DOCTORAL (PH.D.) DISSERTATION

THESIS

INVESTIGATION OF THE CEREBRAL HEMODYNAMICS IN HYPERTENSION AND HYPERTENSION RELATED NEUROLOGICAL DISEASES

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1. INTRODUCTION

Hypertension is one of the most prominent cardio- and cerebrovascular risk factor. However, stroke will not develop in every patient with hypertension. It is important to discern patients with hypertension who have severely impaired cerebral circulation from those who don't. It is important to find a sensitive method to diagnose patients with hypertension at an early stage when neurological symptoms are not yet present but certain, subtle morphologic and functional disorders – predicting the development of stroke - can already be detected. During our research we used various methods to prove the presence of the hemodynamic deficit in different groups of patients with hypertension (chronic, treated; recently diagnosed, untreated; chronic, treated with drugs believed to improve autoregulation) or other neurological diseases associated with hypertension (subarachnoidal bleeding, migraine). If such a deficit is present, which are the best methods to easily and effectively to detect it?

Hypertension is one of the most frequent diseases worldwide. Only 80 percent of those affected knows that he/she has hypertension (slightly more men than women). About two third of the patients receives any treatment and only one third of the treated gets proper medical attendance; that is, his/her blood pressure is set to the level (under 140/90 mm Hg) which is currently believed to be optimal regarding the cardio- and cerebrovascular complications. In Hungary about 30 percent – more than 2 million people - of the adult population suffers from hypertension. Presumably no more than 25 percent of these receive optimal treatment. Hypertension contributes to the high rate of domestic cardio- and cerebrovascular mortality and the strikingly short life expectancy. Hypertension on the long term damages the vessels, promotes the progression of atherosclerosis and impairs the function of the vital organs. Moreover, the disease causes structural and functional changes in the cerebral vessels. In the *large arteries* atherosclerosis and saccular aneurysms develop, while in the *small arteries and arterioles* the wall/lumen ratio increases thus ensuring the contractibility of the vessels even under elevated blood pressure. Hypertension also alters the endothel function.

Hypertension and disorders of the cerebral circulation

One of the most important risk factors of cerebral circulation disorders is hypertension. Systolic hypertension alone increases the incidence of stroke by 2-4 percent, and almost half

the patients with stroke have already had hypertension previously. An effective, early treatment may reduce the incidence of cerebrovascular diseases by 40 percent.

Cerebral autoregulation ensures that the cerebral blood-flow (CBF) remains unchanged despite the fluctuations in the systemic blood pressure. In healthy people this autoregulation is most effective between the mean blood pressure levels of 60 and 150 mm Hg. CBF also affects the autoregulation: higher CBF shortens the autoregulation plateau while lower CBF levels widen it. Due to the increased vascular resistance in hypertension the autoregulation curve shifts to the right, that is, towards the higher blood pressure levels. Pharmacologic blood pressure reduction severely affects the CBF. Proper antihypertensive treatment alters the autoregulation curve; it will lie between the curve of the healthy people and those with untreated hypertension.

2. EVALUATION METHODS

2.1. Ultrasound methods

2.1.1 Echoimpulse sonography:

On the connecting surface of two different tissues the ultrasound beam is being reflected since each tissue has unique acoustic impedance. The intensity of the reflected beam depends on the difference between the two impedances. The examiner sees a black and white image on the screen where the different tissues can be easily separated. This method provides information on the anatomic characteristics of the vessels or any other disorder.

2.1.2. Doppler sonography:

From stationary surfaces the ultrasound beams reverberate with unchanged frequency. However, in the case of moving structures, like red blood cells, the frequency of the reflected beams varies with the velocity of the object. The Doppler unit transforms the reflected signals to audible sounds.

2.1.3. Duplex sonography:

These devices mix the capabilities of both B-mode and Doppler sonography. The transducer contains the necessary parts for both modes thus the examiner can localize the structures in B-mode then evaluate the blood-flow parameters using Doppler method.

