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Chapter

Circadian Rhythm of Blood Pressure in Children and Adolescents

Anastasiia Ledyaeva, Sergey Klauchek and Mikhail Ledyaev

Abstract

Everything in our body is under control of central and peripheral pacemakers that regulate all the processes and functions according to the day-night and sleep-wake cycles. Cardiovascular system is not an exception. Blood pressure, heart rate, and even vascular resistance have circadian patterns. Nowadays new diagnostic devices provide all necessary data on 24-h variation of the hemodynamic parameters in patients of all ages. Due to the complex regulation mechanisms which underline this variation, circadian patterns are not the same in different people. Why do we need to assess these rhythms? First of all, it is a key to the early diagnosis of different cardiovascular diseases and their complications. When the circadian rhythm is impaired, for example, the level of blood pressure is within the normal ranges, but it does not decline at night or even is higher than at daytime, there is an increased risk of the development of arterial hypertension and target organ damage. There is a large amount of studies on 24-h rhythm of blood pressure in adults. On the contrary, in children there is still a lack of data on this topic.

Keywords: circadian rhythm, blood pressure, adolescence, circadian index, ambulatory blood pressure monitoring

1. Introduction

All physiological processes in the organism have a cyclic organization—from thermoregulation and activity of cardiovascular system (CVS) and respiratory systems to expression of genes, mitochondrial activity, and synthesis of proteins [1–3]. Endogenous rhythms in newborns are formed under the impact of exogenous synchronizers, such as light and sound. Circadian organization of excretion with urine of sodium and potassium occurs in a period from the 4th till the 20th week; on 2–3 weeks of the postnatal development, the synchronization of a body temperature with the day-night cycle takes place. At the present time, the active development of biomedical technologies allows to register and analyze the circadian variability of blood pressure (BP), heart rate (HR), and heart rate variability (HRV) by conducting their monitoring during 24 and more hours. The interest of scientists and clinical physicians to the diurnal variabilities of CVS parameters is also connected with the fact that based on the condition of the biological rhythms of a separate system of organs it is possible to judge the functional condition of an organism, the level of

its adaptive opportunities, the risks of development of cardiovascular diseases, and even about the activity of pathological process [4–6].

In the circadian pattern of BP, two peaks are allocated: the first one is registered in the morning, from 6 to 12 a.m., the second one, smaller in amplitude, at about 7 h p.m. Circadian rhythm of BP is determined by numerous exogenous (light, noise, temperature, and eating behavior) and endogenous (melatonin, sympathetic tone, renin-angiotensin-aldosterone system (RAAS), NO and endothelin-1 level, etc.) factors [7, 8].

The group of pacemakers, forming the suprachiasmatic nucleus of hypothalamus (SCN), located directly above the optic chiasm, is a central pacer of circadian rhythms, synchronized with the sleep-waking cycle. SCN mediates the secretion of corticoids that in turn increase the sensitivity of vascular wall to the catecholamines and decrease the production of vasodilators [9]. Peripheral clock genes (Per1, Bmal1, Cry1, and Cry2) control the sensitivity of α-adrenoreceptors to vasoconstrictors [10].

Melatonin is a hormone of pineal gland that stays in the core of our sleep behavior. Regulation of melatonin secretion is controlled by light through the retinothalamic track and suprachiasmatic nucleus of hypothalamus. At the same time, it is an important vasoactive factor, and thus it forms the circadian BP profile [11, 12]. Also it regulates the synthesis of catecholamines by adrenals and mediates the sensitivity of baroreflex [13, 14]. The concentration of melatonin in plasma and 6-sulfaoxymelatonin in urea is decreased in non-dippers [15, 16]. The administration of melatonin in patients with hypertension leads to the decrease of the average values of SBP and DBP without change of sleep behavior [17]. It is interesting that melatonin has two faces: he could be a vasoconstrictor or vasodilator [18]. It is so because there are two types of melatonin receptors: MT1 and MT2. Low melatonin concentrations activate MT1 receptors and lead to vasoconstriction. In high concentration, melatonin provides an opposite effect through the stimulation of MT2 receptors [19].

