ORIGINALNI RAD – ORIGINAL ARTICLE

Blood pressure variability and left ventricular mass index ion children with true ambulatory hypertension
Varijabilnost krvnog pritiska i indeks leve komore kod dece sa pravom ambulantnom hipertenzijom

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Summary This study sought to evaluate the relationship between blood pressure variability and left ventricular mass index (LVMI) in children with true ambulatory hypertension. We conducted a cross-sectional survey among 115 children who were consecutively referred for evaluation of hypertension to our University Children's Hospital. The calculated blood pressure variability (BPV) measures were 24-h average real variability (ARV) and 24-hour weighted SD (wSD). LVMI was estimated by M-mode echocardiography using Devereux's formula and indexed for height.
A total of 35 children had true ambulatory hypertension. We found no correlation between 24-hour ARV and wSD with LVMI. On the other hand, partial correlation analysis revealed statistically significant and inverse correlation between 24-hour ARV and LVMI, controlling for body mass index (r = -0,516; P = 0.002).
Contrary to previous studies, our results indicate inverse association of LVMI and BPV as expressed by ARV in a population of true hypertensive children.

Key words: blood pressure, hypertension, variability,children

Sažetak Ovom studijom se nastojalo da se proceni odnos između varijabilnosti krvnog pritiska i indeksa mase leve komore (LVMI) kod dece sa pravom ambulantnom hipertenzijom. Uradili smo studiju preseka kod 115 dece koja su bila upućena na Univerzitetsku dečiju klinuku za procenu hipertenzije. Varijabilnost krvnog pritiska (BPV) vrednosti su izračunate uz pomoć 24 časovne prosečne realne varijabilnosti (ARV) i 24 časovnog ponderisanog proseka srednjih vrednosti (wSD). LVMI je procenjena uz pomoć M-mod ehokardiografije upotrebom Devereux formule i indeksom visine. Ukupno 35 dece je imalo pravu ambulatornu hipertenziju. Nismo našli korelaciju između 24 časovne ARV i wSD sa LVMI. Sa druge strane, parcijalna korelacijona analiza pokazuje statističku signifikantnu i obrnutu korelaciju između 24 časovne ARV i LVMI, kontrolom indeksa telesne mase
(r = -0,516; P = 0.002). Za razliku od ranijih studija, naši rezultati pokazuju obrnutu povezanost LVMI i BPV, koja je iskazana preko ARV u populaciji dece sa pravom arterijskom hipertenzijom.
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Ključne reči: krvni pritisak, hipertenzija, varijabilnost, deca

Introduction

At this moment there is a lack of reliable data available about the impact of blood pressure variability (BPV) on target organ changes in hypertensive children(1). Nevertheless, increased left ventricular mass (LVM) or left ventricular hypertrophy (LVH) has been commonly interpreted as an early and easily detectable sign of structural organ changes in hypertensive children with or without altered BPV(2). Of note, a few human and animal studies have demonstrated that LVH is associated with increased blood pressure variability even in the absence of hypertension(3–10).

We sought to explore the relationship between two commonly used blood pressure variability measures, average real variability (ARV) as well as weighted blood pressure standard deviation (wBPSD) and left ventricular mass index (LVMI) to identify the group of hypertensive children at risk of left ventricular hypertrophy.

Methods

General design

A cross-sectional survey among 115 children who were consecutively referred for suspected hypertension to our University Children's Hospital from January 2011 to December 2013 was conducted.

All children underwent 24 h ABP measurement and standard echocardiogarphic examination within 3 weeks of the initial examination and the study was approved by the local Ethic Committee No 01-9002-6.

According to the American Heart Association scheme for ABP staging, only children with ambulatory and severe ambulatory hypertension were considered true hypertensives; children with white coat hypertension, masked hypertension, and ambulatory prehypertension were considered normotensive. Children with elevated SBP load but normal average 24-hour SBP and office BP that is either normal (<90th percentile) or hypertensive (≥95th percentile) were also considered normotensive.