2.1.4 Color coded duplex sonography:

The different beam intensities appear as a black and white B-mode image while the changes in phase and frequency are visualized as various colors. The direction of the flow compared to the probe and the velocity is represented by different colors on a yellow-red palette. The advantage of this method over the ones mentioned above is that the impaired flow in the affected vessels, stenosis, plaques or hard-to-spot vessels (like the vertebral arteries) can be easily detected.

2.1.5. Power Doppler sonography

The unit marks the energy of the ultrasound beams reverberated from the flowing particles with different hues of the same color. The signal is independent from the angular correction so low-velocity flows can also be visualized.

2.1.6. Transcranial Doppler (TCD):

Through the relatively thin temporal bone the vessels forming the circle of Willis can be examined using a 2-2,5 MHz probe. Altering the position and detecting range of the probe, the velocity (cm/s) and direction of the blood flow can be easily measured. This method is especially useful in detecting the stenosis or occlusion of the intracranial vessels. In combination with certain vasodilating stimuli (breath withholding, CO_2 inhalation, cognitive tests or acetazolamide provocation), it is possible to continuously monitor the changes in the cerebral hemodynamics.

Assessing the cerebrovascular reserve capacity (CVRC) with TCD

This method uses TCD combined with vasodilating stimuli (acetazolamide, CO_2, breath withholding) to examine the blood-flow velocity in the basal cerebral vessels. If a vessel is already dilated by some pathologic process, the exogen vasodilating stimuli are ineffective.

2.2 Single photon emission computed tomography (SPECT)

SPECT is capable of monitoring dynamic processes in the living being by detecting and imaging the distribution of injected or inhaled radioactive isotopes in the body. Using a tomograph with a resolution of about 8 mm, the cerebral blood-flow, the cerebral blood volume (CBV) or the distribution of the cerebral neurotransmitter receptors can be evaluated. The most commonly used γ-radiating tracers are the Xenon-133 and Technetium-99m-HMPAO since their diffusion and uptake into the cells are closely related to the local

circulation. The Tc-99m-HMPAO reaches its equilibratory distribution in a few minutes and remains unchanged for hours. This way the circumstances present at the time of the injection represented by the distribution of the isotope can be examined even several hours later.

Cerebral regional blood-flow SPECT

After resting in supine position for a few minutes, the patient is injected intravenously with Tc-99m traced HM-PAO or ECD (cc. 600 MBq). After waiting another 15-45 minutes SPECT scans are performed in three different planes: the *transversal* planes are parallel to the line connecting the lower border of the frontal and occipital lobe; the *sagittal* planes are parallel to the midline of the brain dividing the two hemispheres while the *coronal* planes are perpendicular to both. These planes can be used to *compare* the blood-flow of the various cerebral regions; the SPECT scans alone can't provide information on the *absolute* value of the blood-flow (measured in ml/min/100g).

Lassen's correction

In theory the blood-flow can be measured exactly using labeled microspheres. However, in practice the distribution of the radiopharmacons used to assess the blood supply of the different organs may differ. The cerebral distribution of HM-PAO does not match precisely the blood-flow since the reflux also depends on the inflow. The non-linear connection between the initial secretion rate of HM-PAO and the actual blood-flow can described with an empirical formula.

Making a quantitative brain map

If we know the cerebral blood-flow of a reference region, the HM-PAO distribution can be converted into rCBF distribution. The reference region can be either the cerebellum or the whole cerebrum (as compared by $C^{15}O_2$ inhalation dynamic PET scans). The rCBF rates of the hemispheres calculated from a dynamic scan taken one minute after inhaling the radiopharmacon can be used as a reference.

The sensitivity of SPECT can be increased using the CO_2 or the acetazolamide-test. This way the regional vasoreactivity and collateral circulation can be examined.

