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PATHOPHYSIOLOGICAL CHARACTERISTICS OF HORMONAL ACTIVITY IN CHILDREN WITH ARTERIAL HYPERTENSION

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Abstract

We have conducted a complex research of the hormonal status, as well as a thorough study of its possible impact on biorhythmological blood pressure of the 108 children suffering from arterial hypertension. The patients were divided into two groups: 50 children were diagnosed with labial arterial hypertension, while 58 children had stable essential arterial hypertension. The provided data indicates that arterial hypertension patients tend to have excessive amount of cortisol, especially the stable essential arterial hypertension group ($p<0.01$) in comparison to the healthy children. The adrenocorticotropic hormone level of both groups was significantly lower ($p<0.001$) than the healthy group's level. The thorough study of adrenaline level indicates that arterial hypertension patients tend to have higher level of its secretion and makes up to 5.1±0.14 nmole/l ($p<0.001$), which is actually twice higher than children of control group (2.42±0.14 nmole/l). Significant decrease of day fraction by 1.7 times ($p<0.01$), as well as the night one by 4.7 times ($p<0.001$) was detected. The melatonin indices of stable essential arterial hypertension group reflected the increase of the circadian disorder which occurred in minimum difference of hormone during the night and day shifts, excessive decrease of the night fraction by 5.2 times ($p<0.001$) and reliable increase of the day level ($p<0.05$). Serotonin indicated reversed dynamic by exceeding the control group indices by 2 times of the labial arterial hypertension group ($p<0.01$) and reliably increasing within the arterial hypertension stabilization up.

Thus, we may conclude that arterial hypertension children tend to have desynchronization of the endocrine system which causes the increase of cortisol, serotonin and adrenalin secretions, inhibition of adrenocorticotropic hormone production, disorder of transformation of serotonin into melatonin and mismatch of day and night hormone level.

Keywords: *arterial hypertension, hormonal dysfunction, infants, blood pressure, sympathoadrenal system*

Introduction

Hypertension is the leading cause of cardiovascular disease and premature death worldwide. Owing to widespread use of antihypertensive medications, global mean blood pressure (BP) has remained constant or decreased slightly over the past four decades. 31.1% of adults (1.39 billion) worldwide had hypertension [*Mills KT et al., 2020*].

In fact, uncontrolled arterial hypertension (AH) requires an increase of budget expenses of public health services of EU countries, i.e. annual amount exceeds over 190 billion euro [*Mancia G. et al., 2023*]. It is beyond any doubt that the primary cause

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can be traced back to the infancy and adolescence periods. As a matter of fact, statistics show that around 3-35% of children suffer from arterial hypertension. However 50% of patients have asymptomatic disease course which is actually hard to detect and consequently makes it impossible to provide necessary and timely treatment. BP level above average has an increasing tendency which rises during the growth of children. Afterwards high blood pressure remains on 33-42% of the patients and 17-26% of the patients suffer from increased arterial hypertension. As a result every 3rd child with high blood pressure is more likely to suffer from essential hypertension [*Leyvraz et al., 2018; Lou Xet al., 2018; Yang L et al.,, 2020; Agbaje A, 2022*].

Obviously any stressful influence causes change of hormonal status which is connected to a certain degree with the activity of hypophysis of adrenal axis (as a certain chain of stress-releasing system), just like epiphysis, producing synchronizing influence. We are studying essential arterial hypertension as a disease connected with disadaptation of the circadian rhythm of the human body [*Hamer M et al., 2016; Agbaje AO, 2022; Astudillo Y, 2024;*].

According to various studies, the level of endogenous melatonin and its biorhythmic relationship can affect blood pressure levels and the risk of developing arterial hypertension. The use of melatonin may restore normal circadian blood pressure rhythms in non-dippers and improve nocturnal blood pressure control [*Budnevsky AV at al., 2017; Ramos Gonzalez M at al., 2023*]. Hypothalamus paraventricular nucleus, receiving melatonin projections from the superchiasmatic nucleus, is a critical brain region to regulate neuroendocrine and cardiovascular function. Determined the synaptic mechanisms involved in the effect of melatonin on the sympathetic outflow and blood pressure [*Yu Q at al., 2023*].

