	INVESTIGATED GROUPS						
		Hyperthyroid patients					
	Controls (n = 34)	Isolated systolic hypertension (n = 28)			Normal blood pressure (n = 33)		
		Before treatment	After short-treatment	Euthyroid, after treatment	Before treatment	After short-treatment	Euthyroid, after treatment
SBP (mm Hg)	112± 2.0	150 ± 2.4^{bd}	131 ± 3.7§^{b}	126 ± 2.7§^{b}	124 ± 1.8^{b}	118 ± 2.3¶^{a}	117 ± 2.5¶
DBP (mm Hg)	76 ± 1.7	77 ± 2.5	74 ± 2.8	77 ± 3.1	69 ± 1.8^{a}	71 ± 1.9	75 ± 2.2 ¶
MAP (mm Hg)	85 ± 1.6	102 ± 2.1^{bd}	93 ± 2.8*	93 ± 2.9*	87 ± 1.5	87 ± 1.8	89 ± 2.1
Pulse pressure (mm Hg)	36 ± 1.9	73 ± 2.8^{bd}	56 ± 2.3§^{b}	49 ± 1.7§^{bc}	55 ± 2.3^{b}	47 ± 2.0§^{b}	42 ± 1.9§^{a}
HR (beats/min)	78 ± 2.1	108 ± 2.9^{bc}	87 ± 2.6^{a}	79 ± 2.3^{c}	102 ± 2.4^{b}	88 ± 2.2^{a}	84 ± 1.6
CI (l/min/m^2)	3.08 ± 0.20	5.99 ± 0.25^{bd}	4.48 ± 0.28§^{b}	3.93 ± 0.25§^{a}	4.51 ± 0.21^{b}	4.17 ± 0.28^{a}	3.81 ± 0.26*^{a}
TPRI (dyn × s × cm^{-5}/m^2)	981 ± 64	508 ± 23^{bd}	668 ± 55*^{b}	802 ± 74§	681 ± 38^{b}	740 ± 47^{a}	832 ± 63*

SBP - systolic blood pressure, DBP - diastolic blood pressure, MAP - mean arterial pressure, HR - heart rate, CI - cardiac index, TPRI - total peripheral resistance index, *p<0.05, ¶p<0.01, §p<0.001 for the comparison with before treatment, ^{a}p<0.05, ^{b}p<0.001for the comparison with the controls, ^{c}p<0.05, ^{d}p<0.001for the comparison with the normal blood pressure patients

control group and the group of hyperthyroid patients with normal blood pressure p<0.01) (Table 4).

In correlation studies in non-treated HT patients the following correlations were shown: SBP : basal PRA, r=–0.39 (p<0.01), CI:basal PRA, r=–0.43, (p<0.01), SBP:CI, r=0.46, (p<0.01), SBP:HR, r=0.57 (p<0.001), DBP:TPRI, r=0.41 (p<0.01).

DISCUSSION

Our study shows that in premenopausal hyperthyroid females, SBP was higher than in healthy individuals. It was completely consistent with other study results (Kohno *et al.* 1987; Marcisz *et al.* 2002; Palmieri *et al.* 2004; Parlapiano *et al.* 1998; Rolandi *et al.* 1992; Saito & Saruta 1994; Tajiri *et al.* 1990). During HT treatment it was shown that SBP decreases and is almost completely normalized after a short-term administration of thyreostatic medication, especially in ISH patients. Such a quick reduction in SBP demonstrated in the study as a consequence of using only a classic thyreostatic agent can be related to the convergent direction of changes in HR and CI. The values of these hemodynamic parameters clearly distinguished ISH patients not only when compared with the healthy individuals but also with hyperthyroid patients with normal blood pressure. Therefore it can be accepted that increased SBP was the consequence of the remarkable CO increase, especially

Tab. 3. Plasma renin activity (PRA), aldosteronemia (Aldo), plasma concentration of atrial natriuretic hormone (ANH) and arginine vasopressin (AVP) in patients with hyperthyroidism with isolated systolic hypertension and normal arterial blood pressure and healthy controls (x ± SEM).