Ambulatory blood pressure measurement

ABP recording was performed according to the most recent criteria (American Heart Association Scientific Statement), starting between 8 and 9 AM, using a SCANLIGHT measurement device (SCANLIGHT III I.E.M GmbH, Germany)(11).

Before ABP recording we performed three readings by one of two study coordinators on the same arm with a mercury sphygmomanometer using the recorder's SCANLIGHT blood pressure cuff. A mean difference in SBP greater than 5 mmHg was considered technically unacceptable.

Ambulatory BP readings were obtained at 15-minute intervals from 8 AM to midnight, and at 30-minute intervals from midnight to 8 AM and all children were advised to avoid sport and continue their usual activities including school.

From each ABP recording, we calculated the average 24-hour ambulatory SBP (24-h aSBP) and 24-h SBP load (percentage of readings greater than the 95th percentile during a 24-h recording),

The data published by Soergel at al. were used as the reference values for ABPM results(12).

If the first 24 h ABP recording was not successful due to insufficient number of readings, the second one was performed within the next two weeks. We accepted only recordings of good technical quality (at least 70 % valid readings).

Blood pressure variability

The following BPV parameters were evaluated for the entire 24-hour period: average real variability (ARV) as well as 24-hour weighted blood pressure standard deviation (wBPSD).

ARV was calculated from these readings by specifically designed software in Microsoft Office Excel 2003 statistical software, based on the previously reported formula (13).

$$ARV = 1/N\text{-}1 \sum_{K=1}^{N-1} \left| BP_{k+1} - BP_k \right|$$

where N is the number of valid BP measurements and K is the order of measurements from each subject monitoring.
wBPSD was defined as the mean of day and night SD values, corrected for the number of hours included in each of these sub periods according to the formula. wSD = (daytime SD x 14) + nigh-time SD x 6)/20.

Left ventricular mass index

LVM was estimated by M-mode echocardiography using Devereux's formula and indexed for height$^{2.7}$(LVMI)(14). All echocardiographic measurements were performed in triplicate by the same cardiologist (BB) who was unaware of the subject's BP. Average LVMI values were used in the analyzes.

Covariates

Additional clinical evaluation comprised of medical history, physical examination (including office BP measurement using a mercury sphygmomanometer), and body mass index (BMI) calculation according to the formula BMI = (weight in kg)/(height in m)^2.

Based on the BMI percentile, the children were classified as <95th percentile (non-obese) or ≥95th percentile (obese) for the same age and sex according to the 2000 Centers for Disease Control and Prevention growth charts for the United States(15).

Statistical analysis

Descriptive data are presented as mean values ± standard deviation. Pearson's correlation coefficients were used to analyze the correlation between examined BPV measures and LVMI. We also performed partial correlation analyzes to evaluate the relative importance of age, sex, and BMI, respectively, in determining relationship between BPV measures and LVMI. A P value less than 0.05 was considered statistically significant. All statistical analyzes were performed using SPSS version 20 (SPSS, Chicago, IL, USA).

Results

Characteristics

The study finally included 35 children with true ambulatory hypertension, mean age (14.2 ± 2.6 years), age range 8-18 years, of which 30 (83,3 %) were boys. Among them 27 (77,1 %) had severe ambulatory hypertension and 8 (22,9 %) had ambulatory hypertension. With regard to BMI, 19 (14,3 %) were non-obese, BMI < 95th percentile and 16 (85,7 %) were obese, BMI> 95th percentile. There was statistically significant differences between non-obese and obese children in terms of 24-h AVR (7,3 ± 1,7 vs 12,4 ±

3,9; p=0,28), wBPSD (8,3 ± 2,4 vs 14,2 ± 3; p <0,0001) and average 24 h SBP (124,3 ± 6,1 vs 133,3 ± 6,5; p=0,021). On the other hand there was no statistically significant difference between obese and non-obese in terms of LVMI (43,7 ± 6,7 vs 47,79 ± 7,8; p>0,05)

Correlations

Examining the correlation between BPV measures and LVMI in the group of true hypertensive children, none of BPV measures correlated significantly with LVMI.