Serotonin and abnormal serotonergic activity (both central and peripheral) may play a role in pathogenesis of essential hypertension. Besides being vasoactive, it has some inotropic and chronotropic properties and also affects blood rheology. It has stimulating effect on renin and aldosterone secretion. The action of other vasoactive substances like norepinephrine and angiotensin II are amplified. All these physiological effects of serotonin strongly support the hypothesis that it may be involved in hypertension [*Chandra M, Chandra N., 1993; Soslau G., 2021*]. Afterstress state involves a chronic increase of blood pressure. The norepinephrine/epinephrine ratio decreases as epinephrine, prolactin, renin and fatty acids rise. As the outcome becomes still less certain and distress grows, adrenocorticotropic hormone and cortisol levels arise [*Henry JP., 1992*]. Increased norepinephrine levels and a decreased pituitary response to metabolic stress stimuli may represent another manifestation of chronically increased sympathetic tone in early hypertension [*Radikova Z at al., 2006*]. Patients with arterial hypertension demonstrated increased adrenaline concentrations and enhanced stress-induced noradrenaline release compared to that in healthy controls. In obese subjects, stress-induced increase of systolic BLOOD PRESSURE was lower compared to lean individuals [*Garafova A at al., 2014*]. The study of the blood serum adrenaline in hypertensive children discovered its significant increase. The highest concentration of adrenaline was determined in males in the group of children with stable arterial hypertension and with the disease duration the less than 1 year [*Garafova A at al., 2014; Kaladze N, Zyukova I 2014*].

Arterial hypertension is associated with altered levels of blood borne hormones. Contradicting results of studies on the arterial hypertension might be partially explained by diverse effects of hormones on arterial pressures [*Skrzypecki J at al., 2017*].

Further studies are needed to evaluate if hormonal profiling may help to identify arterial pressure in children.

Thus the objective of our research is total evaluation of stress-realizing and stress-limiting hormonal components of arterial hypertension patients.

Material and Methods

According to our data: 108 children (70 boys and 38 girls) diagnosed with arterial hypertension were examined at the age range from 10 to 16 years. 50 children were diagnosed with labial arterial hypertension, while 58 children had stable essential arterial hypertension. The control group consisted of 30 healthy children with corresponding age and gender.

Daily monitoring of blood pressure was defined by average daily rates of systolic blood pressure,

diastolic BP (DBP), hypertense time index and intraobserver variability of systolic and diastolic blood pressure (intraobserver variability of systolic and of diastolic BP), daily index (DI). According to the night decrease of BP (DI) we may form the following types of daily rhythm: "Dipper"- with regular/standard decrease of blood pressure at the night shift for 10-20%; "Non-dipper"-due to insufficient decrease of blood pressure (less than 10%); "Night-peaker"-with higher level of blood pressure at the night shift (sufficient increase of BP) and "Over-dipper"-due to excessive decrease of night BP (more than 20%) [*Soergel M, 1997; O'Brien E, 2003; Kidambi S et al., 2020; Huang QF et al., 2021*]. The protocol included measurements of blood pressure every 30 minutes during the day shift (from 6 am to 11 pm) and hourly during the night shift (from 11 pm to 6 am).

For quantity estimation of the level of cortisol, adrenalin, adrenocorticotropic hormone (ACTH) and serotonin level in blood serum, we had applied the solid phase of enzyme-linked immunosorbent assay (EIA) with the usage of the following set of reagents: "IFAsteroid-cortisol-01", "Alcor-BIO" Ltd, Saint-Petersburg, "Adrenaline ELISA EIA" AND "ACTH ELISA EIA" DRG Germany Stat Fax 2100 (Awareness Tech. Inc., USA). We had determined the level of melatonin in a human body according to the concentration of its main metabolite 6-sulphatoxymelatonin in urine during the day (from 8 am to 8 pm) and the night (from 8 pm to 8 am) shifts. The above mentioned test was conducted by applying the enzyme multiplied immunoassay approach ("Melatonin-Sulfate ELISA" test-system, DRG, Germany).

The following statistic analysis was being conducted by means of Statistica v6 computer software of data processing, during the process the following main statistic features were determined: medium (M), error of medium (m) and standard deviation, reliable results were considered only if $p<0.05$. Hypothesis testing regarding the equality of the two mediums was conducted by the usage of distribution-free statistic methods (Wilcoxon paired calculation and Mann-Whitney U-test). For the evaluation of the degrees of correlation, the correlation analysis was conducted by the calculation of Spearman's correlation coefficient pair (r).

Discussion of findings

Blood pressure circadian rhythm of the children with arterial hypertension is evaluated by the level of daily index. Frequently the systolic blood pressure indexes were used in order to detect the decreasing level of blood pressure during the night shift.

Figure 1 indicates the data distribution according the circadian profile.

Studying the BP circadian profile, we had determined that 39.8% of children of both groups had insufficient degree of BP decrease during the night shift. Whereas 7.4% and 5.6% stable essential arterial hypertension patients were defined as "Night-peakers" and "Over-dippers".

