

ENDOTHELIUM DEPENDENT FACTORS OF VASOCONSTRICTION (THROMBOXANE B₂) AND VASODILATION (6-PROSTAGLANDIN F_{1α}) IN CHILDREN WITH PRIMARY ARTERIAL HYPERTENSION

Czynniki śródbłonna i skurcz naczyń (tromboksan B₂)
i rozszerzenie naczyń (6-prostaglandyna F_{1α})
u dzieci z nadciśnieniem tętniczym pierwotnym

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SUMMARY

Background: Vasoconstriction and vasodilatation substance imbalance plays a major role in the formation of arterial hypertension. But the ratio between thromboxane B₂ and 6-prostaglandin F_{1α} in children with various forms of primary arterial hypertension (PAH) has been insufficiently studied.

Aim of the study: The aim of the study is to explore the features of the content of thromboxane B₂, 6-keto-PGF_{1α} and their correlation in children with different clinical and pathogenetic forms of PAH.

Material and methods: The study involved 83 children aged 9 to 17. The first group included 32 children with stable PAH, the second – 32 children with labile PAH, the third (control group) – 21 children with normal blood pressure. TXB₂ and 6-PGF_{1α} serum levels were investigated by ELISA. All the children also underwent ambulatory blood pressure monitoring (ABPM).

Keywords: primary arterial hypertension, children, thromboxane B₂, 6-prostaglandin F_{1α}

Results: The average TXB₂ levels in boys were 25.05 ± 6.43 ng/ml in the group with stable PAH and 27.26 ± 11.26 ng/ml in labile PAH examinees, which exceeded the levels in the control group (p < 0.05). The girls' TXB₂ level was elevated in labile PAH respondents (to 11.06 ± 1.79 ng/ml, p < 0.05) and did not differ from the control group with stable PAH. The girls' 6-PGF_{1α} level was up to 3.41 ± 0.52 ng/ml in the stable group of PAH and up to 2.63 ± 0.25 ng/ml in the group with labile PAH.

Conclusions: The violation of the ratio between endothelial vasoconstriction (thromboxane) and vasodilatation (prostacyclin) factors in boys with PAH is due to increased TXB₂ levels compared to children with normal blood pressure (p < 0.05). Girls with PAH reflect better compensatory vasodilatation opportunities compared to boys according to the increased prostacyclin production. The latter prevents the progression of endothelial dysfunction and ensures PAH stabilization in girls.



STRESZCZENIE

Wstęp: Brak równowagi pomiędzy zwężającym się naczyniem a działaniem substancji rozszerzających naczynia odgrywa ważną rolę w powstawaniu nadciśnienia. Zależności pomiędzy tromboksanem B₂ i 6-prostaglandyną F_{1α} u dzieci z różnymi postaciami pierwotnego nadciśnienia tętniczego (PNT) nie są wystarczająco dobrze znane.

Cel pracy: Zbadanie zawartości i relacji pomiędzy tromboksanem B₂ i 6-prostaglandyną F_{1α} u dzieci z różnymi klinicznymi i patogenetycznymi postaciami nadciśnienia tętniczego pierwotnego.

Materiał i metody: W badaniu wzięto udział 83 dzieci w wieku od 9 do 17 lat. Pierwsza grupa to 32 dzieci ze stabilnym nadciśnieniem, druga – 32 dzieci z labilnym PNT, trzecia (grupa kontrolna) – 21 dzieci z prawidłowym ciśnieniem. Zawartość TXB₂ i poziom 6-PGF_{1α} w osoczu badano metodą ELISA. U wszystkich dzieci ambulatoryjnie było monitorowane ciśnienie tętnicze (AMCT).

Słowa kluczowe: nadciśnienie pierwotne, dzieci, tromboksan B₂, 6-prostaglandyna F_{1α}

Wyniki: U chłopców w grupie ze stałym PNT poziom TXB₂ wyniósł 25,05 ± 6,43 ng/ml, w grupie z labilnym PNT – 27,26 ± 11,26 ng/ml – było to przekroczenie w porównaniu z grupą kontrolną ($p < 0,05$). Poziom TXB₂ wśród dziewcząt w grupie z labilnym PNT był podwyższony (do 11,06 ± 1,79 ng/ml) i nie różnił się od tego w grupie kontrolnej i grupie dzieci ze stabilnym PNT. Poziom 6-PGF_{1α} u dziewcząt wzrastał do 3,41 ± 0,52 ng/ml w grupie ze stabilnym PNT i wyniósł 2,63 ± 0,25 ng/ml w grupie z labilnym PNT.

Wnioski: Naruszenie stosunku śródbłonkowych czynników skurczu naczyń (tromboksanu) i rozszerzenia naczyń (prostacykliny) u chłopców z PNT związane jest ze zwiększonym poziomem TXB₂ w porównaniu z dziećmi z normalnym ciśnieniem krwi ($p < 0,05$). Dziewczęta z PNT mają większe szanse na rozszerzenie naczyń krwionośnych w porównaniu z chłopcami w związku z wyższym poziomem prostacykliny. Zapobiega to progresji dysfunkcji śródbłonka oraz stabilizuje PNT u dziewcząt.

