Determinants of inappropriate circadian blood pressure variability in children with essential hypertension

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BACKGROUND: Inappropriate daily profile of blood pressure deteriorates the clinical outcome of hypertension and increases distant cardiovascular risk. The problem is important, especially in children and adolescents in whom early intervention helps to prevent complications of hypertension such as left ventricular hypertrophy and hypertensive retinopathy.

OBJECTIVES: To assess circadian blood pressure profile and basic determinants of inappropriate daily blood pressure variability in hypertensive children.

METHODS: The project was conducted retrospectively in 106 children six to 18 years of age (mean [± SD] 14.9±2.5 years) with essential hypertension and no use of antihypertensive drugs. The study group included 43 children with inappropriate daily blood pressure variability ('nondippers') and 63 controls with appropriate daily blood pressure variability ('dippers').

RESULTS: Nondippers, compared with dippers, had higher systolic and diastolic blood pressure at night (systolic, 123.9±10.3 mmHg versus 113.9±8.2 mmHg; diastolic, 65.1±7.6 mmHg versus 59.5±6.5 mmHg; $P<0.0001$), and higher blood pressure load at night (systolic, 61.9% versus 27.6%; diastolic, 20.0% versus 9.6%; $P<0.0001$). Male sex increased the risk for nondipping by 2.5 times (logistic OR=2.45; 95% CI 0.87 to 6.87). However, the increase was statistically nonsignificant ($P=0.08$). No differences were observed between dippers and nondippers in terms of anthropometric profile, family history of hypertension, morphological and biochemical blood parameters, and birth weight.

CONCLUSIONS: Among hypertensive children, nondippers have a more severe degree of hypertension. Male sex increases the risk of nondipping. To assess determinants of nondipping more precisely, further clinical investigations are needed.

Key Words: Ambulatory blood pressure monitoring; Children; Dippers; Essential hypertension; Nondippers

Déterminants d'un cycle nyctéméral inapproprié de la tension artérielle chez des enfants atteints d'hypertension essentielle

HISTORIQUE : Un cycle nyctéméral inapproprié de la tension artérielle (TA) contribue à aggraver l'issue clinique de l'hypertension et accroît le risque cardiovasculaire à long terme. Le problème est de taille, surtout pour les enfants et les adolescents, chez qui une intervention précoce aide à prévenir les complications de l'hypertension, comme l'hypertrophie ventriculaire gauche et la rétinopathie hypertensive.

OBJECTIFS : Évaluer le cycle nyctéméral de la TA et les facteurs de base en cause dans les anomalies qui affectent ce cycle chez les enfants hypertendus.

MÉTHODES : Le projet a été réalisé rétrospectivement auprès de 106 enfants âgés de six à 18 ans (moyenne [± É.-T.] 14,9 ± 2,5 ans) atteints d'hypertension essentielle et ne prenant pas d'antihypertenseurs. Le groupe étudié comportait 43 enfants au cycle nyctéméral anormal (c.-à-d., dont le profil tensionnel restait élevé durant la nuit [non dippers]) et 63 au cycle nyctéméral normal (dippers).

RÉSULTATS : Comparativement aux sujets dont le cycle nyctéméral était normal, ceux dont le cycle était anormal présentaient une tension artérielle systolique et diastolique plus élevée la nuit (systolique 123,9 ± 10,3 mm Hg, vs 113,9 ± 8,2 mm Hg; diastolique, 65,1 ± 7,6 mm Hg, vs 59,5 ± 6,5 mm Hg; $P < 0,0001$) et une charge tensionnelle nocturne plus élevée (systolique, 61,9 %, vs 27,6 %; diastolique 20,0 %, vs 9,6 %; $P < 0,0001$). Le fait d'être de sexe masculin a multiplié par 2,5 le risque que la TA reste élevée la nuit (RC logistique = 2,45; IC à 95 % 0,87 à 6,87). Toutefois, l'augmentation n'a pas été statistiquement significative ($P = 0,08$). Les auteurs n'ont observé aucune différence entre les sujets aux cycles nyctéméraux normaux ou anormaux selon leurs caractéristiques anthropométriques, leurs antécédents familiaux d'hypertension, leurs paramètres morphologiques et biochimiques et leur poids à la naissance.

