ORIGINAL ARTICLE

Effects of neuroendocrine changes on results of ambulatory blood pressure monitoring (ABPM) in adolescent girls with anorexia nervosa

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Abstract

OBJECTIVES: Anorexia nervosa (AN) is characterized by marked neuroendocrine and autonomic dysfunctions. In the recent studies using automatic blood pressure monitoring (ABPM), lower BP values and lack of circardian variation of BP in anorectic patients were demonstrated. Unfortunately effects of hormonal changes, that may explain BP abnormalities were not analysed together.

DESIGN: The aim of our study was the assessment of ABPM and hormonal status in anorectic girls.

SETTINGS: The study was performed on hospitalized 25 female anorectic adolescents aged 12–18 years. Control group was 17 age and height matched girls with normal weight and negative history for hypertension. ABPM was performed between 5 and 7 day of hospitalization, every 30 minutes during active period and every 60 minutes during sleep. Hormones (FSH, LH, estradiol, cortisol and fT_4) serum concentrations were also evaluated.

RESULTS: Mean systolic BP values were significantly lower in patients with AN in comparison to controls. Maximal diastolic and mean arterial pressure values for the whole day and active period but not for sleep were lower in AN than in controls. Anorectic girls showed tendency to night-time bradycardia. Moreover, there were no physiological circadian variation of BP in AN.

CONCLUSIONS: We conclude that hormonal regulation of blood pressure and heart rate in anorectic patients is at least partially preserved. Lower blood pressure values, bradycardia and lack of physiological night fall of BP in anorectic patients may result from altered autonomic system function resulting from hormonal disturbances and other centrally mediated mechanisms.

Abbreviations

ABPM - ambulatory blood pressure monitoring
AN - anorexia nervosa
BP - blood pressure
CRH - corticotropin releasing hormone
DIA - diastolic blood pressure
FSH - follicle stimulating hormone
fT4 - free thyroxine
GnRH - gonadotropin releasing hormone
HR - heart rate
HRV - heart rate variability
LH - luteinizing hormone
LV - left ventricle
MAP - mean arterial pressure
MAX - maximal blood pressure
MIN - minimal blood pressure
NA-VL - ventrolateral nucleus ambiguus
NPY - neuropeptide Y
SYS - systolic blood pressure
T3 - triiodothyronine
T4 - thyroxine
TSH - thyroid stimulating hormone

INTRODUCTION

Anorexia nervosa (AN) is third of the most common illnesses in adolescent girls between 15 and 19 years of age after obesity and bronchial asthma [42]. The diagnostic criteria of AN according to DSM-IV are: self induced weight loss to less than 85% of the weight considered normal for age and height (or BMI less than 17.5 kg/m^2), intensive fear of obesity, disturbed body image and amenorrhea (i.e. absence of at least three consecutive menstrual cycles) in postmenarchal females [1].

Etiology of AN remains unclear. It is characterized by marked neuroendocrine and autonomic dysfunctions, that are not specific to this disorder, as they appear also in starvation of other origin, but some of them are believed to be primary changes underlying pathological background of the disease [38].

It is known that anorectic patients have lower blood pressure values than healthy controls and some of them suffer from bradycardia and orthostatic symptoms [9,28].

Table 1. Anthropometric parameters of examined control and anorectic subjects.

Parameter	MEAN ± SD (range)		p-value
	Control group (n=17)	AN (n=25)	
Age (years)	16.00±1.77 (12–18)	15.07±1.51 (12–18)	NS
Height (cm)	161.47±7.78 (142–173)	161.59±7.20 (145–176)	NS
Weight (kg)	58.88±6.73 (44–66)	39.21±5.56 (26–45)	p<0.00001
BMI (kg/m^2)	22.7±2.01 (18.08–24.24)	14.98±1.72 (12.3–17.5)	p<0.00001

Blood pressure is not a static, but rather a continuous variable that changes from minute to minute. Ambulatory blood pressure monitoring (ABPM) enables BP assessment multiple times during a predefinied period, which better reflects the continuous nature of BP as hemodynamic variable [37]. Lack of physiological fall in BP during sleep (normally at least 10%) is thought to be concerned with autonomic system disturbances as neurovegetative neuropathy in diabetes mellitus, chronic renal insufficiency, Cushing syndrome and orthostatic hypotonia [10,37].