2.3. The role of acetazolamide in the evaluation of the cerebral hemodynamics

Acetazolamide is a reversible inhibitor of the Carbonic Anhydrase enzyme catalyzing the following reaction: $CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^-$

Its effect is dose-dependent. At a dose of 0,15 mg/kg - taken either orally or intravenously – it increases cerebral blood-flow. The CBF starts to increase after 2 minutes and reaches its maximum after 10-12 minutes.

2.4. Assessing the cerebral vasoreactivity

For the proper evaluation of the cerebral autoregulation we need information on the course and scale of the reaction. For this reason two addition parameters has to be defined:

- *cerebrovascular reactivity (CVR),* which marks the course of the reaction in time
- *cerebrovascular reserve capacity (CVRC),* which marks the maximal extent of the reaction; that is, the maximal dilatation of the vessel.

3. OUR INVESTIGATIONS

We performed our investigations in the Department of Neurology, Department of Neurosurgery and Department of Nuclear Medicine of the University of Debrecen, Center of Medicine and Health Sciences.

1.1. Using TCD + acetazolamide in patients with hypertension

1.1.1. We sought answer for the following questions:

Is there any difference in the rest flow parameters detected with TCD between the healthy people and those suffering from hypertension? Is there any difference between the control and patients' group in the effect (flow velocity increase) of acetazolamide? Is this method capable of predicting the development of cerebrovascular complications in patients with hypertension? Is there any relationship between the measured mean blood pressure and the cerebrovascular reserve capacity (CVRC)? Is there any correlation between the duration of hypertension and the CVRC? Is there any detectable connection between the CVRC and the diameter of the left ventricle or the CVRC and the aortic root diameter?

1.1.2. Subjects and methods

- We performed our investigations on 25 patients with chronic, neurologically asymptomatic hypertension (age: 32-60 years; mean age ± SD: 48,4 ± 7,4 years) and 25 healthy people. The duration of hypertension was 2-30 years. The patients took various drugs as antihypertensive medication and were asked to avoid taking their drugs for two days prior to the investigation. Detailed general and neurological physical examination was performed. Only those were included in the investigation (healthy people and patients with hypertension alike) in whom no carotid stenosis could be detected using duplex ultrasonography. Cardiac echography was performed in all the subjects. We measured the diameter of the left atrium, the left ventricle and the aortic root, and the thickness of the left ventricle. Thorough blood tests were taken.
- During TCD sonography we measured the flow velocity rates in both medial cerebral arteries at the depth of 45, 50 and 55 mm using a 2 MHz transcranial Doppler unit. After recording the base velocity values 1g of acetazolamide (Diamox) was administered intravenously. 5, 10, 15 and 20 minutes later we measured the maximal systolic velocity and the end-diastolic velocity, the mean velocity and the pulsation index. The pulse rate and the blood pressure was monitored continuously during the evaluation. Before and 5, 10, 15 and 20 minutes after administering the Diamox, blood-gas analysis was performed. CVRC was defined as the percentile increase in the base mean velocity after taking acetazolamide. We sought the possible connections between the CVRC and the duration of hypertension, the CVRC and the mean blood pressure and the CVRC and the various cardiac parameters.
- For statistical calculations variance analysis and unpaired T-tests were performed.

1.1.3. Results

- Laboratory findings were in the physiological range in both groups. The pO_2, pCO_2, pH values also moved in the physiological range and there was no significant difference between the two groups. The mean blood pressure was significantly higher ($P<0,05$) in the hypertension group both before and after administering acetazolamide. Acetazolamide caused no real change in the tension levels in either group.
- There was no significant difference in the mean velocity values between the two groups either before taking Diamox (hypertension group: 60,8 $\pm$ 2,6 cm/s; control group: 58,8 + 1,9 cm/s), or after it (hypertension group: 85,5 $\pm$ 4,4 cm/s; control group:

84,4 ± 3,2 cm/s). Diamox caused significant velocity increase in both groups after a few minutes. The velocity increased sooner in the control group, reached its maximum after 10 minutes (88,8 ± 2,8 cm/s) then decreased gradually. In the hypertension group the change was less prominent, the velocity/time curve had a different shape and the maximal velocity was reached only after 20 minutes (85,7 ± 4,4 cm/s). The differences of the mean velocity values between the two groups never reached the required significance level. The maximal increase in velocity was reached sooner - after 10 minutes - in the control group (52,6 ± 3,7 %). In the case of patients with hypertension the flow velocity increased slower and reached its maximum only after 20 minutes. The percentile extent of the change at the 5^{th} and 10^{th} minutes differed significantly between the two groups.