CONCLUSIONS : Parmi les enfants hypertendus, ceux dont la TA reste élevée durant la nuit présentent une hypertension plus marquée. Le fait d'être de sexe masculin exacerbe le risque de cycle nyctéméral anormal. Pour évaluer avec plus de précision les déterminants d'un cycle nyctéméral anormal, il faudra approfondir la recherche.

Both mean blood pressure (BP) values and the prevalence of hypertension (HT) increase with age (1,2). High BP in childhood and adolescence promotes the probability of HT incidence in adulthood (2,3).

Cardiovascular mortality correlates with BP value. It has been shown that every 20 mmHg increase in systolic BP and every 10 mmHg increase in diastolic BP above the value of 115/75 mmHg is associated with a twofold higher cardiovascular risk (4). No borderline BP value was found to be the cut-off for the increase in risk. Cardiovascular mortality rises gradually across BP values, including

the reference values (4,5). It is worth being mentioned that the cited data (4) refer to adults and it may not be the same for children.

Inappropriate circadian BP profile deteriorates the clinical outcome of HT, particularly the morbidity of heart disease and its end points. Inappropriate BP profile is especially seen when the nocturnal drop in BP is less than 10% of its diurnal value, which is defined as a 'nondipping' pattern (6).

The problem is important in children and adolescents in whom early intervention helps to prevent complications of HT such as left

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TABLE 1
Patient characteristics

Variable	Study group (nondippers)	Reference group (dippers)	P*
Boys:girls, n	35:8	42:21	0.09
Age, years	14.7±2.4	15.1±2.5	0.1
Weight, kg	69.3±16.5	71.9±17.4	0.4
Height, cm	167.7±13.3	168.9±16.7	0.4
BMI, kg/m ²	24.3±4.0	24.4±5.3	0.7
Overweight, n	22	30	0.7
Familial HT, n	17	29	0.5

Values are presented as mean ± SD for continuous variables and the frequency in n for categorical variables. *Study versus reference group (values of Student's t test or the Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables). BMI Body mass index; HT Hypertension

TABLE 2
Blood pressure profile of patients

Blood pressure (mmHg)	Study group (nondippers)	Reference group (dippers)	P*
24 h			
SBP	130.9±10.5	129.6±8.3	0.5
DBP	70.9±12.8	72.4±6.8	0.6
Day			
SBP	133.2±10.7	134.4±8.4	0.5
%↑SBP, %	56.0±25.9	54.3±23.1	0.6
DBP	74.9±8.3	76.2±7.0	0.1
%↑DBP, %	18.9±22.7	21.3±19.6	0.2
Night			
SBP	123.9±10.3	113.9±8.2	<0.0001
%↑SBP, %	61.9±28.8	27.6±22.8	<0.0001
DBP	65.1±7.6	59.5±6.5	<0.0001
%↑DBP, %	20.0 ± 24.9	9.6±13.3	0.02
Dipping			
SBP	6.9±2.6	15.2±2.9	<0.0001
DBP	13.7±7.0	22.0±5.0	<0.001

Values are presented as mean ± SD. *Study versus reference group (values of Student's t test or the Mann-Whitney U test for continuous and the χ^2 test for categorical variables). DBP Diastolic blood pressure; %↑DBP Diastolic blood pressure load; SBP Systolic blood pressure, %↑SBP Systolic blood pressure load

ventricular hypertrophy and hypertensive retinopathy. The aim of the present study was to assess circadian BP profile and basic determinants of inappropriate daily BP variability in hypertensive children.

