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Blood Pressure Variability in Children With Primary vs Secondary Hypertension

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Increased blood pressure variability (BPV) is correlated with adverse cardiovascular (CV) events in adults. However, there has been limited research on its effect in the pediatric population. Additionally, BPV differences between primary and secondary hypertension (HTN) are not known. Children with primary and secondary HTN underwent 24-hour ambulatory blood pressure monitoring and echocardiography studies. BPV measures of standard deviation (SD), average real variability (ARV), and range were calculated for the 24-hour, daytime, and nighttime periods. Seventy-four patients (median age, 13.5 years; 74% boys) were examined, 40 of whom had primary HTN. Body mass index z score and age were independent predictors of systolic ARV ($R^2=0.14$) and SD ($R^2=0.39$). There were no statistically significant differences in overall or wake period BPV measures between secondary or primary HTN groups, but sleep period diastolic

SD was significantly greater in the secondary HTN group (9.26 ± 3.8 vs 7.1 ± 2.8 , $P=.039$). On multiple regression analysis, secondary HTN was associated with increased sleep period diastolic SD ($P=.025$). No metrics of BPV in the overall, wake, and sleep periods were found to be significantly associated with left ventricular hypertrophy (LVH). The results of this study do not show a strong relationship between overall or wake BPV with primary vs secondary HTN, but the association of secondary HTN with sleep period diastolic BPV deserves further exploration. Contrary to expectation, the findings of this study failed to indicate a relationship between BPV and LVH for all patients as well for primary hypertensive and secondary hypertensive patients. *J Clin Hypertens (Greenwich)*. 2014;16:437-441. ©2014 Wiley Periodicals, Inc.

Hypertension (HTN) has long been considered a precursor to cardiovascular (CV) morbidity and mortality. HTN can be described as either primary or secondary to another cause or condition; the latter having greater association with elevated nocturnal blood pressure (BP), reduced nocturnal dip, and other risk factors for adverse events.^{1,2} Independent of elevated BP readings, however, BP variability (BPV)—the degree of variation between discrete BP readings—has recently been shown to be associated with a myriad of unfavorable outcomes including adverse CV events, progression of renal disease, impaired endothelial function, and all-cause morbidity and mortality.²⁻¹² Specifically, a greater degree of BPV, measured from systolic values in particular, has been found to be predictive of these events, independent of hypertensive status.^{4,7-9} The relationship between BPV and primary vs secondary HTN is unknown.

While BPV has been the subject of investigation in adults, there has been quite limited research into its effect in the pediatric population. HTN in children and adolescents has been well correlated with surrogate outcomes of higher body mass index (BMI), left ventricular hypertrophy (LVH), and early coronary artery disease.¹³ However, given that most severe

adverse CV events are generally the product of many years of strain to the vascular system, these outcomes are seen rarely in children. Nevertheless, the consequences of years of childhood HTN are thought to continue into adulthood, placing these patients at substantial risk for serious CV disease. Early indicators of impaired CV health, such as increased BPV, may prove to be important risk factors for CV disease in the pediatric population. The purpose of this study was to examine potential differences in 24-hour BPV between pediatric patients with primary vs secondary HTN. In addition, we sought to determine the relationship between BPV with left ventricular mass index (LVMI) and LVH in these two groups.

MATERIALS AND METHODS

Patients

Children diagnosed with HTN, aged 5 to 21 years, followed by the nephrology division at a single tertiary care medical center were examined in this retrospective chart analysis (2010–2013). All patients completed 24-hour ambulatory BP monitoring (ABPM) and echocardiography. Primary HTN was defined as ambulatory BP $>95\%$ for height and sex not attributable to another cause.¹⁴ Secondary HTN was defined as elevated BP attributed to another cause, which included nephrotic syndrome, end-stage renal disease, transplantation, systemic lupus erythematosus, diabetes mellitus, polycystic kidney disease, obstructive uropathy, renal artery stenosis, apparent mineralocorticoid excess, and

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steroids. Children were diagnosed with secondary HTN based on radiologic studies, histopathology, genetic testing, or history of kidney transplant. The study protocol was approved by the institutional review board of the North Shore Long Island Jewish Health System. Informed consent was not obtained because of the retrospective nature of the study.

BP Variability

Study patients completed 24-hour ABPM using Space-lab 90217 monitors (Spacelabs Medical, Redmond, WA). Patients taking antihypertensive medications were kept on their medications during the testing. BP recordings were programmed to occur every 20 minutes during the day and every 60 minutes while sleeping. Sleep and wake times were recorded and adjusted for each patient to define the nighttime period. The ABPM study was considered satisfactory for analysis if >75% of readings were valid during the 24 hours, consistent with American Heart Association recommendations for standard ambulatory assessment.¹⁵ Measured variables included systolic and diastolic standard deviation (SD), average real variability (ARV), and range for the 24-hour, daytime, and nighttime periods. Systolic and diastolic SDs were calculated from the systolic and diastolic values, respectively, for each reading. ARV was defined as the mean absolute difference between discrete measurements and was calculated as outlined in Levitan and colleagues.¹⁶ The ranges were computed from the maximum and minimums of the readings.

