

Haemodynamic patterns in children with primary hypertension — preliminary brief report

Wzorce hemodynamiczne u dzieci z nadciśnieniem tętniczym pierwotnym — wstępne wyniki badań

Streszczenie

Wstęp Zakłada się, że początkowy okres nadciśnienia tętniczego pierwotnego (NTP) charakteryzuje się występowaniem krążenia hiperkinetycznego. Nie udowodniono jednak związku między wartościami ciśnienia tętniczego (począwszy od normotensji, aż do ciężkiego ambulatoryjnego nadciśnienia tętniczego) a zaburzeniami hemodynamicznymi u dzieci z NTP. Celem badania było scharakteryzowanie takich parametrów hemodynamicznych, jak wskaźnik sercowy (CI) i całkowity opór obwodowy (TPR) u dzieci z NTP w zależności od stadium nadciśnienia tętniczego.

Materiał i metody Do badania włączono 95 pacjentów ($15,3 \pm 2$ lata; 27 dziewczynek) skierowanych z powodu podwyższonych wartości ciśnienia tętniczego, u których wykluczono wtórne przyczyny nadciśnienia tętniczego. Prędkość fali tętna (PWV), CI i TPR były mierzone przy użyciu funkcji oscylometrycznej analizy fali tętna aparatu Vicorder. Klasyfikacja ciśnienia tętniczego była określana zgodnie z obecnymi wytycznymi na podstawie całodobowego ambulatoryjnego pomiaru ciśnienia tętniczego (ABPM).

Wyniki Pełnemu procesowi diagnostycznemu zostało poddanych 95 pacjentów z podwyższonym ciśnieniem tętniczym. W jego wyniku u 31 pacjentów stwierdzono normotensję, u 14 stan przednadciśnieniowy, u 7 ambulatoryjne nadciśnienie tętnicze, u 43 ciężkie ambulatoryjne nadciśnienie tętnicze. Porównanie średnich wartości CI dla poszczególnych grup wykazało znaczący wzrost CI po-

wiązany z kategorią nadciśnienia tętniczego. Wzrostowi CI towarzyszył nieistotny statystycznie spadek TPR. Wartości CI korelowały ze średnim ciśnieniem tętniczym, częstością rytmu serca, szybkością fali tętna i ładunkiem ciśnienia skurczowego. Wartości TPR korelowały z parametrami antropometrycznymi, w tym ujemnie z obwodem talii, średnim ciśnieniem tętniczym i szybkością fali tętna. Analiza regresji krokowej nie wykazała predyktorów CI, natomiast dla TPR predyktorem okazał się obwód talii (Beta $-0,310$; $p = 0,021$).

Wnioski U dzieci z pierwotnym nadciśnieniem tętniczym stwierdzono zaburzenia hemodynamiczne o cechach krążenia hiperkinetycznego narastające wraz ze wzrostem stadium nadciśnienia tętniczego. Wzrostowi CI towarzyszył jednak jedynie statystycznie nieistotny spadek TPRI. Ten rodzaj zaburzeń hemodynamicznych tłumaczy mechanizm wzrostu ciśnienia tętniczego u dzieci z NTP. Otyłość trzewna wyrażona jako obwód talii ma znaczenie w mechanizmie rozwoju krążenia hiperkinetycznego.

słowa kluczowe: nadciśnienie tętnicze pierwotne, dzieci, krążenie hiperkinetyczne

Nadciśnienie Tętnicze 2014, tom 18, nr 4, strony: 204–210

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Background

It is assumed that the initial phase of primary hypertension (PH) is characterized by the presence of hyperkinetic circulation. Such view is based on the first descriptions of hemodynamic in hypertensive children published already in 60s and 70s of XX century. However, the relationship between blood

pressure (from normal blood pressure through prehypertension, ambulatory hypertension to severe ambulatory hypertension) and haemodynamic patterns in children with PH was not described.

The objective of this study was to characterize the haemodynamic parameters such as cardiac index (CI) and a total peripheral resistance index (TPR) in children with PH depending on the stage of hypertension.