Angiotensin 2 is another powerful oscillator of 24-h dynamic of BP. The peak of activity of renin in plasma and concentration of angiotensin-2 relate to early morning, explaining the morning rise of BP [20]. Thus, the combined influence of exogenic and endogenic oscillators forms the normal circadian rhythm of BP, providing an adequate blood supply of organs and tissues, depending on requirements of an organism.

In healthy humans there is a BP decline by 10–20% and rapid increase of BP in the early morning hours [21]. Circadian BP pattern can be assessed during ABPM by calculation of circadian index (CI)—the main characteristic of the nocturnal BP reduction. CI is a percent decline in mean BP during sleep relative to the mean BP during daytime wakefulness. CI is calculated as ((awake BP mean − asleep BP mean)/awake BP mean) × 100. Due to the value of CI, there are four types of circadian BP patterns: "dipper" 10–20%, "non-dipper" 0–10%, "overdipper" >20%, and "night-peaker" or "riser" with nocturnal increase of BP—CI being negative.

A change of the internal structure of circadian rhythm of BP is followed by the shift of acrophase at a later time and the decrease of BP variability. There is the definite genetic aptitude to change of the daily BP profile. The optimal degree of an overnight decrease is characterized by the presence of allele D, genotype DD gene ACE, and genotype 4a/4b gene of the endothelial synthase of a nitrogen oxide. While insufficient overnight BP decrease is associated with the presence of allele I, genotype II, and genotype 4b/4b gene of this enzyme, as well as the different types of reactivity of the vegetative nervous system.

Misalignment and change of the structure of biorhythms are not independent pathology. It is considered as a prenosological condition that reflects an impaired

system of regulation of physiological functions and the risk of development of cardiovascular diseases [4].

2. Circadian rhythms of peripheral (brachial) and central (aortic) blood pressure in adolescents

The main problem in pediatrics is that new approaches that are developed in medical diagnostics are firstly probated in adults, and it takes sometimes years before they will be approved for usage in children. The ambulatory blood pressure monitoring is not the exception. There are several studies that make a fundament for the guidelines and show the important role of that method in early diagnostic of arterial hypertension (AH) in young population, but it seems that the normal ranges of some chronobiological parameters were taken from adults' guidelines without any changes. But we have to keep in mind that adolescents could have some peculiarities of circadian organization of different biological parameters due to changes in hormonal regulation that follow the puberty. This hypothesis is based also on the data published by some authors. For example, it seems interesting why overdipping pattern for DBP is so common and is not so for SBP.

Due to a lack of data on peculiarities of circadian patterns in adolescents, we performed a study in 354 healthy children from 12 to 17 years old. The average nocturnal BP decline did not differ in boys and girls ($p > 0.05$). Average CI for brachial systolic BP was 12.2%; for brachial diastolic BP, 18.3%; and for brachial mean BP, 15.5%. Average CI for aortic systolic BP was 12%; for aortic diastolic BP, 19.5%; and for aortic mean BP, 16%.

Then we looked at the distribution of different circadian BP profiles in the studied group. The majority (71.8%) of adolescents were "dippers" for SBP, 26.5% were "non-dippers" for SBP, and the minority (1.7%) of adolescents were "overdippers" for SBP (**Figure 1**). In the case of DPB, there were different results: 50.3% "dippers," 10.5% "non-dippers," and 39.3% "overdippers" (**Figure 2**).

The results of descriptive statistics of CI of brachial BP are shown in **Table 1** (girls) and **Table 2** (boys). Our findings supported the hypothesis that the normal ranges for CI in children differ from ranges for adults. The data from percentile rank could be interpreted in the following way: 25–75 percentile is the normal range, 5–25 percentile shows the values of the parameter that are lower than normal, 75–95 percentile is the values that are higher than normal, and <5 percentile and >95% provide the lowest and the highest values that in clinical practice describe the pathological change in the parameter. The normal range for CI of SBP in adolescents

