Characteristics of gender-related circadian arterial blood pressure in healthy adolescents

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Key words: adolescent; blood pressure; gender-related differences; menstrual cycle.

Summary. Objective. To define 24-h characteristics of arterial blood pressure in healthy adolescent girls and boys; to determine gender-related differences of blood pressure, its circadian pattern.

Material and methods. The 24-h blood pressure was monitored hourly in healthy girls (n=22, without no account for the menstrual cycle phase) and boys (n=22). Additionally, blood pressure of adolescent girls (n=15) was examined during different phases of their menstrual cycle (follicular, ovulation, and luteal). Blood pressure was monitored with an auto-cuff automatic outpatient blood pressure monitor.

Results. Investigation showed gender-related differences in 24-h blood pressure. Study results revealed the circadian blood pressure rhythm characterized by a period of low values during nighttime and an early morning increase in both adolescent groups. Nocturnal systolic blood pressure was higher (P<0.05) in boys than in girls in all phases of their menstrual cycle. Diurnal systolic blood pressure in boys was higher than in girls in their follicular phase (P<0.05). The day and night blood pressure differed between boys and girls (P<0.05). A dipping blood pressure pattern as a decrease in mean nighttime blood pressure as compared with mean daytime blood pressure was defined: 10.02±6.7% in girls (n=22) and 13±6.3% in boys (n=22), without gender-related differences (P>0.05). There were no differences in blood pressure dipping among girls' groups in different menstrual cycle phases (P>0.05). Adolescent boys showed a significant positive correlation between their mean diurnal blood pressure and height (P<0.05).

Conclusion. The study proved gender-related arterial blood pressure differences in healthy adolescents. The results demonstrate the gender-specific circadian blood pressure rhythm pattern in both gender groups.

Introduction

Current epidemiological, clinical, and experimental data suggest that the course of primary arterial hypertension may be gender related. Men tend to have a higher predisposition to hypertension; the same antihypertensive treatment shows a different efficacy in men and women (1). There is evidence that even a single routine arterial blood pressure (BP) measurement in adolescence accurately predicts arterial hypertension and total cardiovascular risk in young adulthood (2). Hypertension manifests in adulthood, but may have a latent onset in childhood. Elucidation of gender-related differences in BP regulation in children might help to explain the pathogenesis of essential hypertension. Circadian rhythms have been implicated in the genesis of cardiovascular disorders (3). Biological rhythms may be circadian (with a periodi-

city of approximately 24 hours) and circatrigintan – related to the menstrual cycle in women (4). The prevalent circadian (24-h) pattern of BP in both normotensive and hypertensive individuals reveals a period of low values during night; patients who display the typical nocturnal decrease in BP are termed *dippers*, whereas individuals in whom the nocturnal decrease in BP is absent or blunted are termed *nondippers* (5, 6). Recent advances in molecular genetics of circadian rhythms, BP, and hypertension led to the discovery of separate groups of genes are implicated in their regulation (7). Data on gender-related differences in BP in adolescents are scarce.

The aim of the study was to determine the 24-h BP differences in healthy adolescent boys and girls, to prove changes in BP during different phases of menstrual cycle in girls as well as gender-related

characteristics of circadian arterial BP in both gender groups.

Patients and methods

Permission to carry out the study was obtained from the Lithuanian Bioethics Committee (Protocol No. 01-35; July 11, 2001). Only healthy children on no medication were enrolled. The method of 24-h BP monitoring was explained to every participant, and the questionnaires were completed. The children were advised to stick to a definite day and sleeping regime: to go to bed at about 9–10 PM and to get up at about 7–8 AM; they were not allowed to go in for sports; the day physical activities during the period of measurements were similar in the girls' and boys' groups. The "diurnal" and "nocturnal" hours of BP monitoring were the same in girls and boys, with a diurnal duration of 13.6±1.3 h in girls and 13.7±1.7 h in boys and a nocturnal duration of 10.3±1.3 h and 10.3±1.7 h, respectively. The 24-h BP monitoring was carried out on the nondominant arm; the time of application and the type of device were the same in all patients. Nighttime BP dipping was calculated as the difference between the mean daytime and mean nighttime BP values in accordance with data reported by others authors (8, 9). The mean height was 174.2±8.2 cm in adolescent boys and 165.2±6.4 cm in adolescent girls; the mean weight being 60.6±8.6 kg in boys and 55.7±8.9 kg in girls. There was no statistically significant difference comparing these data in both genders. In adolescent boys (n=22; mean age, 14.5±1.1 years) and girls (n=22; mean age, 14.6±1.0 years, without no account for the menstrual cycle phase), ambulatory BP was monitored hourly for 24 h. Additionally, 24-h BP monitoring was performed in healthy adolescent girls (n=15; mean age, 14.8±0.9 years) dur-

ing different phases of their menstrual cycle. All the girls who had regular menstrual cycles were monitored on the days including the 5th day (during the follicular phase, when estrogen and progesterone levels were close to minimal), on the 13th day (during the ovulation phase, when the estrogen level was maximal), and on the 20th day (during the luteal phase, when the progesterone level was close to maximal).

