Ph.D. Thesis

ASSESSMENT OF INFLUENCING FACTORS IN THE DEVELOPMENT OF

TARGET-ORGAN DAMAGES IN ADOLESCENCE

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I. Introduction and study aims

Although clinical symptoms of hypertension usually get manifested in adulthood only, the clinical picture of hypertension may already develop frequently in the adolescence and target-organ damages may also be demonstrated in this age group. The prevalence of adolescent hypertension is not too high – it accounts for 1-3% according to epidemiological studies – early diagnosis and appropriate treatment is of high importance. It is proven that blood pressure values as measured in adolescent persons are predictive for development of adult hypertension.

Beside cardiovascular system, secondary target organ damages of the cerebral vasculature are the most important when considering appropriate prevention and effective treatment of progression of them. It is clear from previous studies that hypertension results in atherosclerotic lesion of the large cerebral vessels and additionally it causes function disturbance at the level of the cerebral arterioles. A good marker for developing atherosclerosis in the large cerebral arteries is the intima-media thickness of the carotid arteries. It is also proven that thickening of the intima-media layer shows a good correlation with severity of hypertension and other cardiovascular risk factors.

Beside atherosclerotic lesions of the large cerebral arteries, a function disturbance of the cerebral arterioles has been shown in adult hypertension. It is conceivable that the increased wall-lumen ratio, as well as the altered endothelium-dependent relaxation are responsible for these changes of cerebrovascular reactivity. Previous vasoreactivity tests proved that altered cerebral arteriolal function in hypertension may be normalized by an appropriate antihypertensive treatment.

The causative role of the endothel dysfunction and the imbalance between nitric oxide (NO) and endothelin system in the development of hypertension has been

known already for decades. After a thorough search, we where unable to find any previous studies aiming to assess the role of the NO/endothelin system in the development of adolescent hypertension. As stated before, adult hypertension results in increase of the intima-media thickness of the carotid arteries and cerebral arterial function is also altered in adult hypertension. However, before starting our investigations, no results were available about this question in adolescent hypertensives. Similar to this, previously debated results were published regarding the role of the ACE-gene DD genotype in the development of hypertension and target organ damages, such as left ventricular hypertrophy and intima-media thickness.

It was proven previously by our study group that thickening of the intima-media layer and increase of the left ventricular mass may be demonstrated already in adolescent hypertensives. In the further studies we aimed to assess whether the factors known playing causative role in the development of adult hypertension and its target organ damages are of importance in adolescent hypertension as well.

We intended to answer the following study questions:

1. What is the plasma concentration of NOx and endothelin-1 (ET-1) in adolescent hypertension? Is there any correlation between plasma concentrations of NOx and ET-1? Is there any correlation between blood pressures as measured in adolescence and plasma concentrations of NOx as well as ET-1?

2. What factors are playing a role in the development of target-organ damages (such as intima-media thickening and left ventricular mass index)? Is there a role of NOx and ET-1?

3. What is the resting cerebral blood flow velocity of the adolescent hypertensives as compared to healthy teenagers? How is the cerebrovascular reactivity against vasoconstrictor and vasodilator stimuli changes in adolescent hypertensives?

4. Is there any relationship between endothelial factors and resting cerebral blood flow velocity in teenagers? How NO/ET-1 imbalance influences cerebrovascular reactivity against vasoconstrictor and vasodilator stimuli?

5. Can we detect any relationship between ACE gene polymorphism and severity of target-organ damages in adolescent hypertension?

II. PATIENTS AND METHODS

1. Patients

A. Adolescents participating in „Debrecen Hypertension Study"

Previously an epidemiological study has been performed and published which aimed to define the prevalence of adolescent hypertension among all secondary school students of Debrecen. From the overall number of 26 secondary schools finally 10359 adolescents aged between 15-18 were included, among them the results of 10194 teenagers could be taken into account for final analysis.