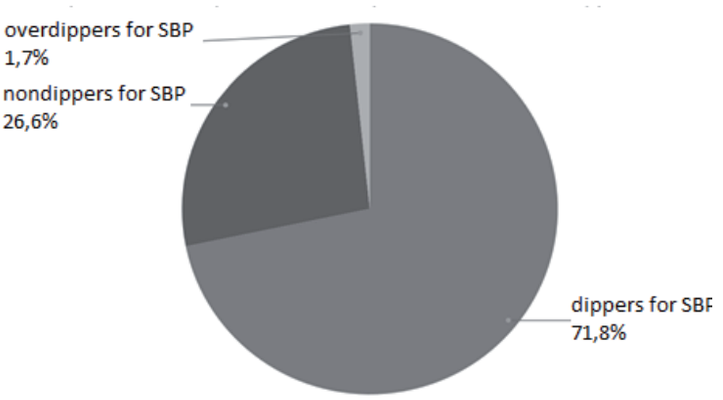


Figure 1.
The distribution of different circadian SBP profiles in the studied group.

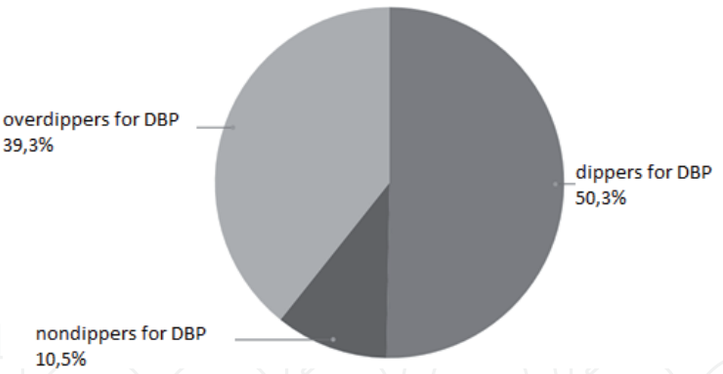


Figure 2.
The distribution of different circadian DBP profiles in the studied group.

Parameter	Mean	Minimum	Median	Maximum	Percentile			
					5	25	75	95
CI SBP (%)	12.1	0	12	26	5	9	15	19
CI DBP (%)	18.2	1	18.5	33	6.3	14	23	28
CI MBP (%)	15.8	2	16	28	6	12	19.5	24

Table 1.
Descriptive statistics of circadian index of brachial BP and its percentile distribution in adolescent girls.

Parameter	Mean	Minimum	Median	Maximum	Percentile			
					5	25	75	95
CI SBP (%)	12.14	1	12	24	5	9	15	19
CI DBP (%)	18.29	2	18	34	7	14	23	29
CI MBP (%)	15.19	3	15	38	6	12	19	24

Table 2.
Descriptive statistics of circadian index and its percentile distribution in adolescent boys.

is 9–15%, for CI of DBP is 14–23%, and for CI of MBP is 12–20%. Thereby for DBP the nocturnal dipping has a greater extend in physiological conditions in comparison with the SBP. This supported by statistical analysis that showed the significant differences in average values 12.1% (CI SBP) versus 18.2 (CI DBP) ($p < 0.05$) in adolescents of both sexes. As shown above, we talk about impaired circadian BP profile in adults using the same normal ranges for SBP and DBP<10% and higher than 20% of nocturnal decline of BP. But in children we found different values: the impaired SBP circadian profile is <5% and higher than 19%, DBP profile <6 and >28%, and MBP profile <6 and >24%. So, one can see that the profile "overdipping" for DBP starts from higher values in children in comparison with adults.

There was similar data for CI of aortic BP (**Table 3** for girls, **Table 4** for boys). Aortic DBP decrease to the greater extend at night in comparison with aortic SBP and MBP ($p < 0.05$).

In adolescents with dipping daily profile of SBP and DBP (a nocturnal decrease from 10 to 20%), the relative power of LF% during day was 35.1 ± 1.1%, LF% at night was 27.1 ± 1.8%, HF% during day was 28.3 ± 2.1%, HF% at night was 35.2 ± 1.9%, and circadian index of LF/HF was 1.3 ± 0.007, showing the physiological daily rhythm of fluctuations in the ratio between sympathetic and parasympathetic regulation contour.