- The CVRC and the mean blood pressure showed no correlation in either group. There was also no correlation between the duration of the hypertension and the CVRC, the diameter of the left ventricle and the CVRC or the thickness of the left ventricular wall and the CVRC. We found inverse correlation between the CVRC and the diameter of the left atrium; that is, the bigger was the diameter, the smaller was the CVRC. Also inverse correlation was proved between the diameter of the aortic root and CVRC.

3.2. TCD and SPECT in patients with untreated hypertension

3.2.1. We sought answer for the following questions:

Is there any difference in the base or in the acetazolamide induced flow velocity rates between the recently diagnosed, untreated group of patients and the control group? Is there any difference between the two groups in the global or regional cerebral blood-flow after Diamox injection? If so, which regions are affected? Is there any correlation between the velocitiy rates measured with TCD and the regional flow parameters calculated from the SPECT scan?

3.2.2. Subjects and methods

- We conducted our examination on 15 patients with recently diagnosed, yet untreated hypertension (38,3 ± 6,2 years, 11 male, 4 female) and 13 healthy volunteers of the same age (11 male, 2 female). Prior written consent was received in every case. In the hypertension group the blood pressure readings repeatedly exceeded 140/90 but remained below 190/120. As in important criterium, regular antihypertensive medication of the patients with hypertension started only after the investigation. Prior

to the acetazolamide stress test, physical and laboratory examination, carotid and transcranial ultrasonography, echocardiography and MRI scan was performed.

- *TCD sonography*

  TCD sonography in this case was performed with two fixed probes on each side. The flow velocity was recorded continuously at the depth of 55 mm before and 10 minutes after administering 0,15 mg/kg of acetazolamide. Otherwise the evaluation was as described previously.

- *SPECT scan*

  15 minutes after administering acetazolamide (when the increase in velocity is estimated to be maximal) 600 MBq Tc-99m HMPAO is injected intravenously. Right after, 70 tomographic scans (1 sec) were taken. 15 minutes later another 120 scans were taken (with a rendered resolution of 128*128) for data collection. Base SPECT scans were not performed due to technical reasons. Since HMPAO has a high tissue concentration for 24 hours, we should have waited at least one day between the base scan and acetazolamide stimulation. However, in this case the same position of the head would have been extremely difficult to ensure.

  - *Hemisphere flow analysis*

  With Matsuda's method – which includes the Patlak analysis - we calculated the mean hemisphere blood-flow (ml/min/100g) from the activities measured in the aortic arc and the hemispheres. By slightly modifying the original method special images were created which better represented the specific regions. Next we determined the time it takes the blood to get from the aorta to the brain using a semi-automatic method. From the tomographic slides the radiopharmacion distribution map of the brain was created with Ichise's method. On this map a fixed sub-region represented each cerebral region.

  - *Regional cerebral blood-flow (rCBF) map*

  By knowing the flow rate of the reference cerebral region, the HMPAO activity values were converted into rCBF values using Lassen's correction. The blood-flow of the whole brain was used as a reference which was determined by averaging the hemisphere rCBF values measured in the dynamic stage of the investigation. The resulted HMPAO distribution was expressed in units of ml/min/100g. From this map the blood-flow of the frontal, temporal, parietal and occipital regions and the cerebellum was computed.

  Statistical analysis

Analysis of the results was done using Student's T-test or Welch's d-test. For proving any possible correlation between the individual parameters, we calculated the correlation coefficient, and then determined the significance level with the help of Student's T-test.

