Anna Niemirska[1], Jacek Michałkiewicz[2], *Mieczysław Litwin[1]

Accelerated maturation of peripheral blood lymphocytes in children with primary hypertension**

Przyspieszone dojrzewanie limfocytów krwi obwodowej u dzieci z pierwotnym nadciśnieniem tętniczym

[1]Department of Nephrology and Arterial Hypertension, The Children's Memorial Health Institute, Warszawa
[2]Department of Microbiology and Immunology, The Children's Memorial Health Institute, Warszawa

Keywords

children, primary hypertension, target organ damage, immune system, immunosenescence

Słowa kluczowe

dzieci, nadciśnienie tętnicze pierwotne, uszkodzenie narządowe, układ immunologiczny, starzenie układu immunologicznego

S u m m a r y

Introduction. Primary hypertension (PH) is associated with immune activation. The isoforms of leucocyte common antigen (CD45) in the CD4 and CD8 T cell subsets are markers of T cells status. Naive cells express the RA^+ isoform and memory cells express the RO^+ isoform. The profile of CD45 isoforms may serve as the marker of T cells functional status and senescence.

Aim. Analysis of distribution of T lymphocytes bearing $CD45RA^+$ (naive) and $CD45RO^+$ (memory) markers and their relationship with hypertension severity and target organ damage (TOD).

Material and methods. 68 children with PH (15.6 ± 2 years, 59 boys) and control group of 26 (14.8 ± 3.7 years, 19 boys) children. The expression of $CD45RA^+$ and $CD45RO^+$ isoforms in the CD4 and CD8 T cell subset was evaluated by flow cytometry technique.

Results. Hypertensive children had greater intensity and percentage of $CD45RO^+$CD4 and CD8 T lymphocytes and lower RA^+/RO^+ ratio of CD4 and CD8 lymphocytes than controls. T lymphocytes markers expression did not correlate with carotid intima-media-thickness. Children with left ventricular hypertrophy had less $CD45RA^+$CD4 T cells, more $CD45RO^+$ CD4 T cells and lower ratio of RA^+/RO^+CD4 cells than PH children with normal left ventricular mass index. The percentage of $CD45RA^+$CD8 T cells decreased with increasing blood pressure status from prehypertension, ambulatory hypertension to severe ambulatory hypertension.

Conclusions. PH children had less naive T lymphocytes and more T cells with 'memory phenotype'. These alterations correlated with hypertension severity and TOD.

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

Wstęp. Nadciśnienie tętnicze pierwotne (NTP) związane jest ze zmianami fenotypu i funkcji limfocytów T. Status limfocytów T można określić poprzez ocenę ekspresji izoform powszechnego antygenu leukocytarnego (CD45 Ag) w limfocytach T CD4+ lub CD8+. Limfocyty T $CD45RA^+$ to tzw. komórki „naiwne", a limfocyty T $CD45RO^+$ i z ekspresją cząsteczek adhezyjnych to komórki „pamięci immunologicznej".

Cel pracy. Wykazanie czy u dzieci z NTP dochodzi do zmian subpopulacji limfocytów T i czy koreluje to z wysokością ciśnienia tętniczego i uszkodzeniem narządowym.

Materiał i metody. 68 dzieci z nieleczonym NTP (śr. 15,6 ± 2 lat; 59 chłopców) i 26 dzieci z prawidłowym ciśnieniem tętniczym (śr. 14,8 ± 3,7 roku; 19 chłopców). Izoformy $CD45RA^+$ i $CD45RO^+$ na limfocytach T oceniono techniką cytometrii przepływowej.