Echocardiography

All patients underwent standard 2-dimensional and M-mode echocardiography following the American Society of Echocardiography pediatric guidelines by an experienced cardiac ultrasound technician.¹⁷ Echocardiograms performed outside of the institution were excluded. LVMI was calculated from each echocardiogram using measurements of the interventricular septum (IVS), left ventricular end-diastolic dimension (LVID), and left ventricular posterior wall (LVPW). The Devereux formula for LV mass was used ($LV\ mass = 0.8 (1.04 [(IVS + LVID + LVPW)^3 - LVID^3] + 0.6)$)¹⁸ and indexed to $height(m)^{2.7}$. LVH was defined as LVMI \geq 95th percentile for age- and sex-specific reference criteria.¹⁹

Statistical Analysis

Descriptive analyses included means, medians, SDs, and ranges of continuous variables and distributions of categorical variables. Demographic and clinical variables, systolic and diastolic BPV ARV, SD, and range for the total monitoring period, wake periods, and sleep periods were compared between groups (primary vs secondary HTN) using independent samples *t* test, Mann-Whitney, or chi-square analysis. The correlation between these variables was determined using Pearson or Spearman correlation coefficients. Anthropometric and clinical variables with $P < .15$ on univariate analysis were tested in stepwise multiple linear regression models

to assess potential predictors of BPV variables. A group variable (primary vs secondary) was then entered into the model to determine the association with BPV. Multiple linear regression models adjusted for age, BMI *z* score, and antihypertensive medications (factors cited in previous literature) were used to examine the association between BPV and LVMI. BPV variables as predictors of LVH were tested using logistic regression models adjusted for age, BMI *z* score, and antihypertensive medications. Models were tested with groups combined and then separate for primary and secondary HTN groups.

While this study involves multiple outcomes, these outcomes (eg, ARV, SD, and range) are highly correlated and a Bonferroni correction is unduly conservative.²⁰ As such, we set the overall level of significance at .05, using 2-tailed tests of hypotheses, and examined the results for consistency across related outcomes. Statistical analyses were performed using SPSS 18.0 (SPSS Inc, Chicago, IL) statistical package.

RESULTS

The 74 children included 55 boys (74%) and 19 girls (26%) with a median age of 13.5 years (interquartile range: 11–16 years). Thirty-four (46%) children had secondary HTN. The proportion of children with primary HTN was 54%. Demographic and BPV data are summarized in the Table. Children with secondary HTN were taking more antihypertensive medications ($P < .001$) and were shorter ($P = .02$) than patients in the primary HTN group. In the entire group, overall systolic ARV ranged from 5.0 mm Hg to 17.9 mm Hg (mean 8.7 ± 1.9 mm Hg). Overall systolic SD ranged from 4.1 mm Hg to 13.7 mm Hg (mean 7.4 ± 2.0 mm Hg).

Predictors of BPV

Examining the group as a whole, BMI *z* score and weight were significantly correlated with measures of ARV and SD. The strongest relationship was found between BMI *z* score and overall diastolic ARV ($r = 0.48$; $P < .001$). Similar relationships were found between BMI *z* score and systolic and diastolic ARV and SD in the overall and wake periods, but not during the sleep period ($r = 0.23$ – 0.48 , all $P < .05$), suggesting that patients with higher BMI values experienced greater BP variability. Comparable results were found for weight during the overall, wake, and sleep periods ($r = 0.24$ – 0.4 , all $P < .05$). Age was found to be significantly correlated with sleep period systolic ARV ($r = 0.29$, $P = .017$), SD ($r = 0.34$, $P = .005$), and range ($r = 0.34$, $P = .004$). Use of antihypertensive medications was not associated with any BPV measures. In a multivariate regression model ($R^2 = 0.14$), BMI *z* score ($\beta = 0.55$; 95% confidence interval [CI], 0.10–0.99; $P = .02$) and age ($\beta = 0.16$; 95% CI, 0.02–0.3; $P = .02$) were found to be independent predictors of overall systolic ARV. BMI *z* score ($\beta = 0.52$; 95% CI, 0.12–0.92; $P = .01$) and age ($\beta = 0.15$; 95% CI, 0.02–0.27; $P = .025$) were also independent predictors of overall systolic SD ($R^2 = 0.39$).