3.2.3. Results

- Laboratory findings were in the physiological range in both groups. In the hypertension group cardiac echography revealed slight left ventricular hypertrophy in three patients. In the control group no such disorder was found. Carotid Doppler showed calcified vessels in four patients from the hypertension group but no stenosis or plaques were detected. There were anomalies in the control group.

TCD sonography

- The flow velocity rate prior to administering Diamox was significantly lower ($p \leq 0,05$) on the right side in the hypertension group than in the control group. 15 minutes after administering acetazolamide the flow rate was significantly lower ($p \leq 0,05$) on both sides in the hypertension group than in the control group. The velocity rates were lower on the left side both groups than on right side. The difference was significant ($p \leq 0,05$) in the hypertension group. The blood flow velocity increased significantly ($p \leq 0,05$) in both groups as an effect of acetazolamide. The CVRC showed no significant difference between the two groups either in the left (hypertension group: $1,46 \pm 0,3$; control: $1,34 \pm 0,3$) [Figure 9] or the right side (hypertension group: $1,39 \pm 0,2$; control: $1,23 \pm 0,3$) [Figure 10], or in the average on both sides (hypertension group: $1,41 \pm 0,2$; control: $1,27 \pm 0,3$).

Results of SPECT scans

- 15 minutes after administering Diamox the global BCF on the left and right side was significantly lower ($p \leq 0,05$) in the hypertension group than in the control group. The regional CBF rates were lower in both hemispheres in patients with hypertension, but the difference was significant only in the medial occipital region. There was no real difference in the rCBF rates between the two hemispheres in either group.

Correlation between the TCD and SPECT data

- Only weak correlation could be proved between the flow velocity rates and the corresponding ipsilateral regional blood flow rates (that is, the temporal and parietal

rCBFs supplied by the ipsilateral medial cerebral artery) 15 minutes after administering Diamox.

3.3. TCD investigations with cilazapril in hypertensive patients

3.3.1. We sought answer for the following questions:

- How does cilazapril affect the blood pressure? Is there any difference (improvement) in the CVRC after 1 year of cilazapril treatment?

3.3.2. Subjects and methods

12 patients (4 male, 8 female) were included in the investigation (mean age ± SD: 59,1 ± 6,2 years). Duration of our investigation was 1 year. We preferred monotherapy. If cilazapril treatment was not sufficient, 2 months later we replaced it with a drug from another group (beta-blocker or diuretics). One patient took Betaloc for 4 weeks; another one took Furosemid for 3 weeks. Administering other kinds of ACE inhibitors was forbidden. Daily dosage of the drug was 2,5-7,5 mg, varying independently.

Examinations performed prior to the cilazapril treatment:

- Detailed general and neurological physical examination and blood tests
- Transcranial Doppler, carotid duplex sonography and cranial CT
- TCD sonography before and after administering acetazolamide (0,15 mg/kg) as described in 3.1.

After performing the above investigations, cilazapril treatment was started. After 6 and 12 months general, neurological and laboratory check-ups were scheduled. During these occasions acetazolamide stress test was also performed.

Statistical analysis was done using paired, two-tailed T-test.

3.3.3. Results

Blood pressure: During the 12 months of antihypertensive treatment no side-effects were reported. After 6 months of cilazapril administration the mean blood pressure decreased (mean ± SD: 118,7 ± 1,3) compared to the base level (125,1 ± 15,0); however, the difference was not significant. During the second 6 month the tension decreased even further (116,5 ± 11,5), at this point the reduction reached the level of significance ($p \leq 0,05$). The mean systolic blood pressure before the cilazapril treatment was 153,1 ± 15,0; 6 months later 145,0 ± 13,1 while 12 months later the reduction (141,0 ± 13,7) was significant ($p \leq 0,05$). During the

acetazolamide stress tests the changes in the blood pressure and pulse rate were not significant.