Parameter		INVESTIGATED GROUPS						
			Hyperthyroid patients					
		Controls (n=34)	Isolated systolic hypertension (n = 28)			Normal blood pressure (n = 33)		
			Before treatment	After short-treatment	Euthyroid, after treatment	Before treatment	After short-treatment	Euthyroid, after treatment
PRA (ng/ml/h)	Bas	1.69 ± 0.16	1.22 ± 0.14[ac]	1.52 ± 0.18	1.40 ± 0.19	1.93 ± 0.25	1.55 ± 0.20	1.60 ± 0.27
	Post	6.12 ± 0.83†	8.66 ± 0.95†	8.17 ± 0.8†	7.94 ± 1.05†	10.96 ± 1.14†[a]	8.22 ± 0.7†*	7.69 ± 0.76†*
Serum Aldo (pg/ml)	Bas	129 ± 9	155 ± 15	165 ± 21	156 ± 21	152 ± 16	135 ± 13	142 ± 12
	Post	390 ± 41†	443 ± 32†	425 ± 24†	377 ± 37†	424 ± 29†	415 ± 34†	381 ± 28†
Plasma ANH (pg/ml)	Bas	44 ± 3	88 ± 3[b]	72± 4¶[b]	51 ± 3§	91 ± 3[b]	79 ± 5[b]	49 ± 3§
Plasma AVP (pg/ml)	Bas	2.6 ± 0.2	3.9 ± 0.3[a]	3.5 ± 0.4	2.6 ± 0.2¶	3.3 ± 0.4	3.3 ± 0.3	2.3 ± 0.2*

Bas - basal, Post - poststimulatory, †p<0.001 for the comparison with basal, *p<0.05, ¶p<0.01, §p<0.001for the comparison with before treatment, [a]p<0.05, [b]p<0.001for the comparison with the controls, [c]p<0.05 for the comparison with the normal blood pressure patients

Tab. 4. Occurrence of sodium sensitivity of blood pressure in patients with hyperthyroidism with isolated systolic hypertension and normal arterial blood pressure and healthy controls

	INVESTIGATED GROUPS						
		Hyperthyroid patients					
	Controls (n = 34)	Isolated systolic hypertension (n = 28)			Normal blood pressure (n = 33)		
		Before treatment	After short-treatment	Euthyroid, after treatment	Before treatment	After short-treatment	Euthyroid, after treatment
PSS	7	15	6	6	5	8	10
PSS (%)	21	54*	21	21	15	24	30

PSS - persons with sodium sensitivity of blood pressure, PSS (%) - percentage of persons with sodium sensitivity of blood pressure (%). *p<0.01 for comparison with normal blood pressure group and healthy controls

in ISH patients, which was demonstrated in our study. The proven positive correlation between the value of SBP and CI and the convergent decrease in the value of these parameters during treatment is also consistent with such an opinion. The relationship between the increased ejection function of the heart and the value of SBP is well known and was most frequently considered in the mechanism which explained the occurrence of arterial hypertension in HT (Biondi *et al.* 2002; Marcisz *et al.* 2002; Prisant *et al.* 2006; Saito & Saruta 1994).

Our study demonstrates that the value of peripheral vascular resistance in hyperthyroid patients was significantly decreased. This symptom is completely consistent with the results from other reports (Biondi *et al.* 2002; Marcisz *et al.* 2002; Palmieri *et al.* 2004). Out of the investigated persons, the lowest values of TPR were observed in ISH patients. It may be suspected that in the compensatory mechanism, wall vessels reacted by the decreased resistance to the remarkable increase in CO. However, in ISH patients such a response was not sufficient to maintain normal blood pressure. That means that the increased CO dominated the diastolic possibilities of the vascular wall to the increased blood flow, which resulted in systolic hypertension in these patients. Another factor which caused the increase in SBP was the increased HR, which on the one hand influenced directly CO increase and on the other hand indirectly influenced the reduction in dynamic compliance of arterial walls (Biondi *et al.* 2002; Liang *et al.* 1999; Palmieri *et al.* 2004; Wilkinson *et al.* 2000). Therefore it is probable that the increased HR and a remarkable increase in CO together with the decrease in cardiac reserve regarding arterial wall compliance contribute to secondary ISH in patients with HT. According to Palmieri *et al.* (2004) the decrease in arterial wall compliance enables faster blood flow from the left ventricle to peripheral vessels resulting in circulatory hyperkinesis. Remarkably high positive correlation between HR and SBP in our hyperthyroid patients can suggest that HR can result in SBP. Biondi *et al.* (2002) suggested that the increased systolic ejection function of the heart accompanying HT is a compensatory response to changes

in peripheral hemodynamics. It might be possible to notice feedback mechanism between the cardiac activity and functional changes in blood vessels, which in the case of excessive thyroid hormones can disturb circulatory homeostasis and result in the increase in blood pressure or even arterial hypertension.

