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Original Scientific Paper

DETERMINING THE FACTORS THAT INFLUENCE BLOOD PRESSURE VARIABILITY IN CHILDREN WITH ESSENTIAL HYPERTENSION

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SUMMARY – This study aimed to analyze blood pressure (BP) patterns, assess blood pressure variability (BPV), and its possible determinants in children with essential hypertension. The study group included 132 children with essential hypertension without antihypertensive therapy. Anthropometric and laboratory parameters were evaluated, office and ambulatory BP were measured. BPV was defined as the standard deviation of BP for the day and nighttime periods. In addition to classical statistical analysis, an unsupervised machine learning approach using the expected maximization algorithm was implemented to find groups of patients with similar characteristics. No differences in BPV were observed between sexes; however, boys had higher levels of creatinine, serum glucose, and uric acid despite similar body mass index values. There was a significant correlation between the Z-score for body mass index and daytime systolic BPV ($r=0.19$, $p<0.05$). Nighttime BPV significantly correlated with total cholesterol and uric acid levels. Within the male population, two clusters were found. The subjects in Cluster 2 had higher daytime and nighttime systolic and diastolic BP values, total cholesterol, triglycerides, and nighttime systolic and diastolic BPV. Our results suggest that the clustering of metabolic factors influences BPV in untreated children with essential hypertension, which may be a sex-specific effect in males.

Key words: *Blood pressure variability; Hypertension; Ambulatory blood pressure monitoring*

Introduction

Hypertension (HTN) is a major health problem in both children and adults. The estimated prevalence among healthy children ranges between 1.6-3.5%.[1, 2] Blood pressure variability (BPV) is a complex physiological phenomenon that includes short- and long-term BP fluctuations, and new evidence indicates that it worsens the clinical outcome and exacerbates the progression of HTN. BPV correlates with the severity of cardiac, renal, and vascular damage; adverse cardiovascular outcomes, and mortality regardless of elevated mean BP.[3] Short-term BPV fluctuations are observed within a 24-hour period (minute-to-minute, hour-to-hour, and day-to-night changes) while long-term BPV fluctuations are observed over longer periods (weeks, months, etc.).

Determinants of HTN, such as sex, obesity, lifestyle, and genetic factors, are well known.[4,5] However, there is a lack of research regarding factors affecting

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BPV in the pediatric population. Most of the research includes observational studies in the last several years since the concept of BPV has gained interest both in adults and the pediatric population. The results of these studies indicate that adverse cardiovascular events, development and progression of cardiac, vascular, and renal damage depend not only on mean BP values but also on BPV, and some have suggested that it could be the target of antihypertensive therapy.[3,4] Several studies investigated the connection between humoral, neural, and environmental factors to BPV. The findings have indicated that these factors should be observed together because of their strong connection and mutual influence, and separating them is pointless in the clinical setting.[6,7] In the light of mentioned results, we tried to determine factors, among laboratory values, gender, anthropometric parameters, and ambulatory blood pressure monitoring (AMBP) values that influence BPV, observing them separately and in clusters created on common characteristics.

Understanding potential determinants of BPV in hypertensive children could help identify patients with increased cardiovascular risk in the early stage of the disease and help improve preventive and therapeutic strategies in clinical practice.

This study aimed to analyze BP patterns and assess BPV and its possible determinants in untreated children with essential HTN.

Table 1. General characteristics of the study population. Anthropometric measures and laboratory values.

	mean ± standard deviation
Birth weight (g)	3334.49 ± 674.76
Age (years)	14.98 ± 2.1
BMI (kg/m^2)	27.45 ± 5.26
BMI (percentile)	88.75 ± 17.15
BMI (Z-score)	1.73 ± 0.98
Total cholesterol (mmol/L)	4.37 ± 0.88
HDL cholesterol (mmol/L)	1.36 ± 0.33
LDL cholesterol (mmol/L)	2.58 ± 0.75
Triglycerides (mmol/L)	1.17 ± 0.59
Serum uric acid (μmol/L)	328.64 ± 69.85
Serum glucose (mmol/L)	4.92 ± 0.59
Serum creatinine (μmol/L)	76.65 ± 14.09

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein

Materials and methods

In this retrospective observational study, 132 children [84 (64%) males and 48 (36%) females] were referred to the Pediatric Nephrology Department from January 2006 to September 2016.