In two recent studies using ABPM [3,11], lower BP values and lack of circadian variation of BP in anorectic patients were demonstrated. Heart rate variability (HRV) measurements showed reduced activity of the sympathetic nervous system in these subjects. Unfortunately hormonal parameters of examined females were not assessed, that unables the interpretation of results according to these data and possible explaination for observed changes. Therefore the aim of our study was the assessment of BP and HR in anorectic adolescent girls using ABPM and implications of hormonal status parameters to observed changes.

MATERIAL AND METHODS

The study was performed on 25 anorectic adolescent girls aged 12–18 years (mean age 16.00±1.77) hospitalized due to acute phase of AN in Dept. of Pediatrics in Zabrze, Silesian University of Medicine in Katowice, Poland meeting the diagnostic DSM-IV criteria for AN. All examined patients were at IV–V Tanner stage [40]. Control group was 17 age- and height- matched girls with normal weight for age and height, hospitalized in the same department due to other problems as abdominal pains, acute diarrhoea, headaches, recurrent respiratory tract infections with negative personal and family history of hypertension. Obviously, control patients had significantly higher weight and BMI in comparison to AN group (Table 1). All patients and/or their parents (legal representatives) gave their informed consent for the study.

Anthropometric measurements (body weight, height, BMI) were performed at the admission to the hospital. Subjects` height was measured using a single stadiometer, weight was measured on electronic scale.

ABPM was performed between 5 and 7 day of hospitalization to minimalize the effect of stress concerned with the admission to the hospital and after dehydratation and mineral disturbances compensation, using BR-102 (Schiller Poland LTD) device. This device uses Korotkoff sound and oscillometric method to measure heart rate (HR), systolic (SYS) and diastolic (DIA) pressures. The BP was measured every 30 minutes from 7.00–22.00 (active period) and every 60 minutes from 22.00–7.00 (sleep). Korotkoff sound data were supplemented by oscillometric measurements. Obtained results were analysed using software program attached to BR-102 device concerning mean, minimal and maximal values

for SYS, DIA, mean arterial pressure (MAP) and HR for the whole 24-hour period, active and sleep phase. Erroneous measurements are automatically rejected by the system basing on widely accepted criteria [10]: DIA is more than SYS, DIA is <30 mmHg, difference between SYS and DIA is <10 mmHg and >110 mmHg, pressure value change compared to the last or the next value is >50%, SYS is >240 mmHg. BP values measured when HR is <40/min or >150/min are also considered as erroneous. The percent sleep decline in BP (dipping) was calculated by subtracting the sleep MAP from the awake MAP and dividing this value by the awake MAP.

Hormones (FSH, LH, estradiol, cortisol and fT_4) serum concentrations evaluation in anorectic girls was performed at the admission on the hospital laboratory using Elecsys 2010 analyser (Roche Diagnostics). All blood samples were collected in fasting state between 8.00 and 9.00 a.m.

Statistical analysis

Data are presented as means ± SD. Statistical analysis was performed using the program Statistica 6.0. Data distribution was assessed using Kolmogorow-Smirnow test. Comparisons between control and anorectic groups were made using T-test for independent samples or U-Mann Whitney test (for distribution different than normal). Correlations were analyzed by Pearson linear correlation or Spearman test (for distribution different than normal). Statistical significance level was established on $p<0.05$.

RESULTS

ABPM data for control and anorectic patients are demonstrated in Table 2. Erroneous measurements rate was 4.22±4.10% in anorectic group and 5.12±4.95 in control group. No patient from control either anorectic group was hypertensive according to normal ranges for height and sex for Polish population, that means all values were below 90th percentile for height and sex [43].

Mean SYS values were significantly lower in patients with AN in comparison to controls during the whole day, and also for active period and sleep period. Moreover, patients with AN demonstrated significantly lower maximal DIA and MAP values for the whole day and active period but the asleep values were similar in both

Table 2. Results of automatic systolic blood pressure measurements (mmHg) in anorectic and control adolescent girls (mean ± SD).