METHODS

The medical documentation of 204 consecutive hypertensive children referred from January 2003 through June 2006 to the pediatric cardiology unit at the Medical University of Silesia (Katowice, Poland) were analyzed. The exclusion criteria were secondary HT and past or current antihypertensive pharmacotherapy. A total of 106 children, six to 18 years of age (mean [± SD] 14.9±2.5 years), participated in the study. The patients were divided into the study group (nondippers, n=43) and the control group (dippers, n=63). All parents or guardians, and children 16 years of age or older gave their written consent.

Twenty-four-hour automatic BP monitoring was performed by using the Tracker NIBP2 (Del Mar Reynolds Medical Ltd, United Kingdom) monitoring device, which is suitable for pediatric purposes (7). The proper cuff, which was placed on the nondominant arm, was selected according to the subject's arm length and width (5,8). Monitoring data were accepted for analysis when at least 90% of valid readings were obtained during both day and night. Automatic BP

TABLE 3
Laboratory findings

Variable	Study group (nondippers)	Reference group (dippers)	P*
White blood cells, $\times 10^3/\text{mm}^3$	6.87±1.3	7.15±1.7	0.6
Red blood cells, $\times 10^6/\text{mm}^3$	4.98±0.4	4.93±0.4	0.6
Hemoglobin, mmol/L	9.06±0.87	9.06±0.81	0.7
Glucose, mmol/L	5.17±1.74	4.61±0.64	0.3
Cholesterol, mmol/L	4.03±0.86	4.0±0.63	0.8
Triglycerides, mmol/L	1.06±0.48	1.14±0.53	0.5
HDL cholesterol, mmol/L	1.28±0.35	1.31±0.47	0.5
LDL cholesterol, mmol/L	2.39±0.91	2.2±0.66	0.8

Values are presented as mean ± SD. *Study versus reference group (values of Student's t test or the Mann-Whitney U test). HDL High-density lipoprotein; LDL Low-density lipoprotein

monitoring data were analyzed by calculating the mean BP, BP load for daytime and nighttime periods, and nocturnal BP dip. BP was recorded every 15 min between 06:00 and 22:00 (daytime period), and every 30 min between 22:00 and 06:00 (nighttime period) during the routine check-up on a ward to minimize the influence of physical activity on results. HT was defined when the mean circadian BP exceeded the 95th percentile of the BP value specific for age and sex, and/or when the BP load was higher than 20% (5,8,9). BP load was defined as the percentage of individual BP values that exceeded the 95th percentile of the BP value specific for age and sex. Nondipping was recognized when the nocturnal BP decrease was less than 10% of the systolic diurnal BP value (5,6).

Basic anthropometric data (ie, age, weight and height) were obtained. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Overweight was defined as a BMI in the 90th percentile or higher of the BMI value specific for age and sex (10). The history of familial HT and birth weight of children were estimated. All patients underwent routine blood tests (ie, morphological and biochemical tests).

The results obtained were statistically analyzed with Statistica 7.1 (StatSoft Inc, USA) procedures. Descriptive statistics are presented as percentages, means and SDs. Univariate analyses for group comparisons of continuous variables were performed using Student's t test or the Mann-Whitney U test. The χ^2 test was used to compare categorical variables. Additionally, multivariate analysis was performed using a logistic regression model, with the nondipping pattern used as the dependent variable. Independent variables included age, sex, BMI and assessed clinical parameters (ie, birth weight, family history of HT and blood test results). Logistic ORs and their 95% CIs were estimated. $P<0.05$ was considered to be statistically significant. In multivariate analyses, 'borderline significance' was defined as $0.05<P<0.1$.

RESULTS

The subjects' characteristics are shown in Table 1. Nondippers did not differ from dippers regarding anthropometric data and history of familial HT. The mean birth weight was 3.1628 ± 0.5555 kg for the study group and 3.3486 ± 0.5752 kg for the reference group ($P=0.2$).