Materials 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 and parents gave consent to participate in the study.

Ninety-five patients (age, 15.3 years, range, 13.3–17.3 years; 27 girls) with newly diagnosed PH were included in the study. The exclusion criteria were the following: the 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 paediatric guidelines and confirmed by 24-hour ambulatory BP monitoring (ABPM) [1, 2].

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 ≥ 20 hours with $\geq 80\%$ of readings were considered as valid and were included in the analysis. We used a recently published classification system based on ABPM to classify patients as having normal BP, prehypertension, ambulatory hypertension, and severe ambulatory hypertension [3, 4].

The night period was defined as 00:00 hours to 06:00 hours, and the daytime period was defined as 08:00 hours to 20:00 hours.

Measurement of cardiac index, total peripheral resistance index and pulse wave velocity

CI and TPRI was assessed indirectly using Vicorder system (SMG Medical GMBH & Co. KG). The Vicorder system provides a simple and quick non-invasive, oscillometric method to obtain pulse wave velocity (PWV), central blood pressure, stroke volume, CI and TPR. TPR was expressed as peripheral resistance units (PRU) according to

algorithm developed by producer of Vicorder device. Measurements were performed in the supine position after 5 minutes of rest using the Vicorder device according to the actual guidelines. A 100-mm wide BP cuff was placed around the right upper thigh to measure the femoral pulse wave and a 30-mm plethysmographic partial inflatable sensor was placed over the carotid region, able 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 analysed using the latest patented technique to accurately extract, in real time, the pulse time delay and the consequent Pulse Wave Velocity [5, 6].

Measurement of central blood pressure (pulse wave analysis)

The Vicorder device analyses the waveform of radial artery pulse and then using transfer function calculates the aortic waveform. Prior to the measurement it was necessary to enter the individual features and the value of blood pressure measured immediately before or at the time of PWV measurement at the brachial artery of contralateral arm. System calculates and presents approximated waveform of the aortic valve. Several parameters are calculated including aortic blood pressure (AoBP), augmentation pressure (Aug Press), augmentation index (Aug Index), cardiac output (CO) and total peripheral resistance index (TPRI) [7–9].

Body surface area calculation

Body surface area (BSA) calculated was calculated using Haycock formula [10]:

$$BSA = 0.024265 \times W^{0.5378} \times H^{0.3964}$$

W — weight

H — height

Statistical analysis

The anthropometrical indices, IMT, WCSA, LVMI, BP and PWV values were expressed as absolute values and SDS values. 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 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

Demographic, anthropometric and clinical characteristics of all patients are given in table I. Of 95 patients, 31 (33%) had normal blood pressure/white coat hypertension, 14 (15%) ambulatory prehypertension, 7 (7%) ambulatory hypertension and 43 (45%) severe ambulatory hypertension. Comparison of the mean values of CI from normotension, through prehypertension, ambulatory hypertension to severe ambulatory hypertension showed significant increase in CI ($p = 0.01$) (table II). In group of children with normal blood pressure mean CI was 2.71 ± 0.56 l/min/m², in children with prehypertension 3.42 ± 0.97 l/min/m², in children with ambulatory blood pressure 3.34 ± 1.65 l/min/m² and in those with severe ambulatory blood pressure 3.5 ± 1.06 l/min/m².

CI increase was accompanied by a non-significant decrease in TPR ($p = 0.07$) (table II). In group of children with normal blood pressure TPR was 1.06 ± 0.23 PRU, with prehypertension 0.98 ± 0.24 PRU, with ambulatory blood pressure 0.97 ± 0.22 PRU and with severe ambulatory blood pressure 0.92 ± 0.24 PRU.

Mean CI values correlated with 24-hour mean arterial pressure, 24-hour heart rate, PWV-SDS and systolic blood pressure load (table III).

Mean TPR values correlated with anthropometric parameters (table IV), including negative correlation with waist circumference, pulse wave velocity, 24 hour heart rate and positive with 24-hour mean arterial pressure.