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Background

The imbalance between the vasoconstriction and vasodilatation substances plays a significant role in the formation of the arterial hypertension [1–5], including the importance of the imbalance value of such endothelial vasoactive factors as thromboxane and prostacyclin [6]. Thromboxane and prostacyclin are the products of arachidonic acid cascade, in which, according to the enzymes' activity that catalyze different parts of the cascade, thromboxane or prostacyclin is formed. The balance between these two substances promotes homeostatic regulation of normal blood pressure (BP) [7]. Prostacyclin activates adenylate cyclase, resulting in the increase of cyclic AMP, which causes the relaxation of blood vessels and reverts platelet activation [8]. The action mechanism of thromboxane is associated with the increased membrane permeability for Ca²⁺ ions, which makes its vasoconstriction effect [9]. In some cases (acute or chronic hypoxia and other stressful situations) the balance between vasoconstriction and vasodilatation factors is disturbed. In this case the vasoconstriction may occur by reducing the vasodilatation factors' production or due to the enhanced synthesis of the substances that have vasoconstriction properties. In clinical practice it is accepted to determine the quantity of inactive metabolites of thromboxane (thromboxane B₂) and prostacyclin (6-keto-PGF_{1α}) in plasma. As the final physiological effect of prostacyclin and thromboxane mostly depends on the relative predominance of one or another and not on their absolute content in plasma, most studies include a calculation of their values' ratio. It was found that adult patients with arterial hypertension have noted the increased thromboxane B₂ (TXB₂) concentration and decreased 6-keto-PGF_{1α} (6-PGF_{1α}) level in plasma compared to non-hypertensive patients [10–12]. It was also determined that high levels of prostacyclin in adults have a protective effect against the hypertension development. The patients with hypertension reflect a reduced protective effect [13]. The studies so far have found a negative correlation between 6-PGF_{1α} plasma levels and systolic, diastolic and mean blood pressure [12] and also that

prostacyclin level (extent of its reduction) determines the severity of hypertension [7]. Despite the considerable number of studies conducted in adult patients with hypertension, the features of prostacyclin and thromboxane ratio in children with primary arterial hypertension (PAH) and their pathogenetic role in the formation of hypertension have not been thoroughly studied. The PAH in children has the features associated with abrupt changes in adaptation processes during puberty that should be considered in assessing homeostasis indicators, including endothelial factors of vasoconstriction and vasodilatation contents.

Aim of the study

The aim of the study was to explore the features of the content of thromboxane B₂, 6-keto-PGF_{1α} and their correlation in children with different clinical and pathogenetic forms of primary hypertension.

Material and methods

The study involved 83 children aged 9 to 17. Depending on the clinical and pathogenic forms of PAH, the children were divided into three groups. The first group included 32 children with stable PAH, the second – 32 children with labile PAH, the third (control group) – 21 children with normal BP. Stable hypertension was determined as steady increased systolic blood pressure (SBP), diastolic blood pressure (DBP) (3 or more visits to a doctor with an interval of 10–14 days) above the 95-th percentile and the time index of hypertension within 51–100% according to the results of ambulatory blood pressure monitoring (ABPM).

Labile hypertension was determined as the unstable climbs of SBP, mostly observed in the daytime. According to the ABPM results, the time index of hypertension was within 25–50%. ABPM was carried out using the apparatus «ABM- 04» («Meditech», Hungary), which was activated by a standard protocol every 15 minutes during a day (6 a.m.–10 p.m.) and every 30 minutes at night (10 p.m.– 6 a.m.). The indices determined dur-

ing the study included: the mean ambulatory SBP and DBP during the 24-hour period, BP load and BP dipping. The levels of TXB₂ and 6-PGF1α in serum were investigated by ELISA (reagents company «ENZO LIFE SCIENCES», Germany).

Results

Table 1 shows the distribution of surveyed children by age, sex and ABPM results.

According to the data in Table 2, children with PAH noted higher levels of TXB₂ compared to the children of the control group. The average 6-PGF1α values did not differ significantly between the main groups and the control group. The distribution by sex showed higher TXB₂ levels in the boys with hypertension compared to the girls (Table 3). The TXB₂ level in the girls with stable PAH did not differ from that of the control group whereas the boys' TXB₂ level exceeded the control group levels by almost 6 times. 6-PGF1α levels in the girls grew with hypertension stabilization (Table 3) while in the boys it did not change. Accordingly, the ratio of TXB₂/6-PGF1α in the boys with a stable and labile hypertension significantly exceeded the data in the control group. The girls, on the contrary, were characterized

by a downward trend compared to the control group because of higher levels of 6-PHF1α. Thus, a significant difference in the ratio of endothelial vasodilation and vasoconstriction factors based on gender was found in children. There is no adequate compensatory increase of 6-PGF1α in boys with the stabilization of hypertension and increased TXB₂ levels, which leads to higher blood pressure in boys and more frequent occurrence of hypertension stabilization.