Table 2 presents the children's circadian BP profile. Nondippers, compared with dippers, had significantly higher nocturnal BP (123.9 ± 10.3 mmHg versus 113.9 ± 8.2 mmHg for systolic BP, and 65.1 ± 7.6 mmHg versus 59.5 ± 6.5 mmHg for diastolic BP, respectively) and nocturnal BP load (mean $61.9\pm 28.8\%$ versus $27.6\pm 22.8\%$ for systolic BP, and $20.0\pm 24.9\%$ versus $9.6\pm 13.3\%$ for diastolic BP). Moreover, children from the study group had a significantly lower nocturnal BP dip than children from the reference group (mean 6.9 ± 2.6 mmHg versus 15.2 ± 2.9 mmHg for systolic BP, and 13.7 ± 7.0 mmHg versus 22.0 ± 5.0 mmHg for diastolic BP, respectively).

The blood test results did not reveal important differences between nondippers and dippers (Table 3).

The results of multivariate analyses showed that the sex of subjects influenced the nondipping pattern remarkably, controlling for assessed clinical features. The logistic regression coefficient (b) was 0.89 ± 0.51 ; $P=0.08$. Male sex increased the risk for nondipping by 2.5 times (logistic OR=2.45; 95% CI 0.87 to 6.87; $P=0.08$ [borderline significance]). BP values were not taken into account in the logistic regression equation because of marked colinearity of variables (Pearson coefficient of correlation $r>0.4$; $P<0.05$ each time).

DISCUSSION

The aim of the present study was to assess circadian BP profile and determinants of nondipping patterns in pharmacologically never-treated children with essential HT.

In the present study, nondippers had significantly higher systolic and diastolic BP loads and BP values at night than dippers. This is in strong agreement with data suggesting that the changes in circadian BP profile are more prominent in adult subjects with hypertension than in persons with reference BP values (11-13); however, the BP profile in children may differ from the BP profile in adults (8).

It is interesting that the 24 h mean BP value did not differ between groups. We assume that the dipping pattern depends mainly on the nocturnal decrease in blood pressure. A review of published data confirmed our assumption (11,12,14).

Special attention should be drawn to the fact that inappropriate BP profile may be more harmful to the arterial vascular wall than the incidence of high BP causing early progress of target-organ damage (6,15). Based on the analysis of the BP profile in both groups, we assume that nondippers have a more severe degree of HT. As a result, young subjects with a nondipping BP pattern are more prone to be at higher cardiovascular risk than dippers.

Based on published data, it is suggested that BP variability is mostly determined environmentally (especially by the lifestyle of subjects), whereas the role of genetic factors is less important (16,17). This is confirmed by the influence of season, outdoor temperature, body mass and smoking habit on BP variability (18-24).

The results obtained in the present study demonstrate the complex nature of the nondipping pattern. It was revealed that the only determinant of nondipping was sex; more frequently occurring in boys than girls. Although the relationship was not statistically significant ($P=0.08$), the value of the adequate OR (2.5 times higher risk) cannot be ignored. An increase in the number of study subjects would likely confirm this finding in a statistically significant way. In accordance with the World Health Organization guidelines concerning sample size determination in health studies (25), a sample of 168 children would be needed in the present study (84 subjects in the study group and 84 controls) to reveal a significant OR (when the power of the study is 0.8 and the level of statistical significance is 0.05).

As far as the relationship between circadian BP pattern and sex is concerned, a literature review revealed contradictory information. It may be the result of dissimilarities in clinical and demographical subject characteristics in the articles cited below. The analysis of BP variability in normotensive patients 14 to 70 years of age revealed that inappropriate daily BP concerned women more frequently than men (35.8% versus 20.7%, respectively) (26). The same dependence was described in healthy young adults, 18 to 25 years of age (20).