Stepwise regression analysis showed no predictors for CI, but for TPR the predictor was waist circumference (Beta -0.310 ; $p = 0.021$).

Discussion

The main finding of our study is the significant increase in CI and tendency to lower TPR in patients with higher BP compared to patients with normal or only slightly elevated BP, what may indicate on the hyperkinetic mechanism in the early phases of cardiovascular disease in children with newly diagnosed PH. Although a lot of studies suggested that the early phases of hypertension are characterized by

a hyperkinetic circulation, the mechanisms of initiation and development of cardiovascular disease and the haemodynamic characteristics of its early phases, remain controversial. There are two major hypothe-

Table I. Characteristic of patients group

Tabela I. Charakterystyka grupy pacjentów

Age (years)	15.3 ± 2.0
Height [cm]	170.3 ± 11.1
Weight [kg]	73.3 ± 15.5
BMI [kg/m ²]	25.1 ± 3.8
BMI-sds	1.24 ± 0.80
Waist circumference [cm]	81.7 ± 10.3
Waist circumference-sds	1.20 ± 0.87
Classification of hypertension based on ABPM	Normal blood pressure/white coat hypertension — 31 Prehypertension — 14 Ambulatory blood pressure — 7 Severe ambulatory blood pressure — 43
ABPM SBP [mmHg]	129 ± 9
ABPM DBP [mmHg]	73 ± 7
ABPM MAP [mmHg]	92 ± 6
ABPM HR	77 ± 11
cIMT [mm]	0.47 ± 0.04
cIMT-sds	1.66 ± 0.92
LVMi [g/m ^{2.7}]	35 ± 8
LVMi centiles	0–10 cc — 1 10–25 cc — 5 25–50 cc — 6 50–75 cc — 16 75–90 cc — 21 90–95 cc — 6 95–100 cc — 23
PWV [m/s]	5.6 ± 0.6
PWV-sds	1.43 ± 1.40
Aug Press [mm Hg]	4 ± 3
Aug Index (%)	8 ± 5
CO [l/min]	6.01 ± 1.72
CI [l/min/m ²]	3.29 ± 1.05
Cholesterol [mg/dl]	160 ± 32
TTG [mg/dl]	101 ± 42
HDL [mg/dl]	50 ± 10
LDL [mg/dl]	90 ± 27
Uric acid [mg/dl]	5.7 ± 1.4
Fasting glucose [mg/dl]	89 ± 6

SDS — standard deviation score; BMI — body mass index; ABPM — ambulatory blood pressure monitoring; 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; CI — cardiac index; TPR — total peripheral resistance; MAP — mean arterial pressure; SBP load — systolic blood pressure load; HR — heart rate

Table II. Anthropometrical and haemodynamic data compared with the category of hypertension**Tabela II.** Dane antropometryczne i hemodynamiczne w grupach pacjentów określonych na podstawie wartości ciśnienia tętniczego

	Normal blood pressure/white coat hypertension (n = 31)	Prehypertension (n = 14)	Ambulatory blood pressure (n = 7)	Severe ambulatory blood pressure (n = 43)	p
	Mean	Mean	Mean	Mean	
Age (years)	15.5 ± 1.7	13.7 ± 2.9	15.3 ± 1.7	14.7 ± 2.8	
BMI-sds	1.4* ± 0.6	0.5* ± 1.0	1.9* ± 0.5	1.2* ± 0.7	< 0.05
Waist circumference -sds	1.4 ± 0.7	0.6* ± 0.8	2.0* ± 0.6	1.1 ± 0.8	0.009
CI [l/min/m ²]	2.71* ± 0.56	3.42 ± 0.97	3.34 ± 1.65	3.5* ± 1.06	0.01
TPR [PRU]	1.06* ± 0.23	0.98 ± 0.24	0.97 ± 0.22	0.92* ± 0.24	0.07
Stroke volume [ml]	75* ± 19	78 ± 16	77 ± 19	90* ± 21	0.01
Heart rate 24h	64 ± 12	67 ± 10	71 ± 20	67 ± 10	n.s.