		WHOLE DAY			ACTIVE PERIOD			SLEEP		
		MIN	MAX	MEAN	MIN	MAX	MEAN	MIN	MAX	MEAN
SYS	**Controls** (n=17)	78.53±12.19	162.88±27.23	112.24±9.01	83.29±11.18	162.41±27.64	114.76±9.00	85.00±14.93	118.93±14.93	101.67±7.13
	AN (n=25)	81.44±10.94	138.32±17.45**	104.28±8.96*	85.88±10.34	136.52±18.41	105.92±8.87**	83.33±10.11	110.54±14.79	95.25±9.42*
DIA	**Controls** (n=17)	44.00±10.54	117.76±27.25	70.00±7.08	47.59±10.53	117.18±27.17	72.17±7.70	47.47±10.15	74.33±18.41	60.07±9.13
	AN (n=25)	47.52±9.27	101.16±19.96*	69.92±7.01	50.16±9.91	99.48±21.12*	71.20±7.35	52.04±8.31	75.00±11.65	61.33±7.68
MAP	**Controls** (n=17)	57.12±11.99	128.41±27.03	84.18±7.44	60.88±12.76	127.76±27.07	86.35±7.80	61.07±9.48	86.67±16.40	73.87±7.60
	AN (n=25)	61.24±8.39	110.88±19.49*	81.36±7.06	64.48±8,00	109.44±20.36*	82.80±7.33	63.63±8.71	85.25±11.64	72.71±7.86
HR	**Controls** (n=17)	49.71±12.42	129.65±45.66	82.53±11.76	49.94±14.06	129.76±45.65	84.47±11.67	61.87±13.11	86.60±12.95	73.60±10.80
	AN (n=25)	49.3416±14.34	138.21±39.45	82.76±14.57	53.83±13.03	130.21±32.55	85.59±14.87	53.14±15.00*	88.61±23.49	66.43±14.79*

*p<0.05; ** p<0.005 as compared to control value

Table 3. Hormonal parameters in examined anorectic patients.

Parameter	Units	Result (mean ± SD)	Normal range	No (%) of patients with result below normal range	No (%) of patients with result over normal range
fT4	ng/dl	1.15±0.25	0.8–1.8	1 (4%)	0
Cortisol	µg/dl	19.31±13.13	7–25	1 (4%)	5 (20%)
FSH	mIU/ml	2.95±2.47	2–10	10 (40%)	0
LH	mIU/ml	0.78±1.54	2–9	23 (92%)	0
Estradiol	pg/ml	32.08±25.04	30–100	19 (76%)	0

examined groups, although they tended to be lower. Minimal and mean night HR values were significantly lower in AN in comparison with control group.

We observed no physiological lack of BP circadian variation in anorectic girls. Percent sleep decline in BP calculated as described above was –11.87±8.67% suggesting higher night-time than active period mean MAP. In control group normal sleep fall 10.71±22.13% in MAP was observed (normal range 10–15%).

Anorectic adolescents presented typical for this condition hormonal disturbances as low mean FSH, LH and estradiol serum concentrations (Table 3). Mean cortisol concentration was within normal range, but hypercortisolemia was found in 5 (20%) of examined individuals. Mean fT_4 serum concentrations were within normal range. Hypothyroidism was found in 1 patient (4%).

Analysis of correlation between BP values and anthropometric or hormonal parameters in patients with AN showed positive linear correlation between minimal SYS and weight ($r=0.48$; $p<0.05$) and BMI ($r=0.42$; $p<0.05$).

Mean SYS, DIA and MAP values positively correlated with serum fT_4 concentrations during the whole day and active period. A positive linear correlation was also found between maximal SYS and MAP values for the whole day and maximal SYS, DIA and MAP values during active period and serum cortisol concentrations. BP values did not correlate with hormonal parameters during sleep period (Table 4). HR values correlated positively with FSH and LH concentration values (details see Table 5).

DISCUSSION

Our findings suggest that despite lower than in control group BP value, hormonal regulation of blood pressure in AN is preserved. In human beings, maintenance of reduced body weight is met by coordinate metabolic, neuroendocrine, and autonomic responses that favor the regain of lost weight [2,36]. In our study mean SYS values, although lower in AN patients in comparison with control groups, correlated well with fT_4 serum concentrations in active period and during the whole day (that was probably influenced by day-time results). DIA values also correlated with fT_4 serum concentrations during the whole day and active period, but the values were similar to control group.