Anthropometric parameters, including birth weight, serum glucose level (sG), serum uric acid

Table 2. Descriptive results of the most relevant blood pressure measurements

Blood pressure (in mmHg)			
	mean ± SD		mean ± SD
office SBP	150.37 ± 13.07	SBPLd	54.83 ± 25.42
office DBP	91.06 ± 10.3	SBPLn	59.31 ± 26.51
24-h SBP	135.01 ± 8.55	DBPLd	29.92 ± 22.92
24-h DBP	75.11 ± 6.07	DBPLn	37.04 ± 26.72
Day SBP	137.62 ± 9.18	Pulse 24 h (1/min)	79.05 ± 9.42
Day DBP	77.41 ± 6.73	SBPV day	12.19 ± 2.75
Night SBP	123.92 ± 9.51	DBPV day	9.77 ± 2.35
Night DBP	65.94 ± 7.11	SBPV night	11.95 ± 4.25
Pulse pressure	59.66 ± 7.74	DBPV night	9.36 ± 3.29

SD = standard deviation; SBP = systolic blood pressure; DBP = diastolic blood pressure; SBPLd = systolic blood pressure load by day; DBPLd = diastolic blood pressure by day; SBPLn = systolic blood pressure load by night; DBPLn = diastolic blood pressure load by night; SBPV = systolic blood pressure variability; DBPV = diastolic blood pressure variability.

Table 3. Differences of the most relevant blood pressure measurements in men and women

	[Blood pressure values (in mmHg).]		
	Male	Female	p
	mean ± standard deviation		
Office SBP	150.35 ± 11.69	150.42 ± 15.33	0.976
Office DBP	91.19 ± 9.96	90.83 ± 10.98	0.849
24-h SBP	136.12 ± 8.74	133.06 ± 7.94	**0.048**
24-h DBP	74.29 ± 5.78	76.54 ± 6.34	**0.039**
SBP day	138.73 ± 9.24	135.69 ± 8.86	0.067
DBP day	76.36 ± 6.49	79.25 ± 6.82	**0.017**
SBP night	124.26 ± 10.09	123.31 ± 8.47	0.583
DBP night	64.9 ± 6.79	67.75 ± 7.38	**0.027**
Pulse pressure	61.49 ± 7.41	56.45 ± 7.3	**<0.001**
SBPLd	54.42 ± 24.61	55.55 ± 27.03	0.807
SBPLn	55.95 ± 27.69	65.13 ± 23.47	0.056
DBPLd	26.5 ± 20.67	35.92 ± 25.53	**0.023**
DBPLn	34.03 ± 26.44	42.24 ± 26.68	0.091
24-h pulse (1/min)	77.95 ± 10.26	80.98 ± 7.47	0.076
SBPV day	12.35 ± 2.75	11.91 ± 2.75	0.381
DBPV day	9.84 ± 2.61	9.63 ± 1.83	0.627
SBPV night	12.31 ± 4.28	11.32 ± 4.17	0.200
DBPV night	9.64 ± 3.37	8.89 ± 3.12	0.210

SBP = systolic blood pressure; DBP = diastolic blood pressure; SBPLd = systolic blood pressure load by day; DBPLd = diastolic blood pressure by day; SBPLn = systolic blood pressure load by night; DBPLn = diastolic blood pressure load by night; SBPV = systolic blood pressure variability; DBPV = diastolic blood pressure variability

(sUA), serum creatinine (sCr), total cholesterol (TCh), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides (TG) were measured in all participants. Office BP and ambulatory BP (AMBP) were measured according to recent European Society of Hypertension guidelines.[8] AMBP monitoring was performed using a Mobilgraf M01100120 (IEM GmbH, Germany) device. The proper cuff, according to arm length and width, was placed on the non-dominant arm, and both parents and children were educated about the device. BP was measured and recorded every 15 min during the day and every 30 min at night. AMBP provided data about average 24-hour systolic (24h SBP) and diastolic (24h DBP) values, average day and nighttime SBP and DBP, pulse pressure, average 24-hour heart rate, and

Table 4. Correlations between laboratory results and BPV.*

	SBPV day	DBPV day	SBPV night	DBPV night
Total cholesterol (mmol/L)	0.03	-0.02	**0.28**	0.17
HDL cholesterol (mmol/L)	-0.09	0.08	0.10	-0.02
LDL cholesterol (mmol/L)	-0.02	0.06	0.23	0.10
Triglycerides (mmol/L)	0.13	-0.15	0.17	0.19
Serum uric acid (μmol/L)	-0.11	**-0.34**	0.03	**0.26**
Serum glucose (mmol/L)	0.06	0.00	0.01	0.17
Serum creatinine (μmol/L)	-0.18	-0.01	-0.23	-0.07
Birth weight (g)	-0.12	- 0.09	- 0.03	- 0.03

*Pearson's correlation coefficient (statistically significant results are bolded); SBPV = systolic blood pressure variability; DBPV = diastolic blood pressure variability; HDL = high-density lipoprotein; LDL = low-density lipoprotein

SBP and DBP loads by day and night (SBPLd/DBPLd, SBPLn/DBPLn). BPV was defined as the standard deviation of systolic and diastolic BP for the day and nighttime periods (SBPV day and SBPV night; DBPV day and DBPV night, respectively).