Table III. Correlation between CI and other haemodynamic parameters (only significant correlations shown)**Tabela III.** Korelacje między wskaźnikiem sercowym (CI) a innymi parametrami hemodynamicznymi (ujęto wyłącznie korelacje istotne statystycznie)

CI vs.	ABPM MAP 24h	p = 0.0004	r = 0.324
	HR 24h	p = 0.001	r = 0.373
	PWV-sds	p = 0.001	r = 0.306
	SBP load	p = 0.005	r = 0.520

Table IV. Correlations between TPRI and other variables (only significant correlations shown)**Tabela IV.** Korelacje między wartościami całkowitego oporu obwodowego (TPR) a innymi parametrami hemodynamicznymi i antropometrycznymi (ujęto wyłącznie korelacje istotne statystycznie)

TPR vs.	BMI-sds	p = 0.003	r = 0.250
	Waist circumference -sds	p = 0.021	r = -0.2855
	ABPM MAP 24h	p = 0.023	r = 0.236
	HR 24h	p = 0.0001	r = -0.414
	PWV-sds	p = 0.0001	r = -0.369

ses, that explain the initial phase of hypertension as a kind of hyperkinetic disease, characterized by an increased peripheral resistance or cardiac output [11].

The first hypothesis suggests that the peripheral resistance increases gradually with age during development of hypertension. The second hypothesis indicates that after an early period of hyperkinetic phase characterized by increased cardiac output, a secondary phase with increase in peripheral resistance develops. The mechanism of haemodynamic transition is explained by the structural and functional changes in cardiovascular system leading to decrease of cardiac output, whereas vascular resistance is caused by vascular remodelling and changes in arteries wall properties. In some studies where patients with “early”, “mild” or “borderline” hypertension were evaluated, an increased cardiac output has been reported [12–15]. However, other studies could not confirm this observations or have reported a decreased cardiac output in young patients with borderline hypertension [16–18]. Some observations also suggest, that in borderline hypertension, an initial high cardiac output decreases and peripheral resistance increases over years and thus, some borderline hypertensive patients develop sustained hypertension [19].

Due to cross-sectional character of our study we could present only preliminary results with no observation of changes of CI and TPR over time. However in some other prospective studies conducted in a hyperkinetic hypertensive patients observed over 20 years, it was found, that although young hypertensive patients had higher cardiac output at the beginning of the disease, after 20 years of follow-up, the elevated blood pressures shifted from the hyperkinetic profile to the phase characterized by low cardiac output and elevated total peripheral resistance [20]. The same transition from cardiac related to vascular related hypertension has been observed in other clinical studies [19, 21–25].

Although during decades, a lot of investigators have studied the changes in cardiac output according to blood pressure status, data regarding this phenomenon in children are rare and inconclusive. In our study we found significant increase in CI and SV in patients with higher BP, however in some studies performed in young hypertensive or normotensive subjects, the correlation between cardiac output and BP was not confirmed [26, 27]. It may be due to the

fact, that most of the studies evaluated early stages of hypertension with borderline, prehypertensive or white coat hypertension subjects, characterized by mildly elevated blood pressure, that often do not show a chronic progression to more advanced cardiovascular disease. On the other hand, although our patients also presented the early phases of cardiovascular disease, the increased CI related to BP status, confirmed the hyperkinetic mechanism in the development of cardiovascular disease in children.

Although faster heart rate has to be the hallmark of the hyperkinetic state and sympathetic nervous system overactivity might contribute primary hypertension, in our study we did not find any differences in HR in patients with different BP status [23, 28, 29]. However we found a correlation between HR and CI. Moreover, in our previous study, we found significant increase in HR in hypertensive children compared with controls [30, 31]. Also in other studies, children with elevated BP were characterized by higher HR and cardiac output, but normal TPR [32, 33]. What is also interesting, in the present study, CI correlated with PWV, which may indicate that also in the early stages of hyperkinetic hypertension, the initial phase of arterial stiffness can be observed.