Flow velocity changes in the medial cerebral artery

Prior to cilazapril treatment: as an effect of Diamox, velocity rates increased significantly in both medial cerebral arteries. The maximal percentile increase in the flow velocity on the left side happened after 10 minutes (39,0 ± 4,1%), on the right side after 20 minutes (37,0 ± 2,3%). The pulsatility index on the left side was significantly lower ($p \leq 0,05$) after 20 minutes (0,92 ± 0,19) than before administering Diamox. The change was not significant on the right side.

After 6 months of cilazapril treatment: the increase in the mean velocity rates due to Diamox administration was significant ($p \leq 0,05$) on both sides from the 5th minute. The maximal percentile increase (CVRC) was registered after 15 minutes on both sides (right: 53,0 ± 3,7%; left: 34,0 ± 2,0%). The pulsatility index hasn't changed considerably. Also there was no significant difference between the CVRCs measured at the 0th and the 6th months.

After 12 months of cilazapril treatment: Diamox caused more prominent increase in the flow velocity rates than during the previous 2 investigations. Maximal reactivity (CVRC) was detected after 15 minutes on the left side (56,0 ± 3,2%) and 10 minutes on the left side (41,0 ± 3,6%). On the left side the increase in CVRC approximated but not reached the level of significance as compared to the change recorded during the first investigation. The pulsatility index showed no substantial difference.

3.4. Investigations in subarachnoidal hemorrhage

3.4.1. Correlation between hypertension and the vasospasm

We sought answer for the following questions: Is vasospasm following subarachnoidal bleeding more frequent in patients with a history of hypertension? Is there any difference in the severity of the vasospasm between the hypertension and control group? How does hypertension affect the outcome of SAB? Does hypertension affect the frequency of late ischemic complications among those who died in SAB?

3.4.1.1. Subjects and methods

- We analyzed the data of 448 patients with subarachnoidal hemorrhage (SAH) caused by a ruptured aneurysm. 189 of these patients (42%) had a past medical history for hypertension (mean age ± SD: 49 ± 11 years), while 259 had normal blood pressure levels (44 ± 12 years). Upon admittance the Hunt-Hess clinical score was determined in

every patient, as well as the timing of the surgical intervention (early: in 0-48 hours, delayed: after the 8th day). Based on the first CT scan, the severity of the bleeding was also assessed using the Fisher's scale. Depending on the condition of the patient, at least one TCD sonography was performed every day (EME TC-2 64B, Eden Medizinische Elektronic GmbH, Überlingen, Germany). The technical details of the examination are described in 3.1.2.

- The flow velocity was recorded in the medial cerebral artery in an individual depth (45-60 mm). The extent of the vasospasm was determined by the maximal recorded flow velocity. The outcome of SAB was assessed according to the Glasgow Outcome Scale (GOS). In the most critical group of patients (GOS1) we determined the cause of the poor outcome, which were the following: severity of the SAB (Hunt-Hess IV-V), repeated rupture, vasospasm, perioperative factors (factors related to the operative stress: early rupture, application of temporary clips, severe brain edema, unusually early vasospasm) and others (cardiopulmonary factors, hydrocephalus).

Statistical analysis:

During statistical analysis the flow velocity rate was the primary outcome variable. Hypertension was considered as the primary variable responsible for the vasospasm, but other contributing factors were also taken into consideration (age, sex, timing of the surgery, Hunt-Hess and Fischer scores). Upon calculating the statistical impact of hypertension, a corrected formula was used in which all contributing factors were implemented.

Linear regression analysis was our primary statistical method. Normality of the continuous variables was checked either in graphical form or using the Shapiro-Wilk test. The correlation between the maximal velocity rates and the possible factors contributing to the vasospasm was analyzed with the linear regression method. The possible factors influencing hypertension were identified with logistic regression analysis. Multiple-regression model was used in which all the factors affecting hypertension were analyzed if a) their regression coefficient was significant b) they had a possible clinical influence c) they had a considerable impact on the regression coefficient of other factors or their standard error.

The final model was checked by plotting the residual values as a function of the adapted values and by representing the normal curve of the residuals.