The present study did not reveal any relationships between body mass and age, and circadian BP pattern, despite strong evidence in the literature. In a study in Ohasama, Japan (21), positive correlations among BP variability, age and BMI were found. Larger BP variability and BP load were also found in 14-year-old normotensive overweight children, compared with children who had a proper body mass (22). Moreover, BP variability was positively associated with BMI value in medical students with reference BP values, but did not differ with age (20). In contrast, our results are consistent with observations of Ijiri et al (14) and Verdecchia et al (27,28). We assume that the influence of body mass and age on nondipping pattern varies individually between subjects and may depend on many cofactors.

Neither the findings of the present study nor those of Ijiri et al (14) or Verdecchia et al (27,28) revealed the differences between dippers and nondippers regarding biochemical blood profile. Although Verdecchia et al (28) showed a significant difference in blood glucose concentration in accordance with BP variability type, it resulted from the difference in the frequency of diabetic patients in the groups being compared. However, published data indicate some associations between circadian BP profile and hemoglobin levels between dippers and nondippers in adult diabetic patients (29). In another study (23) of patients with chronic renal failure, the value of nocturnal BP variability was positively correlated with BMI and blood serum cholesterol concentration. These findings are difficult to explain. It cannot be excluded that seasonal variations in morphological and biochemical blood parameters influenced the cited results (30,31).

Some contradictory data are available in relation to the influence of birth outcomes on BP variability. Lurbe et al (32) found a significant negative correlation between circadian BP variability (SDs of means) and birth weight in healthy children four to 18 years of age, even after adjustment for sex, age, body mass and body height. No influence of birth weight on BP variability was found in both normotensive children six to 16 years of age (16) and children with essential HT (33). Further and more precise investigations are required to assess the relationship properly.

The most important information for our study is included in the results of Cuspidi et al (11,12,34,35) and Feola et al (36). These studies, devoted to the characteristic of never-treated adults with essential HT, revealed that nondippers did not differ from dippers as far as age, sex, BMI, biochemical blood parameters and mean BP values were concerned. Also, Vaz et al (37) found no influence of age and BMI on BP variability in young normotensive male subjects.

Based on the observations of Feig and Johnson (38,39), the possible impact of uric acid concentration on the results should be discussed. The authors (38) revealed that uric acid might have a role in the early development of essential HT. They observed that uric acid concentration directly correlated with both systolic ($r=0.80$) and diastolic ($r=0.66$) BP in a group of 63 children with newly diagnosed, pharmacologically untreated, essential HT and normal renal function. Moreover, uric acid concentrations higher than 5.5 mg/dL were found in 89% of children with essential HT, but in none of the control subjects. The authors also assumed that uric acid may cause an increase in BP through a uric acid-mediated vasoconstriction, followed by induction of renal afferent arteriosclerosis and altered pressure natriuresis, leading to sodium-dependent HT (39). As a result, a possible relationship between serum uric acid concentration and circadian BP pattern cannot be excluded. However, in the present study, no attempt was made to assess the relationship properly. Unfortunately, the parameter was not routinely measured in children; consequently, the results cannot be presented.

It is also worth mentioning that the influence of the use of pharmacological treatment should be taken into consideration because it may impact the results of clinical studies (40).

Based on the aforementioned data, we assume that the nature of circadian BP variability is complex and difficult to assess. In the literature, there is still a lack of satisfactory data describing the problem of determinants of nondipping in children and adolescents with essential HT.

Varied methodology, implemented in cited studies, limits the possibility of comparisons. Undoubtedly, data concerning adults, both with reference to BP value and HT, are only partially valuable in this aspect. Considering the clinical importance of the issue presented in the current study, more precise investigations are needed.

CONCLUSION

Among hypertensive children, nondippers have a more severe degree of HT than dippers. More to the point, male sex increases the risk for nondipping in children with essential HT. To assess risk factors of nondipping in children with essential HT more precisely, further clinical investigations are needed.

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