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee. This is a retrospective observational study, so a confidentiality statement has been signed as a substitute for informed consent.

Statistical analysis

The data were analyzed using R (www.r-project.org) and Statistica software. Categorical variables are described as absolute and relative frequencies, and numerical variables, with arithmetic means and standard deviations. A Kolmogorov-Smirnov test was used to test the normality of the data. Differences between numeric variables were tested using a Student's t-test. Pearson's correlation test was used to assess the correlation between numerical variables. P-values <0.05

Table 5. Most significant differences between the observed clusters

[Blood pressure values (in mmHg)]			
	Cluster 1 mean ± standard deviation	Cluster 2 mean ± standard deviation	p
24-h SBP	142.42 ± 7.72	130.73 ± 5.62	**<0.001**
24-h DBP	78.93 ± 5.37	72.82 ± 5.24	**<0.001**
SBP day	145.44 ± 8.45	133.13 ± 6.18	**<0.001**
DBP day	81.91 ± 6.09	74.8 ± 5.68	**<0.001**
SBP night	130.78 ± 9.99	119.87 ± 6.52	**<0.001**
DBP night	70.33 ± 6.16	63.3 ± 6.26	**<0.001**
Pulse pressure	63 ± 8.87	57.77 ± 6.4	**<0.001**
SBPLd	76.25 ± 18.01	43.46 ± 21.46	**<0.001**
SBPLn	76.47 ± 21.3	50.18 ± 24.41	**<0.001**
DBPLd	45.08 ± 24.29	21.83 ± 17.75	**<0.001**
DBPLn	52.71 ± 25.09	28.56 ± 23.71	**<0.001**
Serum uric acid (µmol/L)	352.76 ± 60.55	314.49 ± 69.02	**0.002**
BMI Z-score	1.99 ± 0.83	1.59 ± 1.02	**0.027**

EM = expected maximization; SBP = systolic blood pressure; DBP = diastolic blood pressure; SBPLd = systolic blood pressure load by day; DBPLd = diastolic blood pressure by day; SBPLn = systolic blood pressure load by night; DBPLn = diastolic blood pressure load by night; BMI = body mass index

were considered statistically significant. Additionally, the expected maximization unsupervised machine learning algorithm with 10-fold cross-validation was applied to find clusters based on the most relevant BPV features.

Results

The general characteristics of our study group are presented in Table 1. The average age was 14.98 ± 2.1 years and mean body mass index value was 27.45 ± 5.26 kg/m^2 (percentiles = 88.75 ± 17.15; mean Z-score for BMI = 1.73 ± 0.98). Blood pressure values are presented in Table 2. The average systolic and diastolic office and AMBP daytime BP were 150.37 ± 13.07 mmHg and 91.06 ± 10.3 mmHg and 137.62 ± 9.18 mmHg and 77.41 ± 6.73 mmHg, respectively. Sex-specific office BP, AMBP, and BPV values are shown in Table 3.

Table 6. Clustering of the male population.

[Blood pressure values (in mmHg)]			
	Cluster 1	Cluster 2	p
24-h SBP	132.17 ± 7.37	141.53 ± 6.84	**<0.001**
24-h DBP	72.94 ± 5.72	77.16 ± 5.34	**0.026**
SBP day	133.83 ± 7.74	144.53 ± 7.75	**<0.001**
DBP day	74 ± 6.51	79.58 ± 6.13	**0.011**
SBP night	121.22 ± 8.68	130.63 ± 9.44	**0.003**
DBP night	62.94 ± 7.08	68.89 ± 4.76	**0.004**
SBPLd	46.27 ± 22.43	70.3 ± 25.74	**0.004**
SBPLn	51.42 ± 26.43	73.06 ± 24.81	**0.014**
Total cholesterol (mmol/L)	3.9 ± 0.73	4.95 ± 1.1	**0.002**
Triglycerides (mmol/L)	1.09 ± 0.34	1.63 ± 0.99	**0.036**
Serum creatinine (µmol/L)	90.67 ± 14.25	79.94 ± 12.15	**0.018**
SBPV night	10.52 ± 3.85	15.01 ± 3.71	**<0.001**
DBPV night	7.95 ± 2.57	12.06 ± 3.3	**<0.001**