B. Selection of patients for the thesis

a. Hypertension group: Hypertension was proved when the results of 3x3 casual blood pressure measurements were above the 95th percentile of the average systolic and diastolic blood pressures as measured in the whole study group. Of the remaining 216 persons those with supposingly secondary hypertension were excluded. After a written informed consent, finally 120 hypertensive adolescents underwent - beside the routine tests - the measurement of intima-media thickness (IMT), the assessment of the left ventricular mass index by echocardiography (LVMI),

and testing of the ACE gene polymorphism. Hypertension was proven among the 120 primary hypertensive adolescents by 24-hour ambulatory blood pressure monitoring (ABPM). ABPM unequocially proved hypertension in cases, among them measurement of the plasma concentration of NOx and endothelin-1 occured in 67 patients. Transcranial Doppler measurement was successfully performed in 61 cases.

b. Control group: There were 8580 adolescents who were diagnosed based on 3 casual blood pressure measurements, of whom both systolic and diastolic blood pressure were below that of the 90th percentile of the age, sex and height-matched values. Randomly selected normotensives were sex- and age-matched to the hypertensive group. Finally, beside routine laboratory parameters, measurement of intima-media thickness, the left ventricular mass index, as well as the plasma concentration of NOx and ET-1 were possible in 58 cases. Among the 58 healthy adolescents, vasoreactivity tests were also performed.

2. Methods

A. Ultrasonic methods

a. Measurement of intima-media thickness (IMT): Measurement of IMT was performed in the common carotid artery, using a 7.5 MHz linear array probe (Hewlett-Packard Sonos 2000 device, USA). After insonating the carotid bifurcation, the septum between the internal and external carotid artery was found first, and IMT was measured at the far wall of the common carotid artery 2 cm proximally from the flow divider. IMT was defined as the distance between the lumen-intima layer and the media-adventitia interface. Measurements were repeated in 3 cases each and averaged values were taken into account for further analysis.

b. Transcranial Doppler measurements: We used DWL- Multidop T (Überlingen, Germany) device for studying intracranial vessels. The 2 MHz-probe was fixed on the temporal bone at the place were the most appropriate acoustic window was found. Blood flow velocities within the middle cerebral arteries were registrated at 50 mm depth. During the TCD measurements systolic, diastolic and mean blood flow velocities as well as pulsatility indices were continously provided by the device.

Assessment of cerebrovascular reactivity: Two sets of vasoreactivity stimuli were used: breath holding (BH) and hyperventilation (HV). Before starting breath holding the procedure was explained by the subjects in detail and thereafter they were asked to hold their breaths for 30 seconds after a normal inspiration. A successful registration was possible in all cases. After a 5-minutes rest, a second transcranial Doppler was performed, followed by voluntary hyperventilation lasting for 60 seconds with an inspiratory frequency of 25-28/minutes. Cerebrovascular reactivity (CVR) after BH and HV was expressed as the percentual change of the middle cerebral artery mean blood flow velocity as compared to resting value.

c. Transthoracic echocardiography: M-mode and bidimensional echocardiography was performed (a 2.0-2.2 MHz- transducer, Hewlett-Packard Sonos 2000 device, HP, USA). Left ventricular mass was measured as suggested previously by Devereux and co-workers: 0.8 X [1.04 X (intraventricular septum + left ventricular end-diastolic diameter + left ventricular end-diastolic posterior wall diameter)^3 - (left ventricular end-diastolic diameter)^3]+ 0.6. Left ventricular mass index (LVMI) was calculated by correcting left ventricular mass on body surface.

B. Laboratory investigations

Blood sampling was performed after a 12-hour fasting period in the morning, using a vacutainer technique (Beckton & Dickinson).

a. Determination of routine laboratory parameters (serum glucose, cholesterin, trigliceride, HDL- and LDL-cholesterin) occured based on the daily used automatic, validated devices.

b. The concentration of endothelin-1 **(**ET-1) in the plasma was measured as follows: The samples were stored on -70ºC until the analysis. For the determination of ET-1 concentration conventionally available kits (Biomedica Group, Vienna, Austria) were used. Concentrations were expressed in fmol/ml.

c. Nitric oxide concentration of the plasma (NOx= NO_2 + NO_3) was determined right after blood sampling using the method of Green and co-workers. The original method was slightly modified by our group, and validation was previously published. The absorption of the samples were measured by spectrophotometer (Hewlett Packard 8453, USA), on 546 nm**.** Plasma NOx concentrations were expressed in µmol/l.

d. Determination of ACE gene polymorphism: We used the method described previously by Huang and co-workers in detail. In brief: this method is based on rapid DNA extraction before PCR test, followed by a sodium-dodecyl-sulphate polyacrylamide gel electrophoresis.

C. Methods of statistical analysis

Statistica for Windows (Statsoft, Tulsa, USA) was used for the analysis. Means and standard deviations are provided for all values. Parametric values were tested by Shapiro-Wilk test, in order to see whether the samples show normal or non-normal distribution. In cases of normal distributed samples ANOVA test was used, while in

cases of non-normally distributed samples a Kruskal-Wallis ANOVA test was used. Non-parametric data were analysed by the chi-square-test. For the assessment of the correlation between intima-media thickness as well as the different laboratory parameters linear regression analysis or Spearman correlation was used.