BP was monitored with an auto-cuff automatic outpatient BP monitor (model ABP-1001, Biotrac, USA).

The impact of anthropogenic factors on BP was investigated by means of correlation analysis. Correlations between two variables were investigated by the method of linear correlations analysis. The Pearson correlation coefficient r, which represents the linear relationship between two variables, was applied. The Student's t test was used to show the significance of the data. Data were expressed as mean ± standard deviation (SD); the unpaired t test was used. STATISTICA for Windows software (StatSoft, USA, 1995) was used to analyze the data. A P value of <0.05 was considered significant.

Results

Nocturnal systolic BP was significantly higher ($P<0.05$) in boys than in girls in all phases of their menstrual cycle: at the beginning of the follicular, in the ovulation and luteal phases (Table). Diurnal systolic BP in boys was significantly higher than in girls during follicular phase ($P<0.05$).

The day and night systolic and diastolic BP significantly differed in boys (n=22) and girls (n=22) ($P<0.01$). BP findings also significantly differed in girls during different menstrual cycle phases as compared with boys (Table). The circadian differences in

Table. **Data of arterial blood pressure measurements of examined healthy adolescents**

Investigated groups	n	Arterial blood pressure, mm Hg						
		systolic		diastolic		mean		
		day	night	day	night	day	night	dipping (%)
Girls:								
follicular phase	15	108±9*♦	98±7*♦	77±6♦	64±4♦	87±6♦	75±4♦	10.9±5
ovulation phase	15	109±7♦	99±6*♦	75±5♦	64±5♦	86±5♦	75±5♦	9.2±6
luteus phase	15	109±8♦	97±6*♦	74±6♦	65±5♦	85±7♦	76±6♦	9.3±6
common group	22	110±9♦	100±6*♦	76±8♦	66±5♦	87±8♦	77±5♦	10.02±6
Boys	22	114±9*♦	105±9*♦	77±5♦	65±6♦	89±6♦	77±6♦	13±6.3

♦P<0.05, comparing day and night blood pressure.
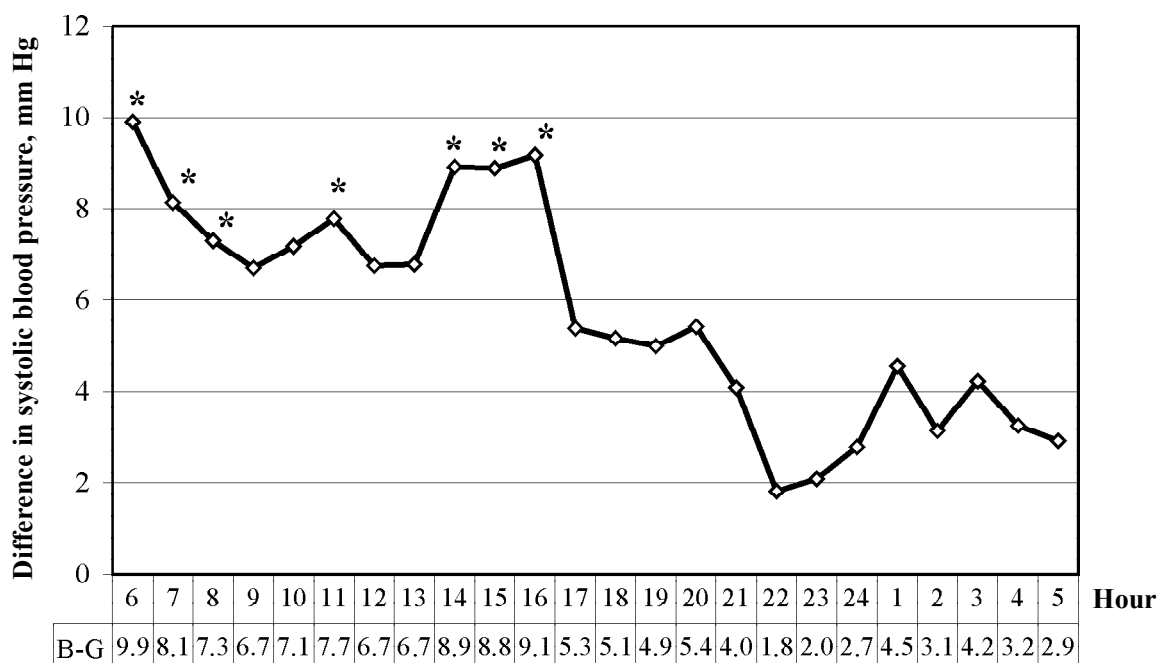*P<0.05, comparing boys and girls.