Discussion

Endothelial vasoconstriction factors in girls are less involved in the pathogenesis of hypertension and the increased blood pressure is accompanied by the increased levels of vasodilation factors (prostacyclin in this case) which prevents the progression of the endothelial dysfunction. We identified similar patterns with those obtained in adult women. It was found that thromboxane levels significantly increased in conditions with hypoestrogenemia and that estrogens have a significant protective role in reducing thromboxane and normalization of the prostacyclin/thromboxane value in women with normal blood pressure and hypertensive [14,15]. Thus, the studies confirm the role of the

Table 1. General characteristics surveyed children and ABPM results

Groups	Gender, number	Age, years	SBP, mm Hg	DBP, mm Hg	SBP load, %	DBP load, %	SBP dipping, %	DBP dipping, %
1. Stable PAH	Boys, n = 21	14.67 ±0.34	143.55 ±1.44***	75.45 ±1.60***	79.80 ±3.0***	31.39 ±5.20***	2.27 ±1.24**	7.39 ±1.96**
	Girls, n = 11	14.45 ±0.74	134.27 ±1.34#***	73.64 ±1.45***	74.88 ±4.22***	33.31 ±5.63***	6.14 ±1.63	14.39 ±1.84
2. Labile PAH	Boys, n = 10	12.6 ±0.56	126.6 ±1.74***	69.1 ±1.88***	36.40 ±3.27***	17.38 ±3.48***	3.28 ±2.88***	8.2 ±3.09
	Girls, n = 22	13.52 ±0.49	120.49 ±0.93#***	66.0 ±0.88***	29.21 ±1.82***	10.58 ±1.55	4.41 ±1.20***	11.36 ±1.95
3. The control group	Boys, n = 11	12.36 ±0.75	105.37 ±2.33	62.19 ±1.09	4.60 ±1.39	2.54 ±1.14	9.80 ±0.84	16.48 ±2.85
	Girls, n = 10	14.22 ±0.63	105.40 ±3.40	59.40 ±2.61	5.09 ±1.76	5.98 ±2.61	9.86 ±1.05	15.33 ±3.11

Note: * p < 0.05 between first and second groups; ** p < 0.05 between first and control groups; *** p < 0.05 between second and control groups; # < 0.05 between boys and girls in groups.

Table 2. TXB₂ and 6-PGF1α in serum of children with various forms of PAH

Groups	TXB ₂ , ng/ml	6-PGF1α, ng/ml
1. Stable PAH, n = 32	18.56 ±4.53*	2.58 ±0.25
2. Labile PAH, n = 32	16.95 ±4.07**	2.69 ±0.22
3. The control group, n = 21	4.42 ±0.62	2.20 ±0.20

Note: * p < 0.05 between first and control groups; ** p < 0.05 between second and control groups.

Table 3. TXB₂, 6-PGF1α and their correlation in serum in children with different forms of PAH depending on gender

Groups	Gender, number	TXB ₂ , ng/ml	6-PGF1α, ng/ml	TXB ₂ /6-PGF1α
1. Stable PAH	Boys, n = 21	25.05 ±6.43*	2.17 ±0.23	12.90 ±3.60*
	Girls, n = 11	5.57 ±0.98#	3.41 ±0.52*:#	1.70 ±0.32#
2. Labile PAH	Boys, n = 10	27.26 ±11.26**	2.79 ±0.45	14.11 ±5.45**
	Girls, n = 22	11.06 ±1.79**	2.63 ±0.25**	4.31 ±0.55
3. The control group	Boys, n = 11	4.10 ±0.64	2.52 ±0.36	1.66 ±0.29
	Girls, n = 10	4.69 ±1.11	1.92 ±0.17	2.90 ±0.82

Note: * p < 0.05 between first and control groups; ** p < 0.05 between second and control groups; # < 0.05 between boys and girls in groups.



imbalance between endothelial vasodilatation and vasoconstriction factors in the stabilization of arterial hypertension in children, mainly, due to the increased thromboxane levels. These changes are more visible in boys. The data is promising for finding the therapeutic agents that can effectively influence the balance between thromboxane and prostacyclin and contribute to more successful treatment outcomes in children with PAH.

Conclusions

Violation of the ratio between endothelial vasoconstriction (thromboxane) and vasodilatation (prostacyclin) factors in boys with PAH is due to increase of

TXB₂ level compared with children with normal blood pressure ($p < 0.05$).

Girls with PAH have better compensatory vasodilation opportunities compared with boys according to increased prostacyclin production. That prevents the progression of endothelial dysfunction and allows PAH stabilization in girls.

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The conflict of interests

The authors do not report any conflicts of interests.

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