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Assessment of central blood pressure as a predictor of target organ damage in children with primary hypertension**

Ocena centralnego ciśnienia tętniczego jako predyktora uszkodzenia narządowego u dzieci z pierwotnym nadciśnieniem tętniczym

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Keywords

children, primary hypertension, central blood pressure, target organ damage

Słowa kluczowe

dzieci, nadciśnienie tętnicze pierwotne, centralne ciśnienie tętnicze, uszkodzenie narządowe

S u m m a r y

Introduction. Central systolic blood pressure (cSBP) is assumed to be the best indicator of cardiovascular risk caused by elevated blood pressure. However, there are no data on the usefulness of cSBP measurments in the assessment of the risk of target organ damage (TOD) in hypertensive children.

Aim. The aim of study was to evaluate the usefulness of noninvasive measurements of cSBP, AugP and AugInd as predictors of increased left ventricular hypertrophy (LVH) and increased carotid intima-media thickness (cIMT) in children with primary hypertension.

Material and methods. 114 children (25 girls), mean age 15.2 ± 2.5 years, referred because of elevated blood pressure and with excluded secondary hypertension, were included in the study. In all patients, 24h ambulatory blood pressure monitoring (ABPM), cSBP, central pulse pressure (cPP), AugP, AugInd, cardiac index (CI), total peripheral resistance (TPR), pulse wave velocity (PWV), LVMI and cIMT were measured.

Results. In 62 patients white coat hypertension was diagnosed, 9 had ambulatory hypertension and 43 had severe ambulatory hypertension. Children with severe ambulatory hypertension had greater AugP, CI and carotid wall cross sectional area (WCSA) and lower TPR. cSBP correlated with WCSA ($p = 0.015$; $r = 0.255$) and AugP with LVMI ($p = 0.02$; $r = 0.220$).

ABPM had greater sensitivity and lower specificity for predicting LVH than cSBP. ABPM and cSBP had similar sensitivity and specificity as predictors of cIMT and WCSA.

Conclusions. Although sensitivity and specificity of cSBP and ABPM as predictors of arterial injury were similar, ABPM performed better as a predictor of LVH. The results of our study indicate a much higher risk of TOD in children with severe ambulatory hypertension and show that the assessment of cSBP, which is also a predictor of LVH, may be a new criterion for drug therapy implementation.

S t r e s z c z e n i e

Wstęp. Centralne skurczowe ciśnienie tętnicze (cSBP) uważane jest za najlepszy wskaźnik oceny ryzyka sercowo-naczyniowego związanego z podwyższonym ciśnieniem tętniczym. Brakuje jednak danych dotyczących użyteczności pomiarów cSBP w ocenie ryzyka wystąpienia uszkodzenia narządowego u dzieci z nadciśnieniem tętniczym.

Cel pracy. Celem pracy była ocena nieinwazyjnych pomiarów cSBP, ciśnienia i wskaźnika wzmocnienia (AugP, AugInd) jako predyktorów przerostu lewej komory serca (LVH) oraz grubości kompleksu błona wewnętrzna-błona środkowa tętnic szyjnych wspólnych (cIMT) u dzieci z nadciśnieniem tętniczym pierwotnym.

Materiał i metody. U 114 dzieci (25 dziewczynek) (15,2 ± 2,5 roku) skierowanych w celu diagnostyki nadciśnienia tętniczego (NT), u których wykluczono wtórne przyczyny NT, wykonano pomiary 24 h ambulatoryjnego pomiaru ciśnienia tętniczego (ABPM), cSBP, centralnego ciśnienia tętna (cPP), AugP, AugInd, wskaźnika sercowego (CI), całkowitego oporu obwodowego (TPR), prędkości fali tętna (PWV), LVMI oraz cIMT.

Wyniki. U 62 pacjentów rozpoznano nadciśnienie białego fartucha, u 18 stwierdzono ambulatoryjny stan przednadciśnieniowy, u 9 ambulatoryjne NT (ANT), a u 43 ciężkie ambulatoryjne NT (CANT).