DBP in hyperthyroid patients was diversified in our investigation. In ISH group DBP showed no difference compared with pressure in healthy individuals and it was decreased in patients with normal blood pressure. However, pulse pressure indicating the difference between the systolic and diastolic pressure was significantly the highest in ISH patients. Increased pulse pressure which is the basic symptom of hyperkinetic circulation (Klein & Danzi 2007; Palmieri *et al.* 2004; Prisant *et al.* 2006), especially in such dimension, indicates considerably increased vascular blood flow. The amount of blood flowing via vessels in ISH patients was probably so high that despite the decreased TPR (more than in patients with normal blood pressure), DBP was not reduced. However, it should be noted that their values in correlative studies indicated positive correlation in non-treated HT patients. The restoration of normal vascular peripheral resistance was possible after long-term HT treatment and after the restoration of the euthyroid state. After a short-term treatment, peripheral resistance increased but only insignificantly despite normalization of the thyroid hormones serum concentration. It was probably related to thyroid hormones action in tissues, their direct influence on the muscular coat of the vascular wall and the maintenance of increased thermogenesis and small vessel dilation related to it.

Studies on sodium sensitivity of blood pressure were very interesting. In our investigation it was shown that in more than 50% of ISH patients blood pressure was characterized by sodium sensitivity since as the consequence of a 3-day low-sodium diet in 54% of patients a considerable (established by Sullivan & Ratts) (1988) over a 5% decrease in MAP was noted. The problem of sodium sensitivity of blood pressure in patients with thyroid abnormalities was undertaken and described by Marcisz *et al.* (2001). According to this pioneering report, a significantly higher frequency of sodium sensitivity of blood pressure concerned only hypothyroid patients. That could be related to a lower increase in PRA after stimulation with a low-sodium diet.

However, the results of Marcisz *et al.* (2001) indicate that persons with sodium sensitivity of blood pressure who are healthy or who present some thyroid abnormalities had significantly higher MAP at the time when they used a normal-sodium diet. In our investigation when sodium sensitivity of blood pressure was analyzed separately in the groups with hypertension and normal arterial pressure, MAP was also higher in ISH patients. It can partly explain the increased frequency of the occurrence of sodium sensitivity of blood pressure in patients with ISH secondary to HT.

It is suggested in medical literature that changes in blood pressure as the consequence of the limited sodium supply depended on the activity of the adrenergic system (Naslund *et al.* 1990). It was proven that a low-sodium diet resulted in the increased sensitivity of β-adrenergic receptors of the vascular wall. That can be related to the vasodilation effect. It is suspected that intracellular sodium influences modulation of adrenergic receptor sensitivity (Naslund *et al.* 1990). Undertaking studies on the activity of adrenergic receptors during a low-sodium diet in hyperthyroid patients would be recommended, especially with the accompanied arterial hypertension, considering its sodium-sensitivity. Such studies could explain a phenomenon of sodium sensitivity of blood pressure.

The activity of the RAA system was also taken into consideration in the mechanism regulating sodium sensitivity of blood pressure. It was shown that in persons with sodium sensitivity of blood pressure, PRA and aldosteronemia stimulated by a low-sodium diet were significantly lower than in the group of persons with sodium insensitivity of blood pressure (Sullivan & Ratts 1988). In our studies the increase in PRA and Aldo serum concentration after stimulation with a low-sodium diet together with the upright position was similar in both groups with HT which were diversified in terms of the value and sodium sensitivity of arterial blood pressure. It can be assumed that the role of these hormones in the mechanism of arterial pressure reaction to sodium in hyperthyroid patients is not significant.