Table 1 indicates the indices of average daily blood pressure load pressure and its variability.

We had detected that during the evaluation of blood pressure indices of arterial hypertension patients subjected to the peculiarities of diurnal system, the average daily indices of systolic blood pressure, diasolic blood pressure and time index of hypertensia decreased with the increase of daily index, "Over-dippers" group according to diastolic blood pressure, which makes them equal to the control group.

However, the max BP variability was detected in the groups with evident signs of desynchronosis, i.e. "Over-dippers" and "Night-peakers". The increase of BP variability of arterial hypertension patients is meant to be an independent factor that strikes one's target organs. Particularly, the great percentage of variability of systolic BP during the day shift causes the increase of atherosclerosis de-

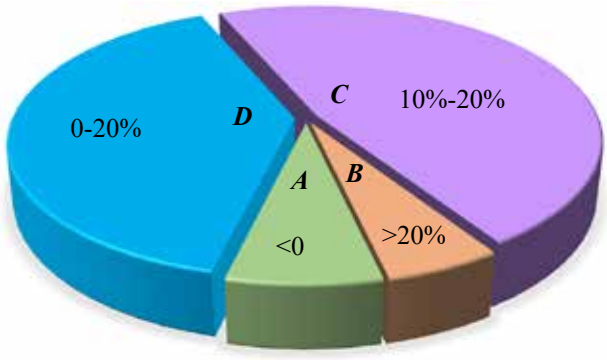

Figure 1. *Distribution of arterial hypertension patients according to the blood pressure indexes of diurnal rhythm (n=108.).* ***Legends:*** *Night-peaker (A), Over dipper (B), Dipper (C), Non-dipper (D).*

Table 1

Blood Pressure indices of arterial hypertension patients according to the type of diurnal rhythm (n=108)

Indices	<0	0-10%	10-20%	>20%	Control Group
Blood pressure					
systolic *(mm Hg)*	124.8±5.9***	125.8±2.3***	122.9±3.4***	118.3±3.8***	105.0±2.7
diastolic *(mm Hg)*	72.0±2.3***	70.9±1.3***	69.2±1.2***	65.5±2.6*	60.2±1.4
Intraobserver variability of blood pressure					
systolic *(mm Hg)*	17.60±2.6***	12.7±0.9	14.8±0.7***	18.5±1.3***	10.3±0.3
diastolic *(mm Hg)*	18.00±2.7***	13.1±0.9*	13.5±0.9*	14.8±1.6***	9.7±0.3
Hypertense time index of blood pressure					
systolic *(%)*	33.5±5.1***	35.2±4.6***	24.5±4.1***	12.2±2.5***	0.2±0.2
diastolic *(%)*	17.0±3.6***	8.8±1.6***	7.5±1.5**	3.8±2.8*	0.1±0.1

Notes: *. * - p<0.0, ** - p<0.0, *** - p<0.00 – reliability of difference with control group.*

velopment and cardiovascular events.

The standard systolic BP indices are considered to be less than 15.2 *mm Hg/per day*; less than 15.5 *mm Hg* during the day shift and less than 14.8 *mm Hg* for the night shift. And accordingly for diastolic BP <12.3, < 13.3, <11.3 *mm Hg*. By comparing the outcome indices with the data of other researchers [*Parati G, Valentini M., 2006; Hardy ST, Urbina EM., 2021*], we can state the formation of the tendency towards the progression of essential hypertension at the adult age of our patients. Thus, the findings of researches traced back to 90-s, indicate insufficient as well as excessive decrease of BP due to the damage of our target organs. It had been proved that the frequency rate of damage to one's brain increases due to the excessive decrease of blood pressure whereas insufficient decrease of BP causes cardiac symptoms during the night shift. arterial hypertension patients under the threat of a stroke tend to change their blood pressure diurnal profile towards "Non-dippers"-"Over-dippers" and "Night-peakers" [*Parati G, Valentini M., 2006; Hardy ST, Urbina EM., 2021*].

The circadian rhythm influences the hormonal rhythm of healthy children in shifted correlative interrelations. The received data defines the state of the main regulatory system of the arterial hypertension patients and indicates the mismatch of hormonal control (table 2).

The provided data indicates that arterial hypertension patients tend to have excessive amount of cortisol, especially the stable essential arterial hypertension group (p<0.01) in comparison to the MG (healthy children). The ACTH level of both groups was significantly lower (p<0.001) than the healthy group's level, labial arterial hypertension's group was 2.5 times lower and stable essential arterial hypertension's group 2 times lower. Thus, all of the above indicate the activation of the hypothalamic-pituitary adrenal in the state of chronic stress – the physical as well as the emotional one.