TABLE. Demographic and Blood Pressure Variability Data

Demographic Data	Overall	Primary HTN	Secondary HTN	P Value
No. (%)	74	40 (54)	34 (46)	
Age, y	13.3±3.8	13.6±3.6	12.9±4.0	.46
Men, No. (%)	55 (74)	32 (80)	23 (68)	.15
Height, cm	159.3±19.9	164.1±17.6	153.1±21.1	.02
Weight, kg	65.2±28.9	70.7±29.5	58.8±27.2	.08
BMI z score	1.1±1.2	1.2±1.2	1.0±1.3	.58
LVMI, g/m ^{2.7}	36.7±9.1	35.4±10.0	38.2±7.9	.20
LVH, No. (%)	23 (31)	11 (28)	12 (35)	.41
Antihypertensive medications, No. (%)	16 (22)	2 (5)	14 (41)	<.001
Overall systolic, mm Hg				
ARV	8.7±1.9	8.9±1.7	8.4±2.2	.19
SD	7.4±2.0	7.7±2.2	7.0±1.9	.22
Range	46.2±14.9	49.9±13.0	44.6±12.3	.43
Overall diastolic, mm Hg				
ARV	9.1±2.4	9.4±2.5	8.8±2.2	.29
SD	7.8±2.0	8.0±2.2	7.4±1.8	.17
Range	47.7±14.8	49.7±16.4	45.2±12.4	.2
Wake period systolic, mm Hg				
ARV	8.6±2.2	8.9±2.0	8.3±2.3	.29
SD	7.5±2.7	7.5±2.3	7.5±3	.9
Range	41.9±14.4	43.5±16	40.0±12.0	.31
Wake period diastolic, mm Hg				
ARV	9.2±2.7	9.7±3.1	8.7±2.0	.15
SD	7.8±2.1	8.1±2.3	7.4±1.7	.19
Range	44.2±14.9	46.2±17.2	41.6±11.0	.19
Sleep period systolic, mm Hg				
ARV	9.5±3.9	10.3±4.3	8.4±3.1	.04
SD	7.0±3.2	7.5±3.7	6.5±2.4	.21
Range	31.1±13.9	31.5±14.1	30.5±13.8	.77
Sleep period diastolic, mm Hg				
ARV	9.2±3.7	9.0±3.5	9.5±3.9	.64
SD	7.1±3.0	6.8±2.7	7.4±3.3	.39
Range	32.1±17.7	29.2±14.0	35.9±21.1	.12

Abbreviations: ARV, average real variability; BMI, body mass index; HTN, hypertension; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; SD, standard deviation. Bold values indicate significance.

BPV in Primary vs Secondary HTN

The sleep period systolic ARV was significantly higher in the primary HTN group than in the secondary HTN group (10.3±4.3 vs 8.4±3.1, $P=.04$), but when children taking antihypertensive medications were excluded, sleep period diastolic SD was significantly higher in the secondary HTN group than in the primary HTN group (9.26±3.8 vs 7.1±2.8, $P=.039$). There were no other statistically significant differences in BPV measures between the secondary and primary HTN groups (Table). In multiple regression analysis, secondary HTN was associated with increased sleep period diastolic SD ($\beta=-2.1$; 95% CI -3.8 to -0.27 ; $P=.025$) after adjustment for age, BMI z score, and antihypertensive

medications. There were no other significant associations of BPV measures with either primary or secondary HTN.

Left Ventricular Hypertrophy

Among the 74 children, we also examined the relationship between LVMI and BPV using multiple linear regression analysis. Systolic ARV adjusted for age, BMI z score, and antihypertensive medications did not predict LVMI ($\beta=-0.22$; 95% CI, -1.5 to 1.1 ; $P=.75$). No other metrics of BPV in the overall, wake, and sleep periods were found to be significantly associated with LVMI. However, when examining the primary HTN group alone, an increase in wake period systolic SD was found to be significantly associated with increased LVMI after adjustment for confounders ($\beta=1.7$; 95% CI, $0.133-3.2$; $P=.034$). In addition, increased wake period diastolic ARV ($\beta=1.3$; 95% CI, $0.075-2.6$; $P=.039$) was significantly associated with increased LVMI. No associations were found for the secondary HTN group alone.

In multiple logistic regression, measures of BPV were evaluated as independent predictors of LVH status. Among the whole group, overall systolic ARV did not prove to be a significant predictor of LVH (OR, 0.97; CI, $0.74-1.2$; $P<.83$). This was the case for overall systolic SD and range as well as the corresponding wake period values for all 3 BPV metrics. Furthermore, these metrics were unable to predict LVH status even when examining both the primary hypertensive group as well as the secondary hypertensive group exclusively.