3.4.1.2. Results

- We found no significant difference in the severity of the vasospasm between the two groups (in hypertension: mean flow velocity ± SD: 139,4 ± 53,1 cm/s; in the control

group: 141,2 ± 52,5 cm/s) [Figures 8-9]. In patients with hypertension the maximal velocity rates were 0,41 cm/s less then in the control group; which is not a significant difference (p=0,905) even if the correction for other possible factors was made. This means that no direct relationship was found between the maximal flow velocity (severity of the vasospasm) and the hypertension.

- Late cerebral ischemic lesions could be thoroughly analyzed only in those who died of subarachnoidal bleeding. Neither the mortality rate, nor the late ischemic lesions proved to be significantly different between the patients who had previous hypertension and those who had not.

TCD – acetazolamide investigation years after SAH

3.4.2.1. We sought answer for the following questions: Is there any difference in the resting flow velocity rates measured with TCD sonography in patients having recovered from a severe vasospasm after subarachnoidal bleeding between those who had a history for hypertension and those who had not? Is the CVRC lower in the former group?

3.4.2.2. Subjects and methods

- 27 patients were included in the investigation (with hypertension: 41,2 ± 5,9 years, 9 female / 4 male; without hypertension: 46,8 ± 7,1 years, 9 female /5 male). Patients recovered from subarachnoidal bleeding caused by cerebral anurysm rupture years before (mean: 4,6 years, ranging from 1-8 years). In every selected patient severe (grade II-III) vasospasm developed 6-8 days after the bleeding.
- TCD sonography, blood tests and acetazolamide stressing was performed as described in 3.1.2. However, the routine of TCD investigation was slightly modified since this time only the resting flow velocity rates and the Diamox-induced maximal velocity rates were recorded, the dynamics of the process was not followed.

Statistical analysis

For statistical analysis ANOVA and unpaired T-test was used.

3.4.2.3. Results

- Flow velocity rates measured in the medial cerebral artery were in the normal range on both sides; there was no significant difference between the two groups. The velocity

increased significantly ($p \leq 0,01$) on both sides as an effect of Diamox. CVRC showed no significant difference - either on the side of the rupture or contralaterally - between the two groups.

3.5. Evaluation of patients with hypertension and migraine using TCD sonography

3.5.1. We sought answer for the following questions: Is there any difference in the resting flow parameters measured with TCD sonography between patients with hypertension and migraine and the control group? Is there any difference in the flow velocity rates between the two medial cerebral arteries?

3.5.2. Subjects and methods

- 31 patients were included in the investigation (mean age ± SD: 38,3 ± 6,9 years, 26 female / 5 male) [Table 12]. In 4 patients the migraine was preceded by an aura, in 24 patients there were no such symptoms. 3 patients reported that their headache usually presented without aura but rarely (1-1 and 3 times, respectively) it was preceded by scotoma. These patients had migraine for 1-18 years, the frequency of the attacks ranged between 1 and 6 months. In more than two third of the patients migraine presented years before diagnosing their hypertension.
- Detailed general and neurological physical examination was performed in every case. TCD sonography was carried out as described in 3.1.2. Patients with migraine were examined when free of symptoms. Acetazolamide stimulus was not performed.

3.5.3. Results

- No significant difference ($p \leq 0,05$) was found in the flow velocity rates and pulsatility index between the control group and patients with hypertension. Also the velocity rates showed no substantial difference between the two sides.

4. DISCUSSION

4.1. TCD + acetazolamide stimulus in patients with hypertension

In patients with chronic hypertension there was no significant difference in the resting flow velocity rates compared to the control group either before or after administering acetazolamide. However, the velocity increase due to the effect of acetazolamide showed

different characteristics in the two groups. In patients with hypertension the change was less drastic; the shape of the velocity/time curve was different and the maximal velocity was reached only after 20 minutes as compared to the control group where it took only 10 minutes. The correlation between the CVRC and the duration of hypertension, the left atrial diameter and the thickness of the left ventricular wall was not significant. Inverse correlation was found between the CVRC and the left ventricular diameter, as well as between the aortic stem diameter and the CVRC.