SBP = systolic blood pressure; DBP = diastolic blood pressure; SBPLd = systolic blood pressure load by day; SBPLn = systolic blood pressure load by night; SBPV = systolic blood pressure variability; DBPV = diastolic blood pressure variability

Comparing sex-specific BP parameters, male children had higher daytime and nighttime SBP, although the difference was not statistically significant (p = 0.067 and p = 0.583). However, females had significantly higher daytime and nighttime DBP values (p = 0.017 and p = 0.027, respectively). Both the average 24h SBP and pulse pressure were higher in males (p = 0.048 and p = <0.001, respectively), while the average 24h DBP and daytime DBP load were higher in females (p = 0.039 and p = 0.023, respectively). No differences were observed in BPV between sexes. For laboratory results, sCR [81.3 ± 13.87 µmol/L, 68.6 ± 10.46 µmol/L, p<0.001], sG [5 ± 0.66 mmol/L, 4.78± 0.42 mmo/L, p = 0.046], and sUA [343.69 ± 69.04 µmol/L, 302.29 ± 63.77 µmol/L, p=0.001] were significantly higher in males, despite similar BMI [27.18 ± 5.27 kg/m^2 (males) vs 27.94 ± 5.27 kg/m^2 (females), p = 0.427].

The correlations between the laboratory parameters and BPV are shown in Table 4. A statistically significant positive correlation was found between the Z-

Table 7. Clustering of the female population.

[Blood pressure values (in mmHg)]			
	Cluster 1	Cluster 2	p
24-h SBP	136.5 ± 8.62	130.467 ± 5.34	**0.031**
SBP day	140.07 ± 10.02	132.07 ± 5.89	**0.013**
SBPLd	67.21 ± 25.63	40.14 ± 23	**0.006**
DBPLd	49.11 ± 29.25	24.85 ± 17.17	**0.011**
DBPLn	52.42 ± 30.38	31.83 ± 22.56	**0.047**
Serum uric acid (μmol/L)	316.79 ± 53.19	277.87 ± 39.62	**0.033**

SBP = systolic blood pressure; SBPLd = systolic blood pressure load by day; DBPLd = diastolic blood pressure by day; DBPLn = diastolic blood pressure load by night.

Abbreviations: BP, blood pressure; BPV, blood pressure variability; AMBP, Ambulatory blood pressure monitoring; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; HTN, hypertension; LDL, low-density lipoprotein cholesterol; sCr, serum creatinine; sG, serum glucose; sUA, serum uric acid; TCh, total cholesterol; TG, triglycerides

score and daytime systolic BPV ($r = 0.19$, $p < 0.05$). Analyzing the possible correlation between laboratory tests and BPV, we found a significant correlation between nighttime systolic BPV and total cholesterol ($r = 0.28$) and between daytime and nighttime diastolic BPV sUA ($r = -0.34$ and $r = 0.26$, respectively).

Using the expected maximum analysis of the entire patient group, two different clusters were observed. Patients in Cluster 1 had higher AMBP, pulse pressure, and higher Z-scores of BMI and sUA (Table 5). Stratified by sex, two clusters were found within the male patients. Patients in Cluster 2 had significantly higher daytime and nighttime systolic and diastolic BP values, TCh, TG, and nighttime systolic and diastolic BPV (Table 6). Within the female patients, two clusters were found. Patients in Cluster 1 had higher SBP values (day SBP, 24h SBP, SBPLd), daytime and nighttime DPBL, and sUA (Table 7).

Discussion

Current knowledge on possible determinants of BPV within a 24-hour period is limited, particularly in pediatrics. However, accumulating evidence indicates that BPV is associated with adverse cardiovascular outcomes and increased risk of vascular and renal damage and mortality, regardless of elevated average BP values.[9-11] Our results showed that daytime systolic BPV correlated positively with BMI Z-scores, suggesting that overweight and obese children have higher BPV. Obesity is a predisposing factor for HTN both in children and adults, and increased BPV may add to the risk of adverse outcomes in this group of patients.[12,13] A similar correlation between systolic BPV and BMI Z-score was found in a study by Leisman et al. investigating BPV in children with primary versus secondary HTN.[14]