"Low T_3 syndrome" or "euthyroid sick syndrome" characterized by markedly decreased T_3, normal or subnormal T_4 and normal TSH serum levels is almost always found in AN and is well-known state in other forms of undernutrition and critical systemic illnesses [38]. Low serum T_3 concentration is generally held to be caused by impaired T_4 peripheral deiodination and increased inactive reverse T_3 formation [12], but some authors postulate an overall dysfunction of the hypothalamo-hypophyseal-thyroid axis in patients with AN [31].

The heart is a major target organ for thyroid hormone action. It is well established that overt hyperthyroidism induces a hyperdynamic cardiovascular state (high cardiac output with low systemic vascular resistance) which is as-

Table 4. Linear correlations of BP values and fT_4 and cortisol serum concentrations in anorectic adolescents.

		WHOLE DAY			ACTIVE PERIOD			SLEEP		
		MIN	MAX	MEAN	MIN	MAX	MEAN	MIN	MAX	MEAN
SYS	**fT_4**	0.32	0.04	0.45*	0.32	0.06	0.46*	0.25	0.16	0.26
	Cortisol	0.01	0.39*	0.23	0.10	0.40*	0.31	0.12	0.15	0.06
DIA	**fT_4**	0.09	0.07	0.40*	0.12	0.12	0.41*	0.11	0.20	0.15
	Cortisol	0.08	0.31	0.21	0.31	0.40*	0.29	0.06	0.25	0.18
MAP	**fT_4**	0.19	0.10	0.44*	0.21	0.10	0.46*	0.17	0.12	0.20
	Cortisol	0.04	0.42*	0.24	0.27	0.42*	0.32	0.13	0.21	0.14

*$p<0.05$

Table 5. Linear correlations of HR values and FSH and LH serum concentrations in anorectic adolescents.

		WHOLE DAY			ACTIVE PERIOD			SLEEP		
		MIN	MAX	MEAN	MIN	MAX	MEAN	MIN	MAX	MEAN
HR	**FSH**	0.46*	0.12	0.42*	0.43*	0.09	0.37*	0.57*	0.31	0.49*
	LH	0.27	0.01	0.14	0.30	0.01	0.08	0.35	0.36*	0.49*

*$p<0.05$

sociated with a faster heart rate, enhanced left ventricular systolic and diastolic function and increased prevalence of supraventricular tachyarrhytmias, whereas overt hypothyroidism is characterized by the opposite changes [13].

Subclinical hypothyroidism as well as impaired peripheral thyroid hormones metabolism leads to impaired LV diastolic function and subtle systolic dysfunction [13]. The influence of thyroid function on blood pressure homeostasis extends into euthyroid range and likely reflects the action of thyroid hormone on peripheral vasculature [18].

It has been demonstrated that AN adolescents have significantly lower left ventricular mass, left ventricular mass index and diminished thickness of cardiac walls [30,41] that may be result of low T_3 syndrome due to underweight as well as malnutrition itself.

Recently the influence of thyroid hormones on autonomic nervous system has been extensively investigated. It is known, that hypothyroidism increases peripheral vascular resistance [29]. In the animal study, Yuan and Young demonstrated that hypothyroidism is associated with increased neuronal acitivity in medullary dorsal motor nucleus of the vagus, nucleus tractus solitarii and area postrema [45]. HRV studies in anorectic females showed an increased parasympathetic activity occurring not in response to increase in sympathetic activity [11,33]. Sympathetic activity in AN generally is diminished [11,21,34], although in one study increased symphatetic activity in abdominal adipose tissue was demonstrated [6]. Yoshida *et al*. in a pilot study suggest that autonomic nervous activity is relevant to changes in heart rate in AN during refeeding and speculate that these increases in thyroid function and other hormonal parameters may be responsible for the mechanisms [44]. This supports the hypothesis that night bradycardia observed in our patients may be at least partially due to low T_3 syndrome.

Another important finding is lack of physiological night fall in BP. Suggested explaination for this phenomenon was reduced activity of sympathetic nervous system in AN [3,11]. Recent study by Guasti *et al*. demonstrated that circadian blood pressure is associated both with sympatho-vagal modulation and baroreflex-mediated arc function [16]. These authors also suggested a reduced sympathoexcitation in short-lasting hypothyroidism compared with the treatment with L-thyroxine phase [17]. These data are in opposition to above mentioned studies revealing increased sympathetic tone in hypothyroidism. However it is possible, that autonomic modulation is dependent on the duration of hypothyroidism. It should be noted, that our patients were in the acute phase of the disease and we think, that decreased sympathetic tone acitivity demonstrated as lower SYS values may be attributred to disturbed peripheral T_4 to T_3 conversion.