Secondary arterial hypertension dependent on HT occurs in 20–30% patients (Prisant *et al.* 2006; Saito & Saruta 1994). It has not been explained why in some hyperthyroid patients it causes arterial hypertension and in others blood pressure remains normal. The speculation that the value of arterial blood pressure depends on the intensity of thyreotoxicosis was not proven in our study since non-treated hyperthyroid patients who were included in the group with arterial hypertension or normal blood pressure did not differ significantly in terms of the concentration of free thyroid hormones in serum, the value of Crooks' index or even the duration time of HT symptoms. However, they were different in terms of HR, CI which were higher and TPRI which was lower in patients with ISH compared with patients with normal blood pressure. What could be the basis of diversified values of these hemodynamic parameters which are known to have a considerable influence on the value of arterial blood pressure, especially in HT patients? All of them depend on the excess of thyroid hormones and the activity of the sympathetic system and in particular β–adrenergic system since the increased β_2 receptor sensitivity resulted in decreased vascular resistance (Scivoletto *et al.* 1986). The increased β_1 receptor sensitivity in the heart resulted in the stimulation of HR and systolic ejection function of the heart (Martin 1993). However,

if both investigated HT groups did not differ in terms of thyreometabolic state, it is probable that they were characterized by different concentration of catecholamines and/or the action of β-adrenergic receptors. The studies on the action of the adrenergic system were not the subject matter of the current study. Undertaking such studies to explain the mechanism of secondary arterial hypertension in HT is well-grounded. It could also expand the knowledge concerning supportive HT treatment with the use of β-blockers.

It is impossible not to mention the possible involvement of hormones influencing the volume of circulating blood and the systolic/diastolic function of the vascular wall in the mechanisms regulating blood pressure level in hyperthyroid patients. First of all, it is necessary to mention components of the RAA system, ANH and AVP which serum concentrations change in the conditions of the excess of thyroid hormones.

In non-treated patients with the ISH related to HT, basal PRA was lower than in patients with normal blood pressure and healthy individuals. However, the prevalent opinion in medical literature is that HT results in stimulation of the renin-angiotensin system, which was manifested by the increased PRA (Hauger-Klevene *et al.* 1972; Shigematsu *et al.* 1989). On the other hand, lack of significant diversity of this parameter influenced by the excess of thyroid hormones was also reported (Kato *et al.* 2009; Marcisz *et al.* 2003; Ogihara *et al.* 1980; Woolf & Moult 1987). A negative correlation shown in our investigation between basal PRA and the value of SBP and CI in non-treated hyperthyroid patients and normalization of this activity together with the compensating blood pressure and ejection function of the heart may suggest that hemodynamic factors and increased renal blood flow in particular were the result of the decreased basal PRA in ISH patients.

The application of a low-sodium diet together with the upright position resulted in the significantly higher increase in PRA in hyperthyroid patients compared with healthy individuals. Similar results were provided in other reports where the upright position stimulus (Hauger-Klevene *et al.* 1972; Shigematsu *et al.* 1989), a low-sodium diet (Marcsz *et al.* 2003) and intravenous furosemide administration (Asmah *et al.* 1997) were used. Both basal and poststimulatory PRA was higher in hyperthyroid patients with the normal blood pressure compared with healthy individuals. Ogihara *et al.* (1980) reported that in some hyperthyroid patients with normal arterial blood pressure, a higher PRA was observed compared with the group of patients with arterial hypertension dependent on the excess of thyroid hormones. Therefore Ogihara *et al.* (1980) suggested that the renin-angiotensin system may play a significant part in blood pressure homeostasis in decreased effective volume of circulating blood related to the tendency to water loss in thyreotoxicosis. It may be suspected that as the result of the decreased sodium supply in diet in hyperthyroid patients, the reduction in effective volume of circulating blood is more evident, since factors which cause the dilation of the vascular bed inhibit compensatory vasoconstriction. These factors include excessive amount of thyroid hormones, increased metabolism and increased thermogenesis in tissues.

In this case the maintenance of arterial pressure homeostasis during a low-sodium diet and the upright position could require more stimulation of the renin-angiotensin system, especially in hyperthyroid patients whose vascular pressosensitivity to angiotensin II was significantly lowered as Hauger-Klevene *et al.* (1972) demonstrated. Therefore it is probable that in order to achieve an essential pressor effect with the decreased response of vascular receptors to angiotensin, compensatory mechanism is initiated. It is based on the stimulation of the renin-angiotensin system, which results in the increase in poststimulatory PRA. Our studies and the data taken from the medical literature allow us to state that the renin-angiotensin system does not seem to play a crucial role in the mechanism of arterial hypertension secondary to HT.