In adolescents the degree of nighttime decline in the SBP exceeded 20%, the relative power of LF% during wakefulness was significantly higher than in adolescents with a normal decrease in the SBP at night (41.2 ± 1.7 vs. 35.1 ± 1, 1%, respectively, $p < 0.05$), and the circadian index of LF/HF was 1.5 ± 0.006. In adolescents with an excessive decrease in DBP, the circadian index LF/HF was 1.7 ± 0.006, and the relative power of LF and VLF% during the day was significantly higher in comparison with adolescents with a normal decrease in DBP (42.6 ± 2.1% against 35.1 ± 1.1% for LF%; 33.7 ± 1.1 vs. 27.2 ± 2.1% for VLF%, $p < 0.05$).

In adolescents with insufficient nighttime decreases in SBP and/or DBP (<10%), the circadian index LF/HF was 1.1 ± 0.007, which indicates a relative absence of a change in the ratio of the parasympathetic and sympathetic regulations at night and, as a result, smaller amplitude of the circadian rhythm of the activity of the autonomic nervous system. The average values of the relative power of LF and HF% in the group with an insufficient decrease in SBP and/or DBP during wakefulness did not significantly differ from the group with normal nocturnal decline in BP ($p > 0.05$). The main characteristic of this group of adolescents was the absence of a significant decrease in the relative power of LF% at night (37.1 ± 2.1% during the day vs. 32.2 ± 1.9% at night).

Puberty is a difficult critical period of the development, and every age in that period has its peculiarities. We performed ANOVA with post hoc Bonferroni test to find out if there are any differences in CI of CBP, DBP, and MBP in three age subgroups: 12–13, 14–15, and 16–17 years. The results are shown in **Table 5** (for brachial BP in boys), **Table 6** (for brachial BP in girls), **Table 7** (for aortic BP in boys), and **Table 8** (for aortic BP in girls). In boys there was a significant difference in the value of CI SBP and CI DBP between boys of different age subgroups ($p < 0.05$). That was supported by the results of Pearson correlation analysis between the CI and age, but the link is weak, so even if it is significant ($p < 0.05$), the hypothesis that the value of CI decreases with age has to be approved in the future studies. In girls, there were neither significant difference in the value of CI between age subgroups nor a significant correlation between CI and age ($p > 0.05$). We suppose that this can be explained by the different times of the puberty onset in boys and girls. As we know,

Parameter	Mean	Minimum	Median	Maximum	Percentile			
					5	25	75	95
CI SBP (%)	12	1	12	25	4	8	16	20
CI DBP (%)	20	3	21	42	8	15	25	31
CI MBP (%)	16	2	17	34	7	13	20	25

Table 3.
Descriptive statistics of circadian index of aortic BP and its percentile distribution in adolescent girls.

Parameter	Mean	Minimum	Median	Maximum	Percentile			
					5	25	75	95
CI SBP (%)	12	0	11	24	5	8	15	19
CI DBP (%)	19	3	19	34	6	14	24	30
CI MBP (%)	16	3	16	28	6	12	19	24

Table 4.
Descriptive statistics of circadian index of aortic BP and its percentile distribution in adolescent boys.

the main hormonal changes in girls start earlier, so by the age of 12–13, they have higher stage of puberty in comparison with boys. It is necessary to provide the same study in younger children. The main limitation of our study was that the adolescents in different age subgroups are not the same, so it was not the same boy or girl who was growing up from 12 to 17 years old. Thus, we cannot rule out other individual peculiarities of adolescent organism that could affect the results.

Parameter	12–13 years old (n = 46)	14–15 years old (n = 68)	16–17 years old (n = 56)	p-value
CI SBP (%)	13 ± 0.6	12 ± 0.5	11 ± 0.5	$p < 0.05$
CI DBP (%)	19 ± 0.9	18 ± 0.8	17 ± 0.8	$p < 0.05$
CI MBP (%)	15.9 ± 1.0	14.0 ± 0.7	15.8 ± 0.7	$p > 0.05$
r Pearson (age/CI SBP)		−0.2		$p < 0.05$
r Pearson (age/CI DBP)		−0.2		$p < 0.05$
r Pearson (age/CI MBP)		−0.1		$p > 0.05$

Table 5.
Value of circadian index of brachial BP in age subgroups of adolescent boys.