The loss of BP circadian rhytm is also observed in Cushing syndrome and in subjects taking exogenous glucocorticoids [19,20]. Hypercortisolemia is well known observation in AN. In our study, although performed in the acute phase of AN, only 20% of patients revealed hypercortisolemia. This may be justified by the fact, that irrespective of the initial weight, weight gains as low as 10% are associated with cortisol secretion [14]. However, anorectics never display cushingoid features and the reason for that may be the lack of metabolic substrate for cushingoid fat and liquid distribution [38]. It has been suggested that hypercortisolemia in AN reflects hypersecretion of CRH rather than cortisol resistance [23]. Activity of the CRH neurons in the hypothalamic paraventricular nucleus (PVN) forms the basis of the activity of the hypothalamic-pituitary-adrenal axis. The hypothalamo-neurohypophysial system is also involved in stress response and hypercortisolemia is found in AN and depression as well [39]. CRH neurons project not only to the median eminence, but also into brain areas where they regulate the adrenal innervation of the autonomic system and affect mood [4]. In animal studies it has been demonstrated that CRH injections into the central nervous system cause lack of appetite and stimulate sympathetic nervous system increasing heart rate, excerting intropic positive action on the heart and increasing blood pressure [2,25]. In the present study maximal BP values during the whole day and active period correlated with serum cortisol concentrations. This may suggest the compensatory role of hypercortisolemia in BP regulation in AN, however above mentioned direct effects of CRH cannot be excluded.

Another interesting finding is correlation between heart rate and FSH and sleep heart rate with LH. Amenorrhea is one of the diagnostic criteria for AN [1]. The diurnal and pulsatile variation of gonadotropin secretion in AN resembles that in prepubertal stage. The same pattern that can be reversed by pulsatile administration of GnRH was stated in starvation. Basal level of LH and LH response to exogenous GnRH injections are correlated with body weight and body fat percentage [38].

Gonadotropins do not directly impact blood pressure and heart rate. However, Lin *et al*. demonstrated that intraventricular administration of LHRH or LH caused tachycardia, hypertension and a reduction in the epinephrine-induced reflex bradycardia [26]. Increased LH is associated with most hot flashes in menopausal women, which are accompanied by abrupt increases in plasma epinephrine and concomitant decreases in norepinephrine [24].

Observed strong correlation between heart rate and serum gonadotropines may result from other suprahypophyseal neuroendocrine mechanisms. We speculate that one of them may be elevated neuropeptide Y (NPY) concentrations in AN. NPY is an important neurotransmitter in the central and peripheral nervous systems. It has a regulatory role in cardiovascular and metabolic functions and control of hormones release. In our previous study [32] we demonstrated that elevated NPY concentrations in AN normalized with weight gain but did not correlate with weight and BMI.

NPY has been reported to have an effect on LH secretion from rat cells [35] but the steroidal conditions under

which the study is performed is important for the results. E.g. NPY has opposite effects in certain endocrine environments, augmenting GnRH-stimulated LH release in proestrus-like conditions, and inhibiting in metestrus-like environment [7,22].

Baranowska *et al*. [5] demonstrated increased gonadotropin release in *in vivo* and *in vitro* experiments in non-starved rats. However, in starved rats the hormonal response after NPY injection was blunted and increased NPY pulsatility may have pathophysiological significance in weight loss-related hypothalamic amenorrhea [5,27].

Central NPY afferents to the ventrolateral nucleus ambiguus (NA-VL) modulate the vagal preganglionic control of atrio-ventral conduction and left ventricular contractility in cats [8] and microinjections of neuropeptide Y (NPY) into the NA-VL cause negative chronotropic effects [15]. According to it, increased NPY concentrations in AN may contribute increased night parasympathetic activity in these patients.

We conclude that hormonal regulation of blood pressure and heart rate in anorectic patients is at least partially preserved. Lower blood pressure values, bradycardia and lack of physiological night fall of BP in anorectic patients may result from altered autonomic system function resulting from hormonal disturbances and other centrally mediated mechanisms.

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