In our study basal aldosteronemia was comparable in hyperthyroid patient groups diversified by the value of arterial blood pressure and in healthy patients. According to other reports, HT did not cause significant changes in terms of Aldo serum concentration either (Asmah *et al.* 1997; Diekman *et al.* 2001; Kigoshi *et al.* 1993). Aldo serum concentration and its increase as the consequence of a low-sodium diet together with upright position were in hyperthyroid patients similar to the values in healthy individuals. In hyperthyroid patients inadequate aldosteronogenesis as the response to the increased poststimulatory PRA was observed, which may prove that in the patients both with ISH and with normal blood pressure the dissociation in the RAA system was observed. The presence of the dissociation in RAA system in HT was reported previously (Asmah *et al.* 1997; Marcisz *et al.* 2003). It suggests the decrease in receptor sensitivity to angiotensin II in adrenal glands as the result of the excess of thyroid hormones. It was also suggested that the increased ANH concentration is involved in the inhibition of such a response (Marcisz *et al.* 2003).

ANH plasma concentration was remarkably high in our hyperthyroid patients. The increased concentration of this peptide as the result of the excess of thyroid hormones has already been reported (Diekman *et al.* 2001; Kato *et al.* 2009; Kohno *et al.* 1987; Marcisz *et al.* 2003; Parlapiano *et al.* 1998; Rolandi *et al.* 1992; Tajiri *et al.* 1990; Woolf & Moult 1987). Two major factors were considered in the mechanism of the increased ANH release into the bloodstream in hyperthyroid patients. The first factor was the direct action of thyroid hormones in the heart and the second factor concerned hemodynamic changes resulting in the increase in blood pressure in the atrium and the distention of its walls. In our studies a high plasma concentration

of ANH in hyperthyroid patients did not differ in the groups of ISH and normal blood pressure despite the fact that these groups were different in terms of HR, SBP, pulse pressure, MAP and CI. Therefore it is probable that the symptoms of hyperkinetic circulation related to HT did not play a significant role in the regulation of the synthesis and release of ANH. Lack of changes in the concentration of this peptide in hyperthyroid patients as the consequence of decreased HR caused by β-blocker administration (Rolandi *et al.* 1992; Shigematsu *et al.* 1989) supports the above argument.

Our study proved in hyperthyroid patients the lack of correlation between component values of arterial blood pressure and ANH plasma concentration, which is consistent with other correlative reports (Kohno *et al.* 1987; Rolandi *et al.* 1992; Tajiri *et al.* 1990). Such lack of correlation indicates that the direct participation of this peptide in the regulation of arterial blood pressure dependent on HT is uncertain.

In hyperthyroid patients with ISH it was shown that AVP plasma concentration was considerably higher than in healthy individuals. However, in the group of hyperthyroid patients and normal arterial blood pressure, AVP plasma concentration did not differ significantly compared with healthy individuals. AVP plasma concentration decreased to the normal level after thyreostatic treatment and the restoration of euthyroid state. There are not many medical reports on AVP concentration in hyperthyroid patients. According to these reports, the release of this neuropeptide into the bloodstream was increased (Arnout *et al.* 1992; Diekman *et al.* 2001; Marcisz *et al.* 2001). The obtained results of our investigation do not explain the mechanisms determining the increase in AVP plasma concentration in patients with ISH dependent on HT. It was suggested that the increase in the concentration of vasopressin as a result of thyroid hormones excess was not related to the osmotic mechanism but it could be dependent on the changes in circulating blood volume (Marcisz *et al.* 2001).

CONCLUSIONS

In conclusion, ISH in hyperthyroid premenopausal women is the consequence of the increased cardiac output and the decreased total peripheral vascular resistance in the volume mechanism insufficiently compensated by vascular bed dilation. ISH related to HT results in the reduction in basal PRA probably as the result of intensified cardiac ejection function. ISH in hyperthyroid patients shows a higher sodium-sensitivity compared with patients with normal arterial pressure.

Disclosure Statement

The authors declare that no competing financial interests exist.

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