III. Results

1. Clinical and laboratory characteristics of the subjects

A total of 125 adolescents were assessed, among them 67 hypertensives and 58 were normotensive. There were no differences between average age (16.5±1.1 vs. 16.8±0.7 years), and the gender-distribution (female/male: 28/39 vs. 29/29) of the hypertensive adolescent groups. The height of the hypertensives was 4 cm, weight was 13 kg, and corresponding to this, body mass was more than 3 kg/m^2 higher as compared to normotensives. The blood pressure of hypertensive teenagers was 29/16 mmHg higher as compared to heatlhy teenagers, the difference between the mean arterial pressure was 20 mmHg. Among the cardiovascular risk factors, blood glucose was slightly higher in the hypertensive group, although the absolute values were within the normal range in both groups (5.6±1.5 vs. 4.7±0.6 mmol/l respectively, p<0.001). Serum cholesterol and LDL-cholesterol was found to be higher in the adolescent hypertensive group (4.3±0.9 vs. 3.9±0.6 mmol/l; p=0.01 and 2.4±0.7 vs. 2.1±0.5 mmol/l; p=0.01). When assessing target-organ damages, LVMI in the hypertensive group was higher than that in the control group (107±32.4 vs. 91.1±25.2 g/m^2; p<0.001). A similar finding was present when comparing intima-media thickness among the two groups (0.54±0.11 vs, 0.48±0.1 cm; p<0.001).

2. Plasma concentration of NOx and ET-1 and their relationship with blood pressure

The plasma concentration of NOx in hypertensive adolescents was significantly lower than that measured in the normotensive group (27.7±13.7 μmol/ml vs. 35.8±7.0 μmol/ml; p<0.05). A difference could be demonstrated when assessing serum concentrations among the two sexes (males: p<0.05; females: p<0.01). Serum concentration of endothelin was higher in hypertensive teenagers than that of controls (3.1±3.9 vs. 1.1±1.1; p<0.01).

In the whole group of subjects (hypertensive plus normotensive) we also checked whether a correlation exists between plasma concentrations of NOx and ET-1. A significant negative correlation could be detected between the two parameters (r= -0.29; p=0.003).

Plasma concentrations of NOx negatively, while ET-1 positively correlated with blood pressures. The strongest correlation was found between systolic blood pressure both with NOx (r= -0.25; p=0.004), and ET-1 (r= 0.32; p=0.0007).

3. Assessment of factors influencing target organ damages

Using regression analysis we analyzed whether antropometrical characteristics, blood pressure values, metabolic factors influenced target organ damages. The actual age of the teenagers aged between 15 and 18 years did not have any influence on IMT and LVMI. Both height and weight played a significant role in determining IMT and LVMI. Body weight correlated mainly with IMT (r=0.24, p=0.006), while height with LVMI (r=0.30, p=0.005). Both IMT and LVMI showed the most significant relationship with systolic blood pressure values (IMT: r=0.26,

p=0.002; LVMI: r=0.39, p<0.001). Metabolic parameters were independent of both IMT and LVMI.

We also assessed, whether factors playing a role in endothelial dysfunction (such as NOx and ET-1) do influence IMT and LVMI values. Serum levels of ET-1 and IMT showed a significant positive relationship (r=0.26; p=0.006). Such correlation could not be proved between LVMI and NOx as well as IMT.

4. Assessment of resting cerebral blood flow velocities and cerebrovascular reactivity in adolescents

A series of 61 hypertensive and 45 healthy adolescents were included in the study aiming to assess cerebrovascular reactivity. Clinical and laboratory parameters of the investigated subjects showed the similar pattern as described above: height, weight, serum cholesterol and LDL-cholesterol values were higher in hypertensives as compared to healthy controls.

Resting cerebral blood flow velocities measured in the middle cerebral artery were found to be higher in hypertensive teenagers as compared to normotensives (74.5±22.4 vs. 62.9±15.7; p<0.001). Hypercapnia (BH test) resulted in a significant increase of the blood flow velocities both in hypertensive and healthy adolescents (79.2±24.7 vs. 73.6±21.3; p<0.05), and hyperventilation-evoked hypocapnia led to a decrease in blood flow velocities in both groups (50.4±19.9 vs. 37.2±9.6; p<0.001).