Fig. 1. Hourly differences in systolic blood pressure of girls (n=22) and boys (n=22)

B-G – hourly differences in systolic blood pressure between adolescent boys (B) and girls (G).
*Value was significantly higher in boys compared to girls (not taking into account the menstrual cycle phase) ($P<0.05$).

systolic BP between the boys and the girls (not taking into account the menstrual cycle phase) were statistically significant early in the morning (from 6 to 8 AM), at 11 AM, and in the daytime from 2 to 4 PM (Fig. 1).

We found a dipping BP pattern as a reduction in mean nighttime BP no less than 10% as compared with the mean daytime BP values in both boys and girls (Table). The BP dipping was 10.02±6.7% in girls (n=22) and 13±6.3% in boys (n=22); no gender-related differences were determined ($P>0.05$). There were no significant differences in BP dipping among girl groups in different menstrual cycle phases: 10.96±5% in follicular phase, 9.2±6% in the ovulation, and 9.3±6% in the luteal phase ($P>0.05$). Data on systolic BP in boys and in girls during their follicular, ovulation, and luteal menstrual cycle phases are presented in Fig. 2.

Adolescent boys showed a significant positive correlation between mean diurnal BP pressure and height ($r=0.55$; $P<0.05$). No such relationship was observed in adolescent girls ($r=0.02$; $P>0.05$). The gender-related differences in the correlation between mean BP and height in adolescents were significant ($P<0.05$).

Discussion

Investigation of gender-related differences in adolescent BP might explain the higher prevalence of hypertension in men as well as elucidate some other mechanisms involved in the turn of the disease. Some changes in BP regularity capable of contributing to arterial hypertension in future may be found in childhood. In our study, adolescent nocturnal systolic BP was significantly higher in boys than in girls. Nocturnal systolic BP was significantly lower in girls in all cycles of their menstrual cycle than in boys. Diurnal systolic BP in boys was significantly higher than in girls in their follicular phase. These findings, which are gender-related, may provide physiological evidence that throughout most of their lives, males have a higher average BP than females. This sexual dichotomy is known to be related to genetic factors including the X and Y chromosomes, genes that control sex hormone levels (10, 11). Investigations have proven that sex steroid-related genes encoding ERalpha and ERbeta receptors may be involved in the genetic regulation of higher arterial BP in men with no associations in women (12). There is a great controversy over the role of androgens in the pathogenesis in cardiovascular disorders; however, the majo-
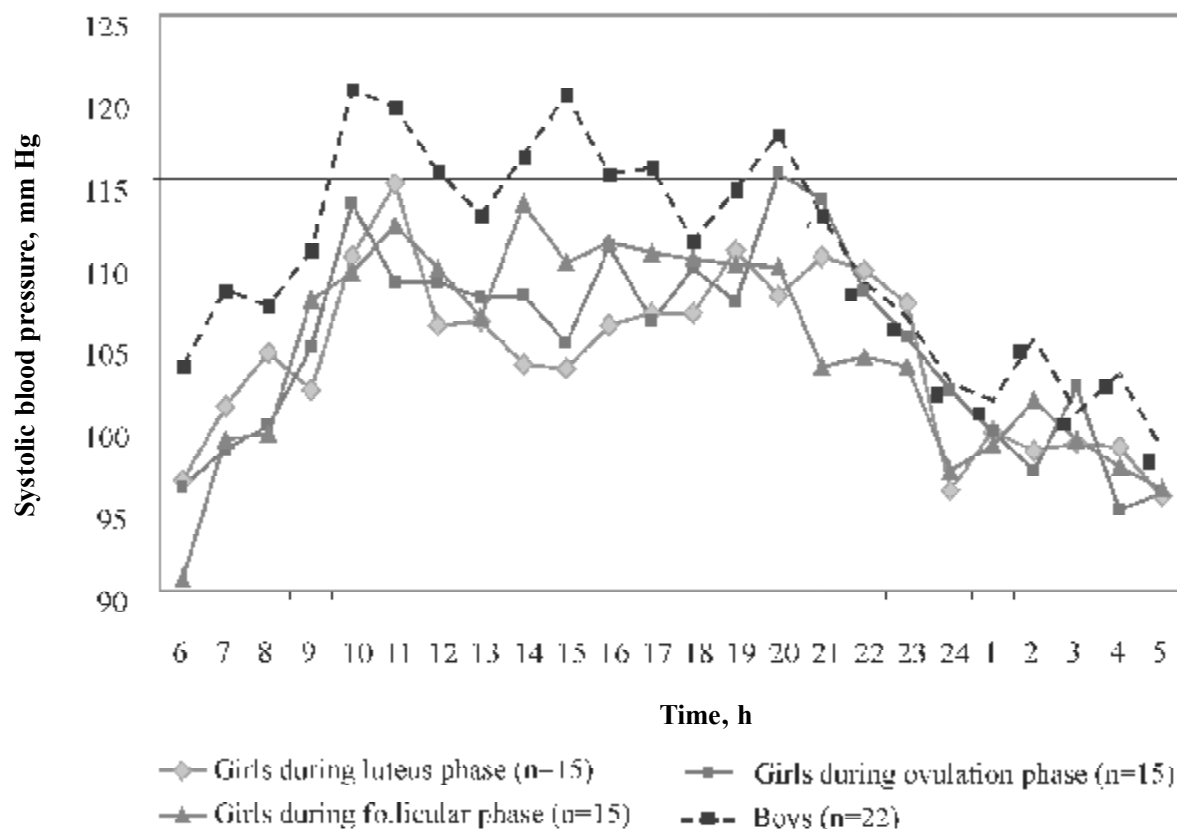
Fig. 2. The data of systolic arterial blood pressure in boys (n=22) and in girls (n=15)
during different phases of their menstrual cycle (follicular, ovulation, and luteal)