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Dzieci z CANT miały większe AugP, CI, pole przekroju tętnicy szyjnej wspólnej (WCSA) oraz mniejszy TPR niż dzieci normotensyjne. Wartości cSBP korelowały z WCSA ($p = 0,015$; $r = 0,255$), natomiast AugP z LVMI ($p = 0,02$; $r = 0,220$). cSBP nie różnicowało dzieci pod względem występowania LVH oraz uszkodzenia naczyniowego. ABPM cechowała większa czułość i mniejsza swoistość w predykcji LVH niż cSBP. Dla wzrostu wartości cIMT oraz WCSA zarówno ABPM, jak i cSBP charakteryzowały się podobną czułością i swoistością.

Wnioski. cSBP oraz AugP korelowały z markerami uszkodzenia narządowego (TOD) związanego z NT. Pomimo że czułość i swoistość pomiarów cSBP i ABPM jako predyktorów uszkodzenia naczyniowego była podobna, ABPM okazał się lepszym predyktorem LVH.

INTRODUCTION

Central systolic blood pressure (cSBP) is assumed to be the best indicator of cardiovascular risk caused by elevated blood pressure. It's predictive accuracy has been demonstrated in a number of studies (1-4). However, there are no data on the usefulness of measurements of cSBP, augmentation pressure (AugP) and augmentation index (AugInd) in assessment of risk of target organ damage (TOD) in hypertensive children.

AIM

The aim of the study was to evaluate the usefulness of noninvasive measurements of cSBP, AugP and AugInd as predictors of increased left ventricular mass index (LVMI) and increased carotid intima-media thickness (cIMT) in children with primary hypertension.

MATERIAL AND METHODS

The study was performed according to the Declaration of Helsinki and with the approval of the Children's Memorial Health Institute Ethics Committee. All patients (pts) and parents gave consent to participate in the study.

One hundred fourteen patients (114 pts; mean age: 15.2 years; range: 12.7-17.7 years; 25 girls) with newly diagnosed and untreated primary hypertension, who underwent full diagnostic approach to exclude secondary hypertension, were included in the study. The exclusion criteria were: presence of any significant chronic disease (except for PH) including diabetes mellitus and chronic kidney disease, any acute illness including infections in the 6 weeks preceding enrolment, and incomplete data.

PH was diagnosed according to The Fourth Task Force Report and European Society of Hypertension guidelines and confirmed by 24-hour ambulatory BP monitoring (ABPM) (5, 6). Blood pressure (BP) status was defined according to the ambulatory blood pressure measurement classification (7).

ABPM measurements

All ABPM measurements were assessed oscillometrically using SpaceLabs Monitor 90207, and the most appropriate cuff was applied on the non-dominant arm. Readings were taken every 20 minutes during daytime and every 30 minutes at night. Recordings lasting $\geq$ 20 hours with $\geq$ 80% of correct readings were considered valid and were included in the analysis. We used a recently published classification system based on ABPM to classify patients as having normal BP, ambulatory hypertension, and severe ambulatory hypertension (7, 8).

Measurement of carotid to femoral PWV

The Vicorder system provides a simple and quick non-invasive oscillometric method of obtaining the Pulse Wave Velocity for an arterial segment. Measurement was performed in the supine position after 5 minutes of rest using the Vicorder device according to the current guidelines (9). A 100 mm-wide BP cuff was placed around the right upper thigh to measure the femoral pulse wave and a 30 mm plethysmographic partially inflatable sensor was placed over the carotid region in order to pick up the carotid pulse wave. Both cuffs are automatically inflated to 65 mmHg and the corresponding oscillometric signal from each cuff is digitally analyzed using the latest patented technique to accurately extract, in real time, the pulse time delay and consequently the Pulse Wave Velocity.