Cerebrovascular reactivity (CVR), the percentual change of the blood flow velocities after BH and HV could not prove any significant difference between the hypertensive and healthy groups.

5. Relationship between endothelial factors and resting cerebral blood flow velocity

Resting cerebral blood flow velocity in the middle cerebral artery and plasma NOx concentrations showed a negative correlation (r=-0.24; p<0.001). In contrast to this, plasma ET-1 concentrations positively correlated with blood flow velocities (r=0.27, p=0.004). No relationship was found between NOx and ET-1 as well as hyper- or hypocapnic cerebrovascular reactivity values.

6. Assessment of the relationship between ACE gene polymorphism and severity of target organ damages in adolescent hypertension

A total of 120 hypertensive and 58 healthy adolescents were studied. Chi-square test showed no significant differences between the distribution of the different genotypes among hypertensives (DD: 23,3%, ID: 47,5% és II: 29,2%) and normotensives (DD: 25,8%, ID: 43,2% és II: 21%).

When analyzing the IMT values within the three different genotypes, ANOVA resulted in the following data DD vs. DI: p=0,25; DD vs. II: p=0,69, DI vs. II: p=0,40. Similar to this, ANOVA indicated no differences between the genotypes when assessing LVMI: DD vs. DI: p=0,55, DD vs. II: p=0,62, DI vs. II: p=0,88. Both IMT and LVMI was independent of ACE genotype in hypertensive teenagers.

IV. Discussion

1. The role of NO and ET-1 in adolescent hypertension

Both endothelin and nitric oxide play a key role in the pathogenesis of primary hypertension. It is clear, that ET-1 isoform of endothelin is responsible for the increased protein synthesis within the vascular smooth muscle, resulting finally in hypertrophy of the vascular wall and vasoconstriction. The other factor in determining

vascular tone is NO, of which the concentration determines the basal tone of both conductance and resistance vessels. Serum concentration of NO increases by advancing wall shear stress, and endothelial dependent vasodilation is affected in primary hypertension.

There are several data available regarding the serum concentrations of NOx and ET-1 in hypertensive patients. The majority of those studies demonstrated the decrease of the circulating level of NO. Most recent data suggested that in the early phase of hypertension the activity of NO-synthase increases, followed by a decrease in NO production. The increase of the concentration circulating ET-1 could not be proved in all studies.

In our series, a decrease of plasma NOx concentrations and an increase of plasma ET-1 concentrations could be demonstrated. The balancing effect of these two factors in determining the vascular tone is underlined by the fact that we proved a significant negative relationship between serum NOx and ET-1 concentrations, which actually corresponds to the adult findings. The key role of NO/endothelin imbalance is further underlined by the fact that serum concentrations of NOx showed a negative, while that of ET-1 showed a positive correlation with blood pressure levels, especially with systolic blood pressures.

2. Relationsip between NOx / ET-1 system and carotid IMT and LVMI

In our study we found that body weight and systolic blood pressure are the most important determinants of IMT and LVMI in adolescence. Among the two endothelial factors we assessed only ET-1 seemed to influence IMT, which corresponds to the previous results. In contrast to adolescent studies, no relationship could be detected between ET-1 and LVMI. We cannot explain these discrepancies.

Presumably adult hypertension results in a more gradual increase of ET-1 and LVMI, which makes the statistically significant relationship possible.

NOx seemed not to be a determing factor of IMT or LVMI. This observation could be explained by the fact that NO is mainly responsible for the determination of the basal tone of the vessels. In hypertensive patients, beside the decreasing production of NOx, an increased activity of endothelin can be observed. Thus, in hypertensives, NOx becomes a second actor of determing the vascular tone. Corresponding to this, we found that NOx was inversely relatad to IMT (r=-0.42; p<0.001), while such relationship could not be found in hypertensive adolescents (r=0.15; p=0.2).

3. The relationship between NO / ET-1 imbalance and resting cerebral blood flow velocities as well as cerebrovascular reactivity

Endothelium-related factors play determining role in the vascular tone, which is also present in cerebral vessels. NO has been shown to play a modifying role in chemical mechanisms of vascular tone, and its role in pressure-related autoregulation is not significant. The NO produced by the vascular endothelium influences mainly the reactions of the cerebral vasculature to hyper- and hypocapnia (vasodilation or vasoconstriction): it shifts the CO_2-reactivity curve toward left. Basically this is the main explanation of the finding that in hypertensives cerebrovascular reactivity is impaired. In previous studies it was also proved that this influencing effect of NO on cerebrovascular reactivity is age-dependent. Before starting our study, we did not have any information on how NO/endothelin-imbalance influences cerebrovascular reactivity in adolescent hypertensives.