On the other hand, 24-h ARV (r = 0,615 p < 0,0001), 24-h wBPSD (r = 0,514 p = 0,006) as well as LVMI (r = 0,445 p = 0,007) significantly correlated with BMI. (Table 1)

Table 1. Linear correlations among BPV measures with LVMI and BMI in true hypertensive children (N=35)

	LVMI	BMI
24-h ARV	-0,47*	0,61‡
24-h wBPSD	0,054*	0,51†

Statistical significance *p>0,05; †p<0,05 ; ‡ p<0,001

After partial correlation analysis between both BPV measures and LVMI controlling for BMI, only 24-hour ARV showed significant negative correlation with LVMI (r = -0,516; P = 0.002).

Partial correlations of BPV measures and LVMI controlling for gender or age, was insignificant.

Discussion

Although correlation analysis in our study revealed no association of BPV measures and LVMI, partial correlation analysis showed a significant inverse association between BPV as expressed by 24-h ARV and LVMI when controlling for BMI.

The association between high BPV and the development of end-organ damage has been demonstrated in a large number of preclinical studies of sinoaortic-denervated (SAD) as well as in the majority of clinical studies on the BPV impact on cardiovascular health or target organ damages in children and adults(3,10,16,17). Nevertheless, some recent research as well as systematic reviews indicate that there is no association between high BPV and adverse cardiovascular events or target-organ damages, or the association become insignificant after adjustment for other well-known risk factors (4,16,18,19,20,21,22,23).
Contrary to these findings we report that children with clinically significant hypertension are more likely to have left ventricular hypertrophy, if they have low BPV. Although the results of our study are quite surprising and unexpected a few explanations are plausible. A number of data show that, over the 24 hours BP exhibit marked variations in response to behavioral changes including (physical activity, sleep, and emotional stimuli) indicating their considerable influence on BP variability, especially short term BPV (22). The majority of our patients were obese (85,7%), thus more likely to have

sedentary lifestyle or low levels of exercise, so we can't exclude the possibility of such coincidence (24). Unlike previous studies that did not adequately control potential confounders such as body mass index, our study accounted for BMI (3,16,23,25). The other explanation is the difference in age of patients between our and previous studies. Aging is strongly associated with increased arterial stiffness which is the principal cause of increasing systolic pressure and has been found to contribute in BPV as a pathological mechanism (26). This influence is likely to be less prominent in children in spite of the fact that they could have advanced structural and functional cardiovascular and/or associated neurohumoral abnormalities. Hence, lack of physical activity may mask other "non-behaviorally and non-mechanically" related influences on BPV in children, it would be necessary to account for and quantify this influence when interpreting BPV reports obtained via ambulatory BP monitoring. In this regard we would like to emphasize the need to delineate ambulatory BP vs. noninvasive continuous beat-to-beat BP reports in future clinical studies estimating clinical utility of BPV measures. Since the analysis of noninvasive continuous beat-to-beat BPV by means of spectral analysis allows the estimation of the relative contribution of neurohumoral systems in blood pressure regulation we are in opinion that this non-invasive method might provide a definitive answer on the clinical implications of BPV measures obtained via ambulatory BP monitoring on subclinical organ damage in true hypertensive children.

To our knowledge to date there are no relevant literature data on the agreement or interchangeability between both of these "complementary" methods.

Finally, we would like cite the great British-American scientist-philosopher Alfred North Whitehad and his words that the key to ultimate success in every scientific research is to view each unexpected or negative result as an opportunity for creating and testing novel hypotheses within the framework of general idea (27). In this regard, our findings are first to provide novel evidence that children with clinically significant hypertension are more likely to develop left ventricular hypertrophy if they have low BPV and are obese.

Limitations

We reported only the results from true hypertensive children, so the range of BP variables was somewhat restricted. On the other hand, all examined children are by definition, at the highest risk for future adverse cardiovascular events making our results more relevant from the clinical view point.

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