Parameter	12–13 years old (n = 52)	14–15 years old (n = 74)	16–17 years old (n = 58)	p-value
CI SBP (%)	13 ± 0.6	12 ± 0.5	12 ± 0.7	$p > 0.05$
CI DBP (%)	21 ± 0.9	18 ± 0.8	19 ± 1.0	$p > 0.05$
CI MBP (%)	16.8 ± 0.7	15.5 ± 0.6	15.4 ± 0.9	$p > 0.05$
r Pearson (age/CI SBP)		−0.01		$p > 0.05$
r Pearson (age/CI DBP)		−0.1		$p > 0.05$
r Pearson (age/CI MBP)		−0.1		$p > 0.05$

Table 6.
Value of circadian index of brachial BP in age subgroups of adolescent girls.

Parameter	12–13 years old (n = 46)	14–15 years old (n = 68)	16–17 years old (n = 56)	p-value
CI SBP (%)	13 ± 0.8	11 ± 0.5	10 ± 0.5	$p < 0.05$
CI DBP (%)	21 ± 1.0	19 ± 0.8	17 ± 0.8	$p < 0.05$
CI MBP (%)	18.3 ± 0.8	16.6 ± 0.7	15.6 ± 0.9	$p = 0.08$
r Pearson (age/CI SBP)		−0.2		$p < 0.05$
r Pearson (age/CI DBP)		−0.2		$p < 0.05$
r Pearson (age/CI MBP)		−0.2		$p > 0.05$

Table 7.
Value of circadian index of aortic BP in age subgroups of adolescent boys.

Parameter	12–13 years old (*n* = 52)	14–15 years old (*n* = 74)	16–17 years old (*n* = 58)	*p*-value
CI SBP (%)	12 ± 0.6	11 ± 0.5	11 ± 0.8	$p > 0.05$
CI DBP (%)	21 ± 0.8	19 ± 0.8	19 ± 1.0	$p > 0.05$
CI MBP (%)	17.5 ± 0.8	17.4 ± 0.7	18.1 ± 0.8	$p > 0.05$
r Pearson (age/CI SBP)		−0.04		$p > 0.05$
r Pearson (age/CI DBP)		−0.1		$p > 0.05$
r Pearson (age/CI MBP)		−0.03		$p > 0.05$

Table 8.
Value of circadian index of aortic BP in age subgroups of adolescent girls.

3. Conclusion

Analysis of the circadian rhythm of the peripheral and central blood pressure revealed gender-related features of the diurnal SBP and DBP profiles—the decrease of the degree of nocturnal decline in brachial and aortic pressure with age in healthy boys and the absence of such changes in girls 12–17 years old. The tendency to decrease with age of the degree of nocturnal dip in peripheral pressure in young men indicates the peculiarities of the age dynamics of the formation of the circadian organization of the vegetative mechanisms of regulation of the vascular wall stiffness that underlie the formation of daily arterial pressure profile. The circadian rhythm of brachial and aortic diastolic pressure in adolescents was characterized by a shift of the 25–75 percentile ranges toward higher levels of the degree of nocturnal dip in DBP compared to that for the SBP (14–23 and 9–15%, respectively). This could be probably due to the different contribution of the vasomotor component to the formation of circadian fluctuations of systolic and diastolic pressures. In addition, the values of 95 percentile, by which the disturbance of the arterial blood pressure profile is pronounced, were 28–29% for brachial and aortic diastolic pressures, which exceeds the generally accepted standard values for the adult population (22%). Thus it is necessary to provide more studies on mechanisms that underline the differences. The obtained data can be used to improve accuracy when decoding data of ABPM and interpretation of the results obtained in adolescents.

Conflict of interest

The authors declare no conflict of interest.

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