Measurement of central blood pressure (pulse wave analysis)

The Vicorder device analyses the waveform of radial artery pulse obtained oscillometrically and then, using transfer function, calculates the aortic waveform. Prior to the measurement, it is necessary to enter the individual features and the value of blood pressure measured at the brachial artery. The system, after having obtained the measurements, calculates and presents an approximated waveform of the aortic valve, from which we can acquire a number of parameters describing the characteristics of the arterial system, including the aortic (central) systolic blood pressure (cSBP), augmentation pressure (Aug Press), augmentation index (Aug Index), aortic pulse pressure (AoPP), cardiac output (CO) and the total peripheral resistance index (TPRI) (9-11). CBP status was defined according to the recently published reference values. Values below the 95th percentile for age and sex were considered as normal (12).

Echocardiography

All echocardiography examinations were performed by 1 examiner who knew the clinical diagnosis, but

was not aware of the severity of hypertension and the effectiveness of treatment. Echocardiography measurements were performed according to the guidelines of the American Society of Echocardiography (13). To standardize the left ventricular mass to height, LVMI was calculated according to the de Simone formula (14). Left ventricular hypertrophy (LVH) was defined as a LVMI value above the 95th percentile for age- and sex-based reference data (15).

Carotid-intima media thickness (cIMT) and wall cross sectional area (WCSA) of carotid arteries measurements

cIMT was evaluated by ultrasound, and SD of normal values for cIMT was obtained according to the methodology described previously (16, 17). Mean WCSA was calculated from the equation:

WCSA = π (dD/2 + IMT)^2 − π(dD/2)^2, where dD is the mean diastolic diameter (16).

Laboratory investigations

The following metabolic cardiovascular risk factors were assessed at diagnosis: plasma glucose level, lipid profile and serum uric acid. Blood samples were taken after 12 hours of fasting. The plasma glucose level was measured by a Dimension analyser.

Statistical analysis

The anthropometrical indices, IMT, WCSA, LVMI and PWV values were expressed as absolute values and SDS values according to the referential normative values published recently (12, 17).

The homogeneity of variance was checked with the Shapiro-Wilk test. Continuous variables with a normal distribution were compared using the Student t-test for independent variables. Continuous values with abnormal distribution were compared using the Wilcoxon test. Variables with normal distribution were presented as mean and SD values, whereas variables with abnormal distribution were presented as median and range values between the 5th and the 95th percentiles. The correlation analysis was performed using Spearman test for abnormal distribution. Variables with significant correlation including changes in anthropometrical parameters and changes in BP and metabolic parameters were then included in the step-wise multiple regression analysis. P values < 0.05 were considered statistically significant, and values between 0.05 and 0.1 were considered as demonstrating trend toward significance.

RESULTS

Out of 114 patients referred because of elevated blood pressure, who underwent full diagnostic process, normotension (white coat hypertension) was diagnosed in 44, prehypertension in 18, ambulatory hypertension in 9 and severe ambulatory hypertension in 43 pts (tab. 1).

Table 1. Characteristic of patients group.

Age (years)	15.2 ± 2.5
Boys/girls	89 (78%)/25 (22%)
Height (cm)	171 ± 13
Weight (kg)	72.6 ± 16.4
BMI (kg/m^2)	24.6 ± 3.9
BMI-sds	1.2 ± 0.8
Waist circumference (cm)	81 ± 10
Waist circumference-sds	1.2 ± 0.9
Classification of hypertension based on ABPM	Normal blood pressure/white coat hypertension – 44
	Prehypertension/white coat hypertension – 18
	Ambulatory hypertension – 9
	Severe ambulatory hypertension – 43
ABPM SBP (mmHg)	129 ± 9
ABPM DBP (mmHg)	73 ± 7
ABPM MAP (mmHg)	92 ± 6
ABPM HR	77 ± 12
cIMT (mm)	0.46 ± 0.04
cIMT-sds	1.9 ± 1.2
LVMI (g/m$^{2.7}$)	34.73 ± 6.56
PWV (m/s)	5.7 ± 0.7
PWV-sds	1.5 ± 1.3
Aug Press (mmHg)	4 ± 3
Aug Index (%)	8 ± 4
CO (l/min)	5.94 ± 1.69
TPR (PRU)	0.98 ± 0.24
CI (l/min/m^2)	3.28 ± 1.05