rity of recent clinical studies provide the evidence of a positive correlation between low levels of total testosterone, free androgen index, testosterone/estradiol ratio and cardiovascular risk factors (13, 14).

Our study revealed gender-related circadian BP characteristics in healthy adolescents. The well-known normal diurnal rhythm of androgen secretion with the pronounced serum testosterone concentrations in early morning hours has been determined in pre-pubertal and pubertal boys (15). Diurnal rhythms of female hormone secretion have also been described before the onset of female puberty: the serum estradiol concentrations are elevated early in the morning (16). The beneficial vascular effects of estrogens in experimental studies provide evidence that estrogens may increase the bioavailability of endothelium-derived nitric oxide (NO), a potent vasodilating substance (17). Estrogens can increase the enzyme endothelial NO synthase at the transcriptional level in blood vessels (18), may enhance the angiotensin-converting enzyme inhibition-mediated improvement of vascular remodeling in hypertension (19), potentiate susceptibility of smooth muscle cells to NO (20).

In our study, significant gender-related differences in diurnal and nocturnal BP were highly notable in the follicular phase. Other researchers have indicated that female sex hormones and their effects on vascular function differ during menstrual cycle: clinical, experimental studies show the endothelial NO synthase, endogenous NO expression to be markedly increased in the follicular phase, to fall after ovulation, in early luteal phases, and then to rise again during the mid-luteal and late-luteal phases (21, 22). The fluctuations in estrogen concentrations during the menstrual cycle are reflected in varying levels of several other circulating factors that regulate the vascular endothelial function by release of NO and other vasoactive factors (21). The experimental and clinical data show the influence of the gender-specific NO synthase gene, NO alterations being significant for blood pressure and cardiovascular disorders in females (23, 24). Preclinical and human studies have shown that estrogens and progesterone act as vasodilatating substances (25, 26). Experimental investigations have proved the hypothesis that progesterone exerts a direct nongenomic effect on rat and pri-

mate coronary arteries, related with activation of endothelium-dependent vascular relaxation and dilatation, including the nitric oxide-cGMP and prostacyclin-cAMP pathways (27, 28). The menstrual cycle hormones, hormone replacement therapy are associated with a decrease of the physiological fall in nocturnal BP (29).

Our data show that the amplitude of systolic BP in boys compared to the girls was significantly higher early in the morning. This could be also associated with gender-related differences in the sympathetic activity during the early morning and waking hours (30). The diurnal rhythm of BP coincides with a rhythmic release of catecholamines (31). Early in the morning, there is a marked rise in sympathetic activity (32), which is higher in men than in women (33). NO is also dependent on circadian variability: its production is increased in the morning, indicating that NO may buffer BP increase, and a decreased formation and activity of NO may contribute to BP alterations (34).