Stress state causes diurnal rhythm abruptness and sharp increase of cortisol level in blood after 25-30 minutes from the be-

Table 2

Hormonal status data of arterial hypertension patients (M ± m)

Indices	Control group (n=20)	Arterial hypertension group	
		labial (n=50)	stable essential (n=58)
ACTH, (*pg/ml)*	36.2 ± 5.6	14.91±2.3***	13.5±3.9***
Cortisol, (*nmol/l)*	326.8 ± 18.2	450.45±28.8*	539.54±29.7**
Epinephrine, (*nmol/l)*	2.42±0.14	4.84±0.19***	5.4±0.21***
Melatonin, (*ng/ml)*			
during the dey	30.45 ± 3.39	18.07±3.1**	57.17±19.9*
during the night	403.67 ± 19.7	85.09±24.4***	6.97±20.8***
Serotonin, (*ng/ml)*	283.57 ± 22.1	645.5 ± 26.8**	517.3 ± 19.7***

Note: *ACTH - adrenocorticotropic hormone, * - p<0.05, ** - p<0.01, *** - p<0.001 – reliable difference with the control group*

ginning of the stress state. The state of chronic stress of stress-releasing system of arterial hypertension patients may increase cortisol level by 1.4 times during the labile course of the disease and increases by 2 times during the stabilization of arterial hypertension. Therefore these changes cause inhibition of secretion of the ACTH just as hypothalamic corticotropin-releasing hormone.

The thorough study of adrenaline level indicates that arterial hypertension patients tend to have higher level of its secretion and makes up to 5.1±0.14 *nmole/l* ($p<0.001$), which is actually twice higher than children of MG (2.42±0.14 *nmole/l*). At the same time it had been determined that there is a significant difference of adrenaline level in the groups of stable essential arterial hypertension (5.4±0.21 *nmole/l*, $p<0.05$) and the labial arterial hypertension group (4.8±0.19 *nmole/l*). The excessive normative characteristic of adrenaline levels has been detected at 86% of kids of stable essential arterial hypertension and 62% of labial arterial hypertension groups. In fact the boys tend to have higher level of this hormone. The correlation of adrenaline and systolic BP ($r=0.30$; $p<0.05$), diastolic BP ($r=0.68$; $p<0.05$), duration of the disease ($r=0.63$; $p<0.05$) indicates the influence and presence of the stress hormone (adrenaline) in the formation of arterial hypertension [*Kaladze N.N., Zyukova I.B. 2014*]. In both arterial hypertension groups, the correlation analysis didn't indicate any connection between adrenaline level, ACTH and cortisol, therefore it allows us to assert the occurrence of the mismatch of the inner regulating system in pituitary adrenal during arterial hypertension, which is peculiar to healthy children (control group). However, excessive level of cortisone and at the same time lowered ACTH levels signify the activation of hypothalamo-pituitary-adrenal system in the formation of arterial hypertension. And in turn all of the above are strongly correlated with the activation of sympathoadrenal links of homeostasis and the formation of stable rise of blood pressure development of desynchronosis resulted in excessive variability and disbalance of diurnal blood pressure.

The previous data represented in table 2, signified that the children with labial arterial hypertension melatonin (6-COMT) secretion submitted to the circadian rhythm that healthy children tend to have (with max indices during the night shift and min during the day shift). However, during the testing a significant decrease of day fraction by 1.7 times ($p<0.01$), as well as the night one by 4.7 times ($p<0.001$) was detected. The melatonin indices of stable essential arterial hypertension group reflected the increase of the circadian disorder which occurred in minimum difference of hormone during the night and day shifts, excessive decrease of the night fraction by 5.2 times ($p<0.001$) and reliable increase of the day level ($P<0.05$). The provided data indicates that children tend to have early formation of desynchronosis of the melatonin secretion. The following disorders of melatonin influence occur: the decrease of tension in vegetative centers and cerebral cortex, vasorelalaxation, cardioprotective effect, the decrease of stress hormone release, the inhibition of the rennin-angeotensin-aldosterone system, state normalization after the stress, which is based on its effect on the neurotransmitter system and the synchronization of the circadian rhythm.