BMI – Body Mass Index; ABPM – Ambulatory Blood Pressure Monitoring; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; MAP – Mean Arterial Pressure; HR – Heart Rate; cIMT – carotid Intima-Media Thickness; LVMI – Left Ventricular Mass Index; PWV – Pulse Wave Velocity; Aug Press – Augmentation Pressure; Aug Index – Augmentation Index; CO – Cardiac Output; TPR – Total Peripheral Resistance; CI – Cardiac Index

The comparison of patients divided into four groups according to BP status revealed that only patients with severe ambulatory hypertension had significantly greater cSBP and Aug Press compared to other groups. Children with severe ambulatory hypertension had also significantly greater AugP, CI and carotid wall cross sectional area (WCSA) compared to others. TPR was lower in patients with severe ambulatory hypertension than in normotensive ones. cSBP correlated with WCSA ($p = 0.015$; $r = 0.255$) and AugP with LVMI ($p = 0.02$; $r = 0.220$).

Children with cSBP above and below the 95th percentile (12) did not differ regarding prevalence of left ventricular hypertrophy (LVH) and arterial injury. ABPM had greater sensitivity (0.67 vs 0.47) and lower specificity (0.56 vs 0.63) for predicting LVH than cSBP. For cIMT and WCSA increase both ABPM and cSBP had similar sensitivity and specificity (tab. 2, 3, fig. 1-3).

Table 2. Sensitivity and specificity of the ≥ 95th percentile of AoBP to detect LVMI ≥ 95cc.; cIMT ≥ 95cc. and WCSA ≥ 95cc.

	LVMI ≥ 95cc.	**cIMT ≥ 95cc.**	**WCSA ≥ 95cc.**
Sensitivity	0.47	0.51	0.54
Specificity	0.63	0.66	0.63

LVMI – Left Ventricular Mass Index; cIMT – carotid Intima-Media Thickness; WCSA – Wall Cross Sectional Area; cc. – percentiles for age, sex and height

Table 3. Sensitivity and specificity of the ABPM: (ambulatory hypertension + severe ambulatory hypertension) to detect LVMI ≥ 95cc.; cIMT ≥ 95cc. and WCSA ≥ 95cc.

	LVMI ≥ 95cc.	**cIMT ≥ 95cc.**	**WCSA ≥ 95cc.**
Sensitivity	0.67	0.53	0.63
Specificity	0.56	0.55	0.61

LVMI – Left Ventricular Mass Index; cIMT – carotid Intima-Media Thickness; WCSA – Wall Cross Sectional Area; cc. – percentiles for age, sex and height

DISCUSSION

In many studies cSBP has been shown as one of the main predictors of adverse cardiovascular events and TOD (18-27). In our study we found that only patients with severe ambulatory hypertension had significantly greater cSBP and Aug Press compared to other groups. The significance of the interpretation problems, leading to the difficulties in diagnosis and treatment of hypertension in children, is worth discussing. The second finding is that cSBP has similar predictive value as ABPM in predicting early, subclinical arterial injury.