Wyniki. Dzieci z NTP miały większą intensywność i więcej limfocytów CD4 i CD8 $CD45RO^+$ w porównaniu do grupy kontrolnej. Stosunek RA^+/RO^+ na limfocytach CD4 i CD8 był mniejszy w porównaniu z grupą kontrolną. Ekspresja RA^+ i RO^+ nie korelowała z grubością kompleksu błona środkowa – błona wewnętrzna t. szyjnej wspólnej, ale pacjenci z NTP i przerostem lewej komory serca mieli mniej limfocytów CD4 $CD45RA^+$, więcej limfocytów $CD45RO^+$ i mniejszy stosunek RA^+/RO^+ w porównaniu do pacjentów z NTP i prawidłową masą lewej komory serca. Odsetek limfocytów CD8 $CD45RA^+$ zmniejszał się

Address/adres:

*Mieczysław Litwin
Department of Nephrology
and Arterial Hypertension
The Children's Memorial Health Institute
Aleja Dzieci Polskich 20, 04-730 Warszawa
tel. +48 (22) 815-15-40,
fax +48 (22) 815-15-39
m.litwin@ipczd.pl

**Authors were supported by grant 2013/11/B/NZ4/03832 funded by National Research Centre.

ze zmianą statusu ciśnienia tętniczego od stanu przednadciśnieniowego, przez ambulatoryjne nadciśnienie tętnicze do ciężkiego nadciśnienia ambulatoryjnego.

Wnioski. Pacjenci z NTP mieli więcej dojrzałych limfocytów T CD4 i CD8 (o fenotypie komórek pamięci) oraz mniej limfocytów nieaktywnych (naiwnych). Te zaburzenia były związane z ciężkością nadciśnienia i uszkodzeniem narządowym.

INTRODUCTION

There is an increasing amount of data indicating that primary hypertension (PH) is not only a hemodynamic phenomenon but also a complex syndrome involving abnormal fat tissue distribution, over-activity of the sympathetic nervous system, metabolic abnormalities and activation of the immune system. It has been also reported that accelerated ageing of the immune system may play a role in the pathogenesis of hypertension and atherosclerosis in adults, with the special role of the innate and adaptive immune responses (1, 2). Immune system maturation and ageing is associated with increased populations of memory lymphocytes with highly diverse repertoire of antigenic specificity that enables their wide reactivity against both foreign and auto-antigens possibly including the vascular ones. The role of these cells in the PH pathogenesis is still obscure, especially in humans.

AIM

The aim of our study was to find out if the PH children differ from controls in terms of their CD4 and CD8 T cells 'naive' and 'memory' subsets distribution and if these changes correlate with target organ damage (TOD) or hypertension severity.

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.

68 pts (mean age: 15.6 ± 2 years; 59 boys) with newly diagnosed and untreated PH, who underwent full diagnostic approach to exclude secondary hypertension, were included to the study. The exclusion criteria were: the presence of any significant chronic disease (except for PH) including diabetes mellitus, chronic kidney disease, chronic inflammatory disorders, any acute illness including infections in the 6 weeks preceding enrolment, and incomplete data. The control group consisted of 26 (19 boys) normotensive children in mean age 14.8 ± 3.7.

PH was diagnosed according to The Fourth Task Force Report and European Society of Hypertension guidelines and confirmed by 24-hour ambulatory blood pressure monitoring (ABPM) (3-5). Blood pressure status was defined according to the ABPM classification (5, 6). Hypertensive TOD (intima-media thickness of carotid arteries and left ventricular hypertrophy) and metabolic risk profile were assessed in PH group.

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 ≥ 80% of readings were considered as valid and were included to the analysis. We used a recently published classification system based on ABPM to classify patients as having normal blood pressure, ambulatory hypertension and severe ambulatory hypertension (5, 6).

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 (7). To standardize the left ventricular mass to height, left ventricular mass index (LVMI) was calculated according to the de Simone formula (8). Left ventricular hypertrophy (LVH) was defined as a LVMI value above the 95th percentile for age- and sex-based on reference data (9).

Carotid-intima media thickness (cIMT) measurements

cIMT was evaluated by ultrasound, and SD of normal values for cIMT was obtained according to the methodology described previously (10, 11).

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.

Evaluation of lymphocyte subsets by flow cytometry

The distribution of $CD45RA^+$ and $CD45RO^+$ isoforms of CD45 common leukocyte antigen in the CD4 and CD8 T cell subsets was determined by conventional three-color direct immuno-fluorescence. The samples of heparinized whole blood (50 ul) were stained for 30 min at room temperature with fluorescein (FITC), phycoerythrin (PE) and R phycoerythrycyanin 5.1 (PC5) conjugated mouse-anti-human monoclonal antibodies (mAbs). After staining, the samples were exposed to lysing solution (OptiLyse C, Beckman-Coulter), then washed and resuspended in PBS containing 2% of FCS and 0.1% sodium azide. The lymphocyte popu-

lation was gated according to the forward-and side scatter light profile. Fluorescence was measured with a Beckman-Coulter FC-500 flow cytometer. Measurements were made on the FL1-channel (FITC-conjugated mAbs), the Fl-2 channel (PE-conjugated mAbs) and the PC5 mAbs (Fl-4 channel). The gates were adjusted into the appropriate negative control quadrant. A total of 10.000 events was collected. The FITC, PE and PC-5 conjugated mAbs were used in the following combinations, respectively: 1) CD4/CD8/CD3 and CD3/CD56/CD19 (for estimation of the basic lymphocyte subsets distribution), 2) $CD45RA^+CD4$ or CD8, and $CD45RO^+CD4$ or CD8, in combination with CD3 (for evaluation of $CD45RA^+$ and $CD45RO^+$ isoforms expression in the CD4 and CD8 T cell subsets). Simultest Leuco-Gate (CD45-FITC/CD14-PE) as well as gamma-FITC, gamma-PE and gamma-PC5 (Simultest control) were included in each staining panel. The fluorescence intensity (FI) was calculated as a relative mean channel fluorescence (RFI) for each surface molecule as described previously (12, 13).

Statistical analysis

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 were 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

In children with newly diagnosed primary hypertension, after full diagnostic procedures, white coat hypertension/prehypertension was diagnosed in 13 pts, ambulatory hypertension in 30 pts and severe ambulatory hypertension in 25 patients. PH children and normotensive controls did not differ regarding age and gender distribution. PH children presented greater intensity (7.6 ± 3.8 vs 5.4 ± 1.2; $p = 0.0001$) and greater percentage of $CD45RO^+$ CD4 lymphocytes in comparison with normotensive children (tab. 1). Similarly, CD8 lymphocytes of PH patients presented greater percentage of $CD45RO^+$ cells (25.0 ± 9.1 vs 19.4 ± 6.9; $p = 0.008$) than controls. $CD45RA^+/RO^+$ ratio of CD4 and CD8 lymphocytes was lower in PH group (tab. 1). There were no correlations between the expression of these markers on lymphocytes and cIMT. However, PH children with LVH ($n = 14$) had lower percentage of $CD45RA^+$ CD4 cells (48.8 ± 9.9), greater percentage of $CD45RO^+$ CD4 cells (33 ± 5.6) and lower ratio of $CD45RA^+/RO^+$ CD4 cells (2.0 ± 0.7) in comparison with PH children with normal LVMI ($n = 54$) (55.2 ± 10, $p = 0.04$; 28.0 ± 6.6, $p = 0.019$; 2.6 ± 0.5, $p = 0.025$; respectively) (fig. 1 and 2). Further analysis revealed that percentage of $CD45RA^+$ CD8 cells steadily decreased from white coat hypertension (80.6 ± 7.3), ambulatory prehypertension (74.4 ± 10.7) to ambulatory hypertension (74.9 ± 8) and severe ambulatory hypertension (73.3 ± 10) and there was significant difference between patients with white coat hypertension and severe ambulatory hypertension ($p < 0.024$) (fig. 3).

Table 1. $CD45RO^+$ isoform expression in CD4+ and CD8+ T cells in the PH children and healthy controls.

	Primary hypertension (N = 68)	Normotensive controls (N = 26)	P
$CD45\ RO^+$ CD4 (%)	43.6 ± 10.2	38.6 ± 9.9	$p = 0.04$
$CD45\ RO^+$ CD8 (%)	25.0 ± 9.1	19.4 ± 6.9	$p = 0.008$
$CD45RA^+/RO^+$ CD4 ratio	1.3 ± 0.5	1.6 ± 0.8	$p = 0.04$
$CD45\ RA^+/RO^+$ CD8 ratio	3.6 ± 2	4.6 ± 1.7	$p = 0.03$

DISCUSSION

In our study we found that children with PH presented changes in the peripheral blood T lymphocytes activation status with decreased population of naive (non-activated) T lymphocytes and increased subset of T cells with 'memory phenotype' both in the CD4 and CD8 T cell populations. Moreover, these alterations (up-regulation of $CD45RO^+$ expression) were associated with hypertension severity and hypertensive target organ damage.

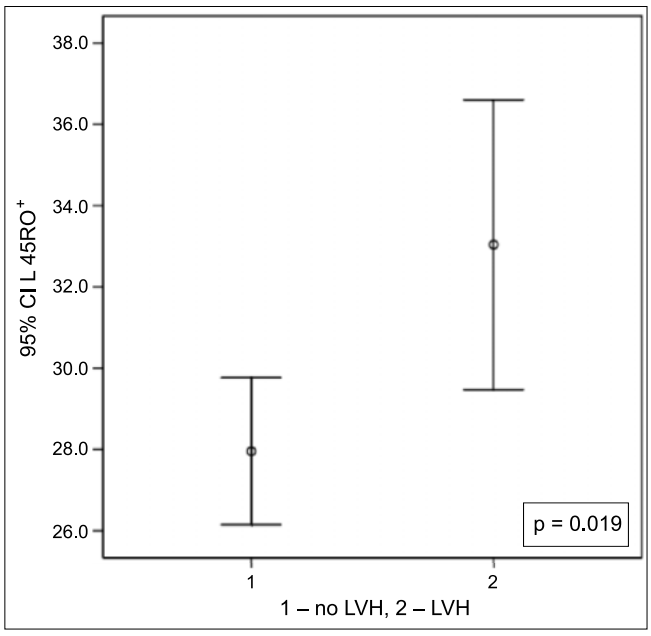

Fig. 1. The comparison of $CD45RO^+$ expression betwen PH patients with and without left ventricular hypertrophy.
LVH – left ventricular hypertrophy, no LVH – normal left ventricular mass, CI – confidence interval, L $45RO^+$ – CD8 T lymphocytes bearing RO^+ antigen

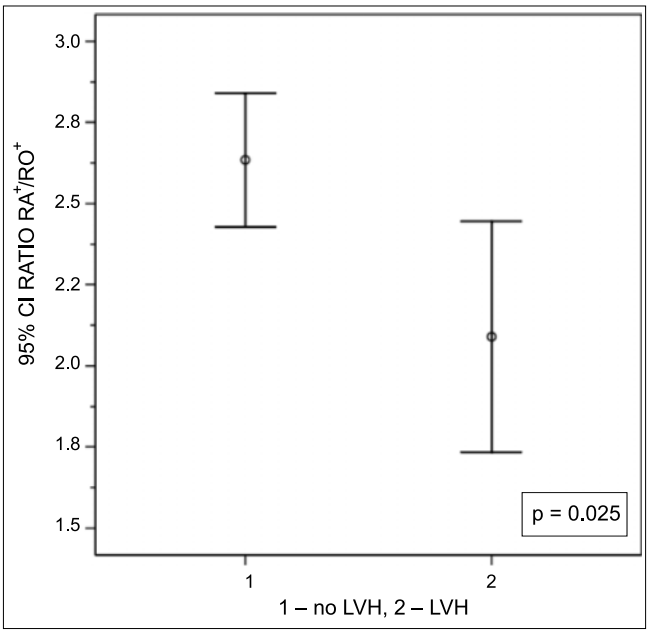

Fig. 2. The comparison of $CD45RA^+/RO^+$ expression between PH patients with and without left ventricular hypertrophy.
LVH – left ventricular hypertrophy, no LVH – normal left ventricular mass, CI – confidence intervale, RA^+/RO^+ – ratio of CD4 T lymphocytes bearing RO^+ and RA^+ antigens

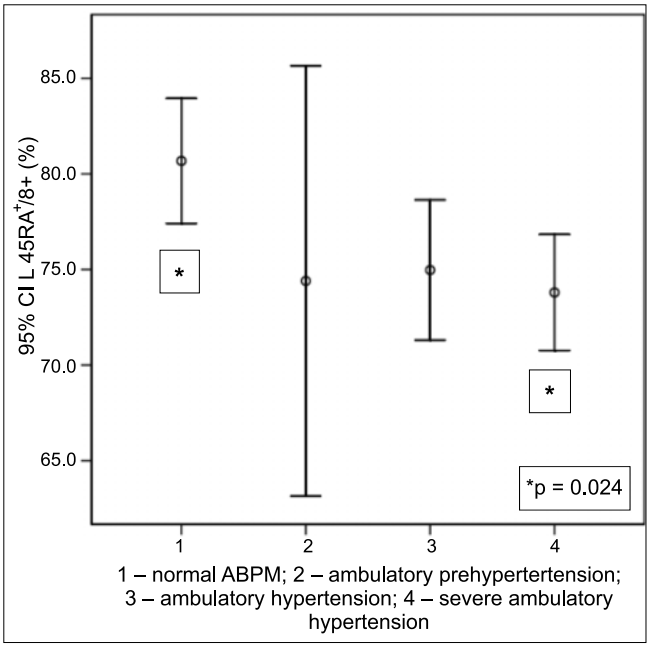

Fig. 3. The comparison of RA^+ expression between patients with different blood pressure status.
ABPM – 24 hour ambulatory blood pressure measurement, CI – confidence interval, L $45RA^+/8+$ – CD8 T lymphocytes bearing RA^+ antigen

Despite the fact, that traditionally only atherosclerosis has been considered as an inflammatory disease, an increasing number of evidence suggests that inflammation and activation of immune system also contribute to hypertension and cardiovascular disease (14-16). Recently, a large number of data from experimental studies indicated the immunological origin of PH, however there are still relatively few reports from clinical studies, especially involving children (17-19).

The estimation of immune system in adults with cardiovascular disease revealed an increased serum concentration of many inflammatory mediators such as acute phase proteins, cytokines, chemokines, adipokines, metalloproteinases, collagen degradation products, oxidative stress markers, and many others (20). Also the analysis of the immune profile of hypertensive children revealed that immune activation occurs already at the early stages of PH (21, 22). In our previous study we found that children with PH presented an increased activation of the immune system with the increased serum concentration of highly sensitive C reactive protein (hsCRP) and chemokines (RANTES, MIP1β), correlated with metabolic parameters, oxidative stress and hypertensive TOD (23, 24). In the present study, the number of more activated T lymphocytes was greater in PH children, than in healthy controls.

Despite the fact, that the activation of both innate and adaptive immune system plays a role in the pathogenesis of PH, it is known that the innate immune system can be non-specifically activated by metabolic or hemodynamic factors, and the activation of the adaptive T-cell-dependent system is essential for maintaining hypertension and development of cardiovascular disease (17, 25-28). In our study we assessed homogenous group of children, with newly diagnosed PH, without any additional cardiovascular risk factors and concomitant chronic diseases usually present in adults. Moreover, we excluded patients with any acute or chronic systemic or local inflammatory process, what indicate that the activation of immune system and the expansion of senescent T lymphocytes in our patients is the intimate consequence of PH.

The pathogenic role of T cells in hypertension has been established mainly in experimental studies (29-32). It was documented that an intact thymus was necessary for maintaining elevated blood pressure, and that the athymic mice did not develop hypertension (31, 33). Guzik et al. found that mature T and B cell knockout mice are protected from angiotensin II or salt-induced hypertension and that the experimental transfer of T cells induce hypertension (29, 34). Interestingly, the role of thymus-derived lymphocytes was not demonstrated at the early stages of cardiovascular disease, however, in the advanced stages of experimental hypertension, the presence of intact thymus was related to more advanced degenerative changes within the cardiovascular system (33). Similarly, an enhanced risk of cardiac and arterial injury was found especially in elderly patients with chronic inflammatory diseases, what suggests that age-related immune changes play a role in the pathogenesis of cardiovascular diseases (28, 35).

These age-related changes of the immune system, are commonly termed 'immunosenescence' and affect both the innate and adaptive immune systems. However, the most important changes are observed in T cell immunity and include thymic involution, and an imbalance of T cell populations with the domination of more activated and senescent T cells. Recent studies have shown that adults with PH presented a higher number

of circulating lymphocytes with markers of ageing compared to normotensive controls (36-38). In our study we found that disturbed immune profile with the increased number of more mature and more activated T lymphocytes is observed already in children with PH. Hypertensive children presented greater percentage of CD4 and CD8 lymphocytes with $45RO^+$ antigens and lower ratio of RA^+/RO^+ cells, compared to normotensive, healthy children. This accumulation of $CD45RO^+$ T cells has been considered as one of the prominent marker associated with ageing and a hallmark of immunosenescence. These results follow our previous data, where we found that patients with PH presented an accelerated tempo of growth with metabolic, immunological and arterial alterations, suggesting the premature ageing of cardiovascular system in the early phases of hypertension (39). In the present study, we found that the alterations of the immune system and the quantity of senescent T cells were greater in patients with TOD and higher blood pressure. We observed the greater percentage of more mature and more activated lymphocytes with the phenotype of $CD45RO^+$ antigens in children with LVH, and steadily decreasing of $CD45RA^+$ markers from normal blood pressure, through prehypertension, ambulatory hypertension to severe ambulatory hypertension. These observations give us an additional evidence that the premature ageing of the immune system is present at the early stages of primary hypertension and is related to the progression of cardiovascular disease. These immunological determinants of hypertensive organ injury and the immune and hemodynamic ageing of cardiovascular system leads to the question if there are any possibilities to interrupt the cardiovascular senescence or even rejuvenate cardiovascular system. Although there are some data indicating that immunosuppressive treatment prevent development of hypertension, the role of traditional pharmacological and nonpharmacological antihypertensive therapy in the immunological basis of PH, should be discussed and analysed (40-43).

CONCLUSIONS

Our preliminary data indicate that untreated adolescents with PH presented changes in the peripheral blood T lymphocytes activation status with increased subset of T lymphocytes with 'memory phenotype', what indirectly indicates on the senescence of the immune system. These alterations are associated with hypertension severity and hypertensive target organ damage, what gives an additional information about the pathogenesis of cardiovascular disease in its early phase and confirmed that primary hypertension is not a simple hemodynamic syndrome, but a complex immuno-metabolic phenomenon. Thus, the further investigation of the role of immunosenescence in the pathogenesis of hypertension and the possibilities of the rejuvenation of cardiovascular system, is desirable.

BIBLIOGRAPHY

1. Abais-Battad JM, Rudemiller NP, Mattson DL: Hypertension and immunity: mechanisms of T cell activation and pathways of hypertension. Curr Opin Nephrol Hypertens 2015; 24: 470-474.
2. Rodríguez-Iturbe B, Pons H, Quiroz Y et al.: The immunological basis of hypertension. Am J Hypertens 2014; 27: 1327-1337.
3. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on diagnosis, evaluation and treatment of high blood pressure in children and adolescents. Pediatrics 2004; 114: 555-576.
4. Lurbe E, Cifkova R, Cruickshank JK et al.: European Society of Hypertension. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. J Hypertens 2009; 27: 1719-1742.
5. Urbina E, Alpert B, Flynn J et al.: American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee. Ambulatory blood pressure monitoring in children and adolescents: recommendations for standard assessment: a scientific statement from the American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young and the Council for High Blood Pressure Research. Hypertension 2008; 52: 433-451.
6. Flynn JT, Daniels SR, Hayman LL et al.: American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. Hypertension 2014; 63: 1116-1135.
7. Nagueh SF, Appleton CP, Gillebert TC et al.: Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009; 22: 107-133.
8. De Simone G, Deveraux RB, Daniels SR et al.: Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. J Am Coll Cardiol 1995; 25: 1056-1062.
9. Khoury PR, Mitsnefes M, Daniels SR et al.: Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr 2009; 22: 709-714.
10. Jourdan C, Wuhl E, Litwin M et al.: Normative values of intima-media thickness and distensibility of large arteries in healthy adolescents. J Hypertens 2005; 23: 1707-1715.
11. Doyon A, Kracht D, Bayazit AK et al.: 4C Study Consortium. Carotid artery intima-media thickness and distensibility in children and adolescents: reference values and role of body dimensions. Hypertension 2013; 62: 550-556.
12. Motkowski R, Michałkiewicz J, Mikołuć B et al.: Peripheral blond T lymphocyte subsets in children with congenital asplenia. Human Immunology 2012; 7(3): 1091-1097.
13. Michałkiewicz J, Barth C, Weemaes C et al.: Abnormalities in the T and NK lymphocyte phenotype in patients with Nijmegen breakage syndrome. Clin Exp Immunol 2003; 134: 482-490.
14. Lee VW, Wang Y, Harris DC: The role of the immune system in the pathogenesis of hypertension. Curr Hypertens Rev 2013; 9: 76-84.
15. Libby P, Ridker PM, Maseri A: Inflammation and atherosclerosis. Circulation 2002; 105: 1135-1143.
16. Ammirati E, Cianflone D, Vecchio V et al.: Effector memory T cells are associated with atherosclerosis in humans and animal models. J Am Heart Assoc 2012; 1: 27-41.
17. Harrison DG, Guzik TJ, Lob HE et al.: Inflammation, immunity and hypertension. Hypertension 2011; 57: 132-140.
18. Verlohren S, Muller DN, Luft FC et al.: Immunology in hypertension, preeclampsia, and target-organ damage. Hypertension 2009; 54: 439-443.
19. Litwin M, Feber J, Niemirska A et al.: Primary hypertension is a disease of premature vascular aging associated with neuro-immuno-metabolic abnormalities. Pediatr Nephrol 2015 Feb 28 [Epub ahead of print].
20. Chae CU, Lee RT, Rifai N et al.: Blood pressure and inflammation in apparently healthy man. Hypertension 2001; 38: 399-403.
21. Lande MB, Pearson TA, Vermilion RP et al.: Elevated blood pressure, race/ethnicity, and C-reactive protein levels in children and adolescents. Pediatrics 2008; 122: 1252-1257.
22. Litwin M, Michalkiewicz J, Niemirska A et al.: Inflammatory activation in children with primary hypertension. Pediatr Nephrol 2010; 25: 2489-2499.
23. Litwin M, Michalkiewicz J, Trojanek J et al.: Altered genes profile of renin-angiotensin system, immune system, and adipokines receptors in leukocytes of children with primary hypertension. Hypertension 2013; 61(2): 431-436.

24. Litwin M, Michałkiewicz J, Gackowska L: Primary hypertension in children and adolescents is an immuno-metabolic disease with hemodynamic consequences. Curr Hypertens Rep 2013; 15: 331-339.
25. Harrison DG, Vinch A, Lob H et al.: Role of adaptive immune system in hypertension. Curr Opin Pharmacol 2010; 10: 203-207.
26. Jurewicz M, McDermott DH, Sechler JM et al.: Human T and natural killer cells possess a functional renin-angiotensin system: further mechanisms of angiotensin induced inflammation. J Am Soc Nephrol 2007; 18: 1093-1102.
27. Hoch NE, Guzik TJ, Chen W et al.: Regulation of T cell function by endogenously produced angiotensin II. Am J Physiol Regul Integr Comp Physiol 2009; 296: 208-216.
28. Youn J-C, Yu HT, Lim BJ et al.: Immunosenescent CD8? T cells and CXC chemokine receptor type 3 chemokines are increased in human hypertension. Hypertension 2013; 62: 126-133.
29. Guzik TJ, Hoch NE, Brown KA et al.: Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med 2007; 204: 2449-2460.
30. Vinh A, Chen W, Blinder Y et al.: Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. Circulation 2010; 122: 2529-2537.
31. Svendsen UG: Spontaneous hypertension and hypertensive vascular disease in the NZB strain of mice. Acta Pathol Microbiol Scand A 1977; 85: 548-554.
32. Barhoumi T, Kasal DA, Li MW et al.: T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. Hypertension 2011; 57: 469-476.
33. Svendsen UG: The role of thymus for the development and prognosis of hypertension and hypertensive vascular disease in mice following renal infarction. Acta Pathol Microbiol Scand A 1976; 84: 235-243.
34. Marvar PJ, Thabet SR, Guzik TJ et al.: Central and peripheral mechanisms of T-lymphocyte activation and vascular inflammation produced by angiotensin II-induced hypertension. Circ Res 2010; 107: 263-270.
35. Madhur MS, Harrison DG: Senescent T cells and hypertension new ideas about old cells. Hypertension 2013; 62: 13-15.
36. Park S, Youn J-C, Yu HT et al.: Immunosenescent CD8+ T cells and CXCR3 Chemokines Are Increased in Human Hypertension. Hypertension 2013, 62: 126-133.
37. Yu HT, Park S, Shin EC et al.: T cell senescence and cardiovascular diseases. Clin Exp Med 2015 Jul 19 [Epub ahead of print].
38. Weng NP, Akbar AN, Goronzy J: CD28(−) T cells: their role in the age-associated decline of immune function. Trends Immunol 2009; 30: 306-312.
39. Pludowski P, Litwin M, Niemirska A et al.: Accelerated skeletal maturation in children with primary hypertension. Hypertension 2009; 54: 1234-1239.
40. Bravo Y, Quiroz Y, Ferrebuz A et al.: Mycophenolate mofetil administration reduces renal inflammation, oxidative stress, and arterial pressure in rats with lead induced hypertension. Am J Physiol Renal Physiol 2007; 293: 616-623.
41. Herrera J, Ferrebuz A, MacGregor EG et al.: Mycophenolate mofetil treatment improves hypertension in patients with psoriasis and rheumatoid arthritis. J Am Soc Nephrol 2007; 17: 218-225.
42. Baradaran A, Nasri H, Rafieian-Kopaei M: Oxidative stress and hypertension: Possibility of hypertension therapy with antioxidants. J Res Med 2014; 19: 358-367.
43. Benicky J, Sanchez-Lemus E, Pavel J et al.: Anti-inflammatory effects of angiotensin receptor blockers in the brain and the periphery. Cell Moll Neurobiol 2009; 29: 781-792.

received/otrzymano: 08.09.2015
accepted/zaakceptowano: 30.09.2015