Our study showed a circadian BP rhythm profile characterized by BP reduction in nighttime, i.e. the so-called *dipper* status. Investigations define nocturnal dipping as reduction in mean blood pressure at night no less than 10% as compared with mean daytime blood pressure values (9, 35). On the contrary, prospective data of several studies have shown that "nondippers" have a higher damage level of target organ, greater risk for cerebrovascular and cardiovascular complications than do "dippers" in both normotensive and hypertensive subjects (36, 37).

Our investigation revealed a significant positive correlation of height with nocturnal and diurnal BP in boys, but not in girls. The childhood data of anthropometrical findings are important for BP and development of arterial hypertension: height may be a risk factor of hypertension in boys (38, 39). Further investigations and analysis of the mechanisms of the abovementioned gender-related differences, circadian BP rhythm profile, the role of anthropometrical data for arterial BP in children might explain a predisposition to arterial hypertension and cardiovascular risk in adults.

Conclusion

The study proved significant gender-related blood pressure differences in healthy adolescents. The results demonstrate a gender-specific circadian blood pressure rhythm pattern in both genders. Determination of these blood pressure characteristics could be important for understanding the pathogenesis of primary arterial hypertension, a higher risk of boys to develop hypertension, and for the evaluation of similar gender-related investigations in the essential hypertension population.

Su lytimi susijusio sveikų paauglių cirkadinio arterinio kraujospūdžio ypatybės

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Raktažodžiai: paauglys, arterinis kraujospūdis, su lytimi susiję skirtumai, mėnesinių ciklas.

Santrauka. *Tikslas*. Nustatyti sveikų paauglių (mergaičių ir berniukų) 24 valandų arterinio kraujospūdžio ypatybes, su lytimi susijusius arterinio kraujospūdžio skirtumus bei cirkadinio kraujo spaudimo ritmo ypatumus.

Tyrimo medžiaga ir metodai. 24 val. stebėtas sveikų mergaičių (n=22, nepriklausomai nuo mėnesinių ciklo fazės) ir berniukų arterinis kraujospūdis, kuris matuotas kas valandą. Papildomai arterinis kraujospūdis buvo matuojamas paauglėms mergaitėms (n=15) mėnesinių ciklo skirtingų fazių metu (folikulinės, ovuliacinės ir liutealinės). Arterinis kraujospūdis buvo matuojamas ambulatorinėmis sąlygomis visą parą automatiniu kraujo spaudimo matavimo prietaisu.

Rezultatai. Tyrimas parodė su lytimi susijusius 24 valandų arterinio kraujospūdžio skirtumus. Tyrimo rezultatai atskleidė arterinio kraujospūdžio cirkadinio ritmo ypatybes, t. y. spaudimo sumažėjimą naktį ir padidėjimą anksti rytą abiejų lyčių paaugliams. Naktinis sistolinis arterinis kraujospūdis berniukų buvo aukštesnis (p<0,05), lyginant su mergaičių, joms arterinį kraujospūdį matuojant mėnesinių ciklo visų fazių metu. Dieninis sistolinis arterinis kraujospūdis berniukų buvo didesnis nei mergaičių folikulinės fazės metu (p<0,05). Nustatyti dienos ir nakties arterinio kraujospūdžio skirtumai (p<0,05) abiejose tiriamųjų grupėse. Nustatytas naktinio arterinio kraujospūdžio sumažėjimas (angl. *dipping*), t. y. naktinio vidutinio arterinio kraujospūdžio sumažėjimas, lyginant su dieniniu vidutiniu arteriniu kraujospūdžiu: 10,02±6,7 proc. mergaičių

(n=22) ir 13±6,3 proc. berniukų (n=22), nesant lyties skirtumų (p>0,05). Naktinio arterinio kraujospūdžio sumažėjimo skirtumų mergaičių grupėse, vertinant jų arterinį kraujospūdį mėnesinių ciklo skirtingų fazių metu (p>0,05), nenustatyta. Paaugliams berniukams būdingas aiškus ryšys tarp vidutinio dienos arterinio kraujospūdžio ir ūgio (p<0,05).

Išvada. Tyrimo duomenys rodo sveikų paauglių su lytimi susijusius 24 val. arterinio kraujo spaudimo skirtumus, taip pat su lytimi susijusio cirkadinio arterinio kraujospūdžio ritmo ypatybes paauglių berniukų ir mergaičių grupėse.

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