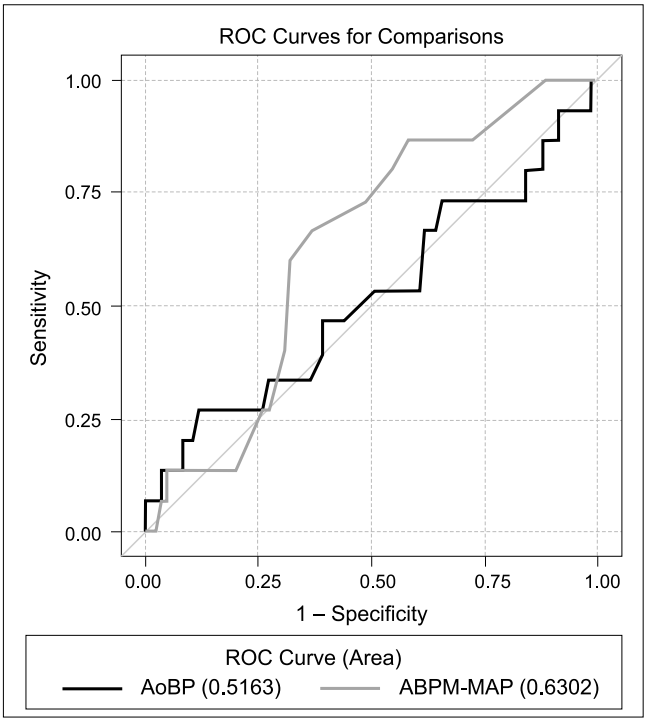

Fig. 1. Receiver operating characteristic (ROC) curve of the AoBP and ABPM MAP to detect LVMI ≥ 95cc.
AoBP – Aortic Blood Pressure; ABPM – Ambulatory Blood Pressure Monitoring; MAP – Mean Arterial Pressure; LVMI – Left Ventricular Mass Index; cc. – percentiles for age, sex and height

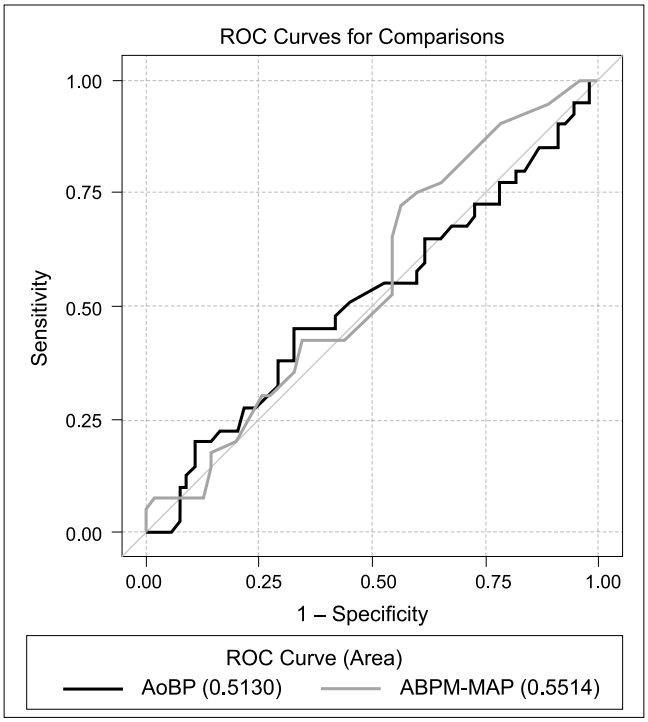

Fig. 2. Receiver operating characteristic (ROC) curve of the AoBP and ABPM MAP to detect cIMT ≥ 95cc.
AoBP – Aortic Blood Pressure; ABPM – Ambulatory Blood Pressure Monitoring; MAP – Mean Arterial Pressure; cIMT – carotid Intima-Media Thickness; cc. – percentiles for age, sex and height