Only a small number of publications can be found on the evaluation of BFV and CVRC in patients with hypertension. In these patients the base BFV is similar to the rates measured in healthy people, but the vascular resistance is higher and the hypocapnia-induced higher velocity rates decrease to the base level faster. Investigating patients with hypertension Ameriso et al. reported the lack of the hypercapnia-induced vasodilatation present in healthy people. Cho et al. detected increased pulsatility index – representing a decreased flow in the MCA and increased vascular resistance – in patients with hypertension.

We believe that our results are explained by the increased peripheral resistance in the medial cerebral artery, the increased wall/lumen ratio and the decreased wall flexibility. The presence of various contractile factors produced by the vascular endothelium may also contribute to our findings. These factors are probably being released continuously due to the elevated blood pressure levels found in patients with hypertension thus increasing the tension of the vessel wall and resulting in a constant, mild vasoconstriction.

The different kinetics of the response given to acetazolamide administration may be explained by the following facts: in healthy people Diamox causes a rapid increase in the blood flow (occuring after only 2 minutes). In patients with hypertension the effect of acetazolamide must first compensate the already present slight vasoconstriction, only then can the precapillary vasodilatation develop. The same process can be observed in healthy people, except that here it takes more time to complete due to the vascular remodeling. In long-standing and/or more severe hypertension the CVRC may be narrowed due to the vascular remodeling. We found no correlation between the CVRC and the duration of hypertension. However, this can be misleading since the duration of hypertension is difficult to determine. Our hypothesis that long-standing, more severe hypertension decreases the CVRC and yields corresponding pathological findings with electrocardiography – like thickening of the left ventricular wall - was only partly proved. This may be explained by the fact that the thinner left atrium and aorta react more rapidly to the increased peripheral resistance, thus the left atrial dilatation can be sooner detected.

4.2. TCD and SPECT investigation in patients with untreated hypertension

The base flow velocity rate on the right side and the rates on either side measured 15 minutes after administering acetazolamide were significantly lower in patients with hypertension than in the control group. The CVRC showed no significant difference on either between the two groups. The global CBF on the left and right side was both significantly lower in patients with hypertension. In the group of hypertensive patients lower flow velocity rates and regional CBF were measured on the left side than on the right, although the difference was not significant. Only slight correlation could be proved between the flow velocity rates measured 15 minutes after administering acetazolamide and the corresponding ipsilateral regional blood flow rates (that is, the rCBF of the ipsilateral temporal and parietal region supplied by the MCA).

Previously it was stated that hypertension accelerates the decrement of CBF which accompanies the normal aging processes. This theory is supported by the fact that stroke has its predilection spots (basal ganglia). Although the process damages the whole cerebral vascularity, it is possible that some areas are more vulnerable than others. Fuji detected impaired rCBF rates in the supratentorial region (mainly in the striated body and thalamus) in patients with hypertension. Rodriguez et al. confirmed these results in patients with neurologically asymptomatic, untreated hypertension. According to Fujishima's findings, the decrease in rCBF was most prominent in the frontal cortex and in the basal ganglia, as compared to the control group.

Our investigations revealed that in patients with hypertension flow parameters of the left hemisphere (flow velocity, blood flow volume) were worse than on the other side. We haven't found any data in the relevant literature whether stroke is more frequent in the left hemisphere or not. We analyzed the reports of patients treated at the Department of Neurology (University of Debrecen, Center of Medicine and Health Sciences) between November 1, 1994 and December 31, 2000. The following statistics were found: left hemisphere: encephalomalacia: 877, bleeding: 223; right hemisphere: encephalomalacia: 606; bleeding: 198. We can see that both bleeding and encephalomalacia was more frequent in the left hemisphere. The precise explanation for this is not known; we presume it may be because the internal carotid artery originates from the brachiocephalic trunk on the right side and directly from the aortic