In our series we found that middle cerebral artery blood flow velocities were higher among hypertensive teenagers as compared to heatlhy adolescents.

Furthermore, we proved that resting blood flow velocities were negatively related to plasma concentrations of NOx and positively to that of ET-1. Blood flow velocities whithin the middle cerebral arteries are mainly determined by two factors: the actual tone of the resistance arterioles in the corresponding vascular territory and the diameter of the large cerebral vessels (in this case: middle cerebral artery). If resistance arterioles are dilated, cerebrovascular resistance decreases, resulting in an increase of blood flow velocity whithin the large vessel (middle cerebral artery). In contrast to this, an increase of the cerebrovascular resistance leads to a decrease in cerebral blood flow velocity. The other factor playing a role in determining the blood flow velocity whithin the middle cerebral artery is the diameter of the artery itself: the decrease in diameter results in a decreased, while an increase results in an increased blood flow velocity.

In our subjects, an increase in middle cerebral artery mean blood flow velocities was present in hypertensive adolescents along with an increase in serum concentration of ET-1 and a decrease in serum concentration of NOx. This indicated the effect of these two endothelial factors on the large cerebral arteries (middle cerebral artery) rather than on cerebral arterioles. This relationship is maintained during assessment of middle cerebral artery mean blood flow velocity and NOx as well as ET-1 concentrations during vasocontrictor (HV) and vasodilator (BH) stimuli.

We found that cerebrovascular reactivity to hyper- and hypocapnic stimuli did not differ among hypertensive and healthy adolescents. Taking into account that hypo- and hypercapnia exert their action basically on cerebral arterioles, this finding supports the concept that the effect of NOx and ET-1 is predominantly exerted on large cerebral arteries. Previous animal experiments and human studies also proved that NO-imbalance may play a role in alteration of cerebral vasoreactivity. We have to

point out, however, that such finding could not be proved in young hypertensives. There are studies referring to a decreased cerebral blood flow velocities after inhibition of NO synthase, but this block does not affect hyperemic response of the cerebral vasculature to hypercapnia. Another data supporting our results is that serum concentration of ET-1 remains within the normal level under hyper- or hypocapnic conditions. Our results are in accordance with the observations of Chao et al, who found that no relationship exists between NO/endothelin imbalance and cerebral vasoreactivity in young hypertensives.

We have to mention the limitations of our study. The first limitation is related to transcranial Doppler sonography. As mentioned above it does not directly measure cerebral blood flow, but previous studies showed fairly good reproducibility and relationship with cerebral blood flow measurements and therefore it is a widely accepted method for non-invasive assessment of cerebral blood flow. The second one is breath holding test. The most important limitation is that, this method need the patient's cooperation. To avoid bias during breath holding, in a previous study we described a method for better measurement circumstances, which may be useful in young individuals. In that study we also proved that pCO_2 in capillary blood does not change significantly during breath holding test, whereas pCO_2 significantly decreases after hyperventilation. Previous studies reported on satisfactory reproducibility of both methods and a good agreement with other vasodilatory testing using different stimuli.

4. Relationship between ACE gene polymorphism and IMT as well as LVMI

The deletion/insertion polymorphism of the ACE gene is known to modulate circulating and cellular activity of the angiotensin-converting enzyme. The frequency distribution of the different genotypes in hypertensive patients depends on ethnic and

geographical factors. Our data are similar to those obtained from hypertensive

patients from Italy and from Australia and are definitely different from the Asian data,

where the DD genotype is quite rare. As there are no reference values available from

Hungary or from Middle-Europe, recently we examined the ACE genotype frequency

in 58 non-hypertensive adolescent subjects. Data-collection will be continued, but in

this small cohort of non-hypertensive controls we are already able to estimate the

frequency of the different genotypes. We found a DD genotype in 15 (25.8%), a DI

genotype in 25 (43.2%) and an II genotype in 18 cases (31%). This is comparable

with those obtained from hypertensive subjects. Thus, at least in Hungarian

adolescents there are no differences between the ACE genotypes among

hypertensive and healthy subjects. There are few reports on the frequency of the

different ACE genotypes in adolescent population and the results are comparable to

ours.