Hyperkinetic circulation at the early stages of PH and of cardiovascular disease has been reported to be associated not only with the adrenergic activation, but also with the metabolic risk factors related to disturbed body composition and fat tissue distribution [34]. It was shown, that the hyperkinetic circulation in the adult population is associated with increased levels of fasting and postglucose insulin, triglycerides and body fatness [35]. According to these findings, some authors postulated that hyperkinetic circulation related to insulin or other metabolic disturbances can be the early feature of the metabolic syndrome. A number of studies have shown that metabolic abnormalities, especially related to insulin resistance, can increase cardiac output, cardiac contractility and heart rate [36–39]. In our study we did not find any correlation between CI or TPR and metabolic risk factors, but we found a positive correlation between TPR and BMI and negative with WC. It is confirmed by other studies, which indicate that in hypertensive individuals with a hyperkinetic status, high cardiac output, low peripheral resistance, and rapid heart rate is related to obesity and adiposity [40–42].

Limitations and strengths of the study

The limitations of the study include a cross-sectional character of the study, what makes unfeasible to observe any changes in CI and TPRI over time.

Although the preliminary results of the current study allowed us to characterize haemodynamic mechanism of the early phases of cardiovascular disease in children, however this approach did not allow us to assess the relationship between haemodynamic markers of essential hypertension and target organ damage.

A strength of our study was the large number of young participants at the early stage of disease, that helped us to assess the pathomechanism of the development of cardiovascular disease in paediatric population. Moreover, different BP status in our patients, from normotension, through prehypertension to severe ambulatory hypertension, enabled to compare commonly used haemodynamic parameters with different BP status.

Conclusions

In conclusion, our results indicated on the differences in cardiac output between patients with different stages of hypertension and supported the presence of a hyperkinetic circulation in the early phases of primary hypertension in children and adolescents.

Summary

Background It is assumed that the initial phase of primary hypertension (PH) is characterized by the presence of hyperkinetic circulation. However, the relationship between blood pressure status (from normal blood pressure to severe ambulatory hypertension) and haemodynamic patterns in children with PH were not described.

The objective of this study was to characterize the haemodynamic parameters such as cardiac index (CI) and a total peripheral resistance index (TPRI) in children with PH depending on the stage of hypertension.

Materials and methods The study included 95 patients (15.3 ± 2.0 years; 27 girls) referred due to the elevated blood pressure, in whom secondary hypertension was excluded. Pulse wave velocity (PWV), CI and TPRI were assessed indirectly using Vicorder device. PH was diagnosed according to the European Society of Hypertension paediatric guidelines and confirmed by 24-hour ambulatory BP monitoring (ABPM).

Results Of 95 patients, 31 had normal blood pressure, 14 prehypertension, 7 ambulatory hypertension and 43 severe ambulatory hypertension. Comparison of the mean values of cardiac index (CI) for each

group showed significant increase in CI linked to the category of hypertension. CI increase was accompanied by a non-significant decrease of TPR. Mean CI values correlated with 24-hour mean arterial pressure, 24-hour heart rate, PWV-SDS and systolic blood pressure load. Mean TPR values correlated with anthropometrical parameters, including negative correlation with waist circumference and positive with 24-hour mean arterial pressure and negative with pulse wave velocity. Stepwise regression analysis showed no predictors for CI, but for TPR the only predictor was waist circumference

Conclusions Children with PH are characterized by haemodynamic patterns typical of hyperkinetic circulation increasing with increasing stage of hypertension. Non-significant decrease in TPR in children with increased CI explains haemodynamic basis of elevation of blood pressure. Visceral Obesity expressed as a waist circumference seems to play role in the mechanism of the development of hyperkinetic circulation

key words: primary hypertension, children, hyperkinetic circulation

Arterial Hypertension 2014, vol. 18, no 4, pages: 204–210

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