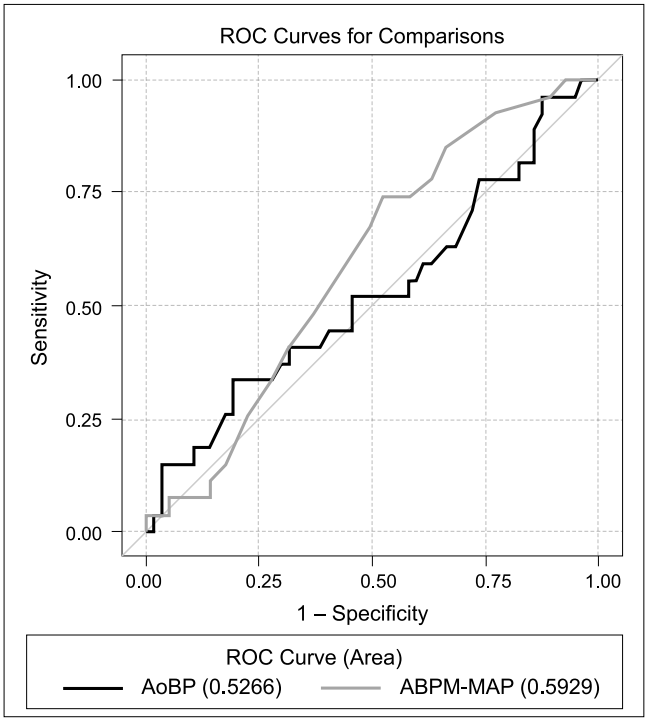

Fig. 3. Receiver operating characteristic (ROC) curve of the AoBP and ABPM MAP to detect WCSA ≥ 95cc.
AoBP – Aortic Blood Pressure; ABPM – Ambulatory Blood Pressure Monitoring; MAP – Mean Arterial Pressure; WCSA – Wall Cross Sectional Area; cc. – percentiles for age, sex and height

Thus, it indicates that assessment of cSBP may have a role in diagnosis of arterial hypertension, assessment of cardiovascular risk and may be used as an additional criterion for starting a pharmacological treatment.

Current guidelines for the diagnosis and management of high blood pressure in adults are based on the evaluation of cardiovascular risk and the effectiveness of treatment in prevention of cardiovascular episodes. Since cardiovascular incidents are extremely rare among children with primary arterial hypertension, diagnostic criteria for hypertension are based upon indirect risk indicators, such as TOD or metabolic parameters.

Another issue worth pointing out is the problem of blood-pressure cut-off values for the identification of hypertension. Only for 18 years old boys, the value of the 95th percentile, which is typically used as the cut-off point, equals 140/80 and therefore corresponds to the value of arterial blood pressure used for diagnosing hypertension in adults. 95th percentile values for girls are lower even for the 18 year olds (28).

In our study, as well as in other, previously conducted investigations, hypertension rarely coincided with TOD. It seems that only severe, ambulatory hypertension, diagnosed using ABPM is clinically significant. Therefore, it is worth emphasizing that pediatric definitions may lead to diagnosis of hypertension in children who do not actually suffer from that affliction or who do not have any TOD caused by the elevated blood pressure. On the other hand, the overdiagnosis of hypertension may lead to positive changes in life style, which may induce short-term (TOD) and long-term improvements (a reduction in cardiovascular related mortality). Furthermore, during diagnostic tests in patients with suspected hypertension, some children with severe, secondary hypertension may be identified, who otherwise would not be subjected to those examinations.

The aforementioned difference between the blood pressure values of the 95th percentile in 18 years old girls and boys is also worth accentuating. For boys, the value corresponds with the cut-off point of 140/80 mmHg used for diagnosis of hypertension in adults, whereas the 95th percentile for 18 years old girls is equal to approx. 131/78 mmHg. As the results of our study do not indicate that there exists a difference between boys and girls in the relationship between TOD and the stage of hypertension, it is worth considering whether the employment of different blood pressure reference values depending on sex is a correct course of action.

CONCLUSIONS

cSBP and AugP assessed non-invasively with oscillometric method correlated with markers of hypertensive TOD. Although sensitivity and specificity of cSBP and ABPM as predictors of arterial injury were similar, ABPM performed better as a predictor of LVH. Elevated cSBP significantly differentiated patients with severe ambulatory hypertension from other groups.

Thus, the assessment of cSBP, allows to detect patients with significantly elevated blood pressure, i.e. those with severe ambulatory hypertension, subclinical arterial injury and who require more intense treatment. It is important because there is no evidence that antihypertensive drugs significantly reduced cardiovascular risk in adults with first degree hypertension (29). Even less evidence for pharmacological treatment exists for children with first degree hypertension and ambulatory hypertension without TOD. Thus, because drug-free treatment should be preferred whenever it is possible, the assessment of cSBP may be a new criterion for drug therapy implementation.

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