DISCUSSION

To our knowledge, the effect of primary vs secondary hypertensive status on BPV and subsequent outcome has not previously been described in adults or children. We felt this to be an important avenue to explore, particularly for this population, because of the character of both forms of HTN in children in adolescents. Specifically, secondary HTN tends to be more closely associated with unfavorable risk factors (eg, higher systolic BP, decreased nocturnal dip, nocturnal HTN), but primary HTN is more associated with increased BMI in children.^{1,2,21-32} This study sought to determine differences in 24-hour BPV between pediatric patients with primary vs secondary HTN as well as to examine the relationship of BPV with LVMI and LVH in these two groups. We hypothesized that BPV would be different between the groups and could potentially become a variable to aid in the diagnosis and management of primary vs secondary HTN.

Overall, our results did not demonstrate robust differences in 24-hour BPV between pediatric patients with primary vs secondary HTN with the exception of the association of secondary HTN with sleep period diastolic BPV. The findings of this study also failed to indicate a relationship between BPV and LVH in any group, suggesting that BPV is not a good predictor of heart target organ damage in children and adolescents.

However, greater wake period systolic BPV was found to be associated with increased LVMI in primary hypertensive children alone. Last, we found that BPV has a positive correlation with BMI, a well-established risk factor for all-cause morbidity and mortality, and CV problems in particular in adulthood.^{31–34} Interestingly, the degree of overall ARV and SD showed a positive correlation with age, suggesting that older hypertensive patients experienced greater BPV.

While BPV has been well described in the adult literature, the significance of BPV in children and adolescents is not well defined. Twenty-four-hour BPV has been tied to CV risk, renal disease progression, and impaired endothelial and smooth muscle function in adults.^{3,7} Additionally, these studies have found BPV to be a substantial risk factor for these outcomes independent of HTN.^{4,8,9} The literature has generally suggested that the systolic component of BPV exhibits more of an interaction with determinants of CV health than does its diastolic counterpart.³⁵ Interestingly, though, we found that increased diastolic BPV during the nighttime was found to be significant in patients with secondary hypertension. Children with secondary HTN have been shown to be prone to both diastolic HTN and nocturnal HTN.^{1,2,26–30} Therefore, our findings that children with secondary HTN experienced greater sleep period diastolic BPV than those with primary HTN warrant further attention.

In adults, greater 24-hour BPV has been associated with left ventricular systolic dysfunction in newly diagnosed hypertensive patients.¹¹ While most research has suggested that BPV has prognostic value for many stages of CV disease, it is worth noting that a recent Russian study in adults found that 24-hour BPV did not independently predict LVH.³⁶ Also in agreement with our findings, a recent pediatric study found only a weak association between 24-hour BPV and LVMI, and found no relationship between 24-hour BPV and LVH in children evaluated for hypertension.³⁷ Another pediatric study examined the relationship of 24-hour BPV and LVH in pediatric patients with HTN.³⁸ Investigators determined that daytime systolic SD had significant associations with LVMI after adjustment for age, sex, and BMI z score. However, the study examined only a single measure of variability, SD, as opposed to our study, which included a more direct measure of discrete variability, namely ARV. Furthermore, this study examined only primary hypertensive patients, and excluded individuals who experienced secondary HTN.

STUDY LIMITATIONS

The limitations of this study include sample size and the inability to look at long-term BPV data in these patients because of the retrospective nature of the study. While it would have been ideal to be able to examine both long- and short-term BPV, we feel important information can be garnered solely from the 24-hour BPV, as the latter has been shown to be independent of visit-to-visit BPV and independently predictive of adverse outcomes in

adults. The most significant limitation is the reliance on LVH as a surrogate outcome measure because of the nature of CV disease in children and adolescents.

CONCLUSIONS

Our findings suggest that there is no relationship between BPV and LVH in children, which contrasts with the substantial volume of literature linking BPV with CV health in adults. Thus, BPV may not hold the same clinical relevance in pediatric patients. Admittedly, some of the issue may lie in the reliance on surrogate markers of CV disease in this population. This possibility could stem from the nature of CV illness in children, specifically their shorter exposure to adverse vascular strain. It is also possible that variability increases with age and increased BMI as suggested by our study, perhaps implying that BPV is also a phenomenon symptomatic of prolonged CV strain. Additionally, while we conclude that there is no difference in overall and wake period BPV for patients with primary vs secondary HTN, we feel the increased sleep period diastolic BPV in the secondary group deserves further investigation. Future studies should seek to confirm these results in a larger population. Additionally, longitudinal study may be warranted to determine whether higher BPV in children exhibits interaction on outcome in adulthood, despite a possible benign nature in children and adolescents.

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