On the other hand, birth weight showed an inverse relationship. Several studies on BPV in adults and children showed that a lower birth weight correlated with an increased BPV from childhood to adulthood and elevated BP in adulthood.[15,16] The authors hypothesized a possible relationship between increased *in utero* sympathetic nervous system activity, birth weight, BP, and BPV.[15,17] In our study, although we did not find a statistically significant correlation, the results suggest a negative correlation between BPV and birth weight; however, larger sample size is necessary to confirm this relationship. Our results suggest that there are no sex-specific differences in BPV, but there are some sex-specific differences in 24-h BP patterns. Compared to girls, boys had higher 24h SBP and pulse pressure, whereas girls had higher 24h DBP, day and nighttime DBP, and daytime DBP load. Using a different approach, other researchers found similar sex-specific differences in BP patterns, suggesting that BPV positively correlates more with SBP than DBP.[2] This direct relationship between BPV and mean BP may suggest a promising target for antihypertensive therapy by stabilizing BPV.[3]

The results of our laboratory analysis showed that boys had higher sCr, sG, and sUA levels despite similar BMI. There was also a positive correlation between nighttime systolic and diastolic BPV and sCr and sUA values. Several observational studies indicate that higher levels of sUA are related to the risk of cardiovascular disease.[18] The association between sUA level and cardiovascular risk in children is less known. A study investigating cardiometabolic risk factors in overweight and obese youths revealed that sUA levels were higher in boys, and a significant association was found between sUA and office BP and day and nighttime SBP.[19] In our study, we found two different patterns. Patients in the first cluster had significantly higher SBP values, BMI Z-score, and sUA. Comparing this with previous statements about the impact of sUA levels and SBP values on cardiovascular risk, and BMI Z-score on BPV, it is hypothesized that patients in Cluster 1 may have multiple risk factors for adverse cardiovascular outcomes.

The results of our study showed the complexity of BPV in children. However, there are several limitations, such as a relatively small sample size, single time point estimate, and the lack of a follow-up. Furthermore, when using noninvasive ambulatory BP monitoring, it is hard to precisely quantify the magnitude of the BPV, especially in children, due to poor compliance and a low attention span. We pointed out several factors that could influence BPV separately, such as SBP, sUA, Z-score for BMI, and male sex, while observing these factors in clusters may show a broader underlying picture. Recognizing the clustering of metabolic factors influencing BPV in untreated children with essential HTN will help identify patients with a higher risk of adverse cardiovascular outcomes, especially among the male population. Current knowledge about BPV in children has certain limitations, but it is important to pay attention to BPV values when assessing AMBP and its influence on mean BP values. Additional prospective outcome studies are needed to better understand the underlying mechanisms and factors influencing BPV, which will help improve current therapeutic strategies. Further research is needed to investigate whether BPV can serve as a rational target for antihypertensive therapy to prevent or postpone adverse cardiovascular outcomes.

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Sažetak

ČIMBENICI KOJI UTJEČU NA VARIJABILNOST KRVNOG TLAKA U DJECE S ESENCIJALNOM HIPERTENZIJOM

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Cilj studije je analizirati vrijednosti krvnog tlaka i varijabilnost krvnog tlaka (BPV), te čimbenike koji bi mogli utjecati na BVP u djece s esencijalnom hipertenzijom. Istraživanje uključuje 132 djece s prethodno neliječenom esencijalnom hipertenzijom. Promatrani su antropometrijski i laboratorijski parametri, ambulantne vrijednosti krvnog tlaka (BP) i 24-satno kontinuirano mjerenje arterijskog tlaka. Varijabilnost krvnog tlaka definirana je kao vrijednost standardne devijacije noćnih i dnevnih vrijednosti BP. Uz klasičnu statističku analizu, u svrhu pronalaženja skupina pacijenata sa zajedničkim karakteristikama korištena je tehnika maksimizacije očekivanja. Nije nađena razlika u BPV ovisno o spolu, dok su dječaci su imali viši serumski kreatinin, urate i šećer u krvi, unatoč sličnom indeksu tjelesne mase. Postoji statistički značajna povezanost Z-score ITM-a i dnevne sistoličke BPV ($r=0.19$, $p<0.05$). Noćne vrijednosti BVP-a su u značajnoj korelaciji s vrijednostima ukupnog kolesterola i urata. Među dječacima definirane su dvije skupine prema zajedničkim karakteristikama. Ispitanici u drugoj skupini imali su značajno više dnevne i noćne sistoličke i dijastoličke vrijednosti BP-a, kolesterol i trigliceride te noćni sistolički i dijastolički BPV. Rezultati pokazuju utjecaj pojedinih čimbenika na BPV. Grupiranje metaboličkih čimbenika u skupine daje bolji uvid u njihov utjecaj na BPV, osobito u populaciji dječaka.

Ključne riječi: *Varijabilnost krvnog tlaka, Hipertenzija, Kontinuirano mjerenje arterijskog tlaka*