The precursor hormone of melatonin is serotonin, in fact, indicated reversed dynamic by exceeding the control group indices by 2 times of the labial arterial hypertension group ($p<0.01$) and reliably increasing within the arterial hypertension stabilization up to 581.5 ± 19.7 *ngr/ml*. The most influencing factor of the vasoconstriction of arterial hypertension pathogeny is characterized by an exceeding level, disorder of serotonin biochemical transformation. The melatonin/serotonin ration of healthy children made up to 1.53 which indicates proper serotonin metabolism in melatonin, while arterial hypertension patients' rate was up to 0.2. Insufficient production of melatonin out of hormone precursor levels stress-protective vascular effects. Our research findings have proved modern scientists' opinion regarding the hormone stress-releasing and stress-limiting system ratio of the human body – serotonin and melatonin in arterial hypertension genesis with following disorder of serotonin transformation into melatonin. The insufficient integration of serotonin occurs due to functional disorder of arylalkylamines-N-acetyltransferase and results in melatonin shortage.

Serotonin occurs to control the functioning of some neurotransmitters, particularly, adrenalin. Children suffering from the serotonin shortage may suffer a decrease of the control of the adrenal reaction transmission into the brain causing vegetative crisis. In our opinion, the excessive levels of

both of neurotransmitters (adrenaline, serotonin), detected in children's bodies with arterial hypertension, prove to be the cause of chronic vasoconstrictive effect within the mismatch of hormone control over the transmission of nerve impulses from one cell to another.

In order to find out the intercorrelation of studied indices we had conducted a correlation analysis. As a result, the average straight correlative dependence of daily index and melatonin night level ($r=0.63$; $p<0.05$), daily index and systolic BP ($r=0.62$; $p<0.05$) prove the great influence of melatonin in the development of desynchronosis of the children with arterial hypertension. The statistically significant correlation between age, ACTH content and cortisol was determined while the age had direct correlation of average power with the ACTH indices ($r=0.54$; $p<0.05$) and cortisol ($r=0.46$; $p<0.05$). The reliable reversed weak correlation was also determined with ACTH content from one side, and the melatonin concentration during the day shift ($r=-0.26$; $p<0.05$) and the night shift ($r=-0.30$; $p<0.05$) from the other side. The cortisol level is slightly correlated with melatonin day concentration ($r=0.27$; $p<0.05$). The weak reverse correlation of adrenalin concentration and day melatonin ($r=-0.33$; $p<0.05$) and night melatonin ($r=-0.22$; $p<0.05$) was detected as well. By summarizing the correlation analysis data we may prove the stress-releasing hormones involvement in the pathologic process, such as adrenaline, cortisol and ACTH and the occurrence of stable formation of desynchronosis in hormonal state under the control of the stress-limiting system hormone – melatonin.

In fact, other scientists in their chronobiological researches of adolescence period happen to come up with similar findings, stating melatonin hormone to be the main regulative element of the circadian rhythm (indole-N-acetyl-methoxytryptamine). According to the polioscillatory theory of circadian rhythms (offered by Pittendraem in 1961) the primary pacemaker which synchronizes rhythms of the secondary (some parts of the brain, the striate body which control motor activity and mental processes, Ammon's horn connected with the formation of emotional and motivational behavior) and tertiary (internals) pacemakers are suprachiasmatic nucleus of the hypothalamus. All of the above explains the correlation between suprachiasmatic nucleus and the stimulating effect of sympathetic nerve, just like the release of catecholamine, glucocorticoid etc. Thus, this process easily explains the increase and decrease of BP in a rhythmic sequence. "Disinhibition" of vasomotor center leads to the vasospasm and the rise of BP and makes them rather sensible to catecholamine. Vasospasm results in tissue hypoxia which from one side increase of ACTH secretion and release of gluco- and mineralokorticoid hormones, and from the other side activates rennin-angeotensin-aldosterone system which results in high BP [*Arangino S et al., 1999; Scheer FA et al., 2004; Grossman E et al., 2006; Baltatu O et al., 2017; Costa-Barbosa F et al., 2022; Tain Y, Hsu C., 2022; Franco C et al., 2022*].

Thus, we may conclude that arterial hypertension patients (children) tend to have desynchronization of the endocrine system which causes the increase of cortisol, serotonin and adrenalin secretions, inhibition of ACTH production, disorder of transformation of serotonin into melatonin and mismatch of day and night hormone level. The children with a stable-formed hypertension tend to have evident imbalance of melatonin which results in minor difference between day and night levels. And children of the labial arterial hypertension group tend to keep adequate average daily hormone distribution. The children with circadian disorder of BP with insufficient decrease and increase of night BP tend to have rather high but stable average daily BP indices which results in negative formation of possible complications in the course of arterial hypertension. The high BP variability of "Over-dipper" and "Night peakers" groups is an uncontrolled risk factor which may destroy target-organs of the arterial hypertension patients.

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