IMT of the common and internal carotid arteries has been reported as a good

indicator, for developing atherosclerosis in association with different vascular risk

factors. Previous investigations on hypertensive patients suggested that IMT is higher

in this patient group as compared to non-hypertensive subjects. Furthermore, a

correlation between the blood pressure and the IMT was described, which is most

probably in stronger association with the systolic blood pressure. Very recently, an

association between IMT and the different ACE genotypes has been suggested by

Jeng, who found that IMT is higher in patients with DD than with II genotype. A

similar observation was published by Huang et al. in a middle-aged population.

In our study, we were unable to detect such a relationship between ACE

genotype and severity of the IMT. A significant limitation of our study is the relatively

low number of subjects. Based on a retrospective power analysis, for the comparison

of IMT between DD and DI groups 247, between DD and II groups 1521, while between DI and II groups 499 subjects would be necessary to detect significant differences. Taking the highest number of subjects needed (n=1521) into consideration and calculating with 2% prevalence of adolescent hypertension, 76050 would be the minimal number of adolescents in order to detect significant differences in IMT among the different groups. However, although we included all secondary school students, their number was limited (n=10359), as the overall number of inhabitants in Debrecen is 230 000.

Beside this, different other factors have to be considered for explaining the disagreement between our, and the previously reported data. The most important among them is the age of the subjects. The mean age of our subjects was 16.4±1.06 years, while in Jeng's population it ranged between 55.1±11.0 and 58.0±8.8 years. Several studies proved that age is an independent contributor of carotid IMT, thus IMT increases with advanced age. Beside this, hypercholesterolemia, increased triglyceride levels, blood glucose concentrations have to be taken into account while analyzing the differences. In our population only slightly abnormal changes, in a relatively small number of patients have been observed while investigating these factors, which is another explanation for the observed difference. Third, there are also data indicating that IMT is independent from the ACE genotype in low-risk patients.

The relationship between left ventricular hypertrophy and ACE gene polymorphism is controversial. There are data suggesting that left ventricular hypertrophy is associated with the presence of DD genotype, while other investigators were unable to prove the relationship between hypertension and ACE gene polymorphism. In our study none of the ACE genotypes were associated with a

more severe left ventricular hypertrophy. Again, there is a question whether this finding is just due to the short exposition time of hypertension or whether such a relationship between the two factors does not exist. Another possibility for explaining our results is methodological: given the short exposition time functional (e.g. flow dependent vasodilation) rather than morphological parameters may be more sensitive. We cannot answer this question based on our data.

V. SUMMARY

1. We demonstrated that the plasma NOx concentration decreases, ET-1 concentration increases in adolescent hypertension.

2. We showed a significant negative relationship between plasma levels of NOx and ET-1 in adolescence.

3. A significant relationship was found between adolescent hypertension and NOx and ET-1 concentrations:

    a. Plasma NOx negatively correlated with blood pressure values

    b. A positive correlation could be detected between plasma ET-1 concentrations and blood pressure values.

4. We demonstrated a significant positive relationship between IMT and plasma concentration of ET-1.

5. We have shown that middle cerebral artery velocities in adolescent hypertensives are higher than that of healthy teenagers.

6. Cerebrovascular reactivity values (as assessed by breath holding and hyperventilations tests) did not differ between hypertensives and normotensives.

7. Although both NOx and ET-1 influenced resting cerebral blood flow velocity, it did not have any effect on cerebrovascular reactivity.

8. No relationship was found between severity of target-organ damages and ACE gene polymorphism in adolescent hypertension.

VI. LIST OF PUBLICATIONS

1. Publications used in the thesis

1. **Katona É**, Settakis G, Varga Z, Juhász M, Paragh G, Bereczki D, Fülesdi B, Páll D: Both nitric oxide and endothelin-1 influences cerebral blood flow velocity at rest and after hyper-and hypocapnic stimuli in hypertensive and healthy adolescents. **Kidney and Blood Pressure Research**, 29(3):152-158; 2006. **(IF: 2,408)**

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7. Páll D, **Katona É**, Fülesdi B, Jenei Z, Paragh G, Polgár P, Kakuk G: A serdülőkori hypertonia epidemiológiája és a vérnyomást befolyásoló tényezők. **Orv Hetil** 142(35):1891-6; 2001.

8. Páll D, **Katona É**, Fülesdi B, Polgár P, Paragh G, Kakuk G: A serdülőkori hypertonia diagnosztikájának és terápiájának aktuális kérdései. **Lege Artis Medicinae** 11(6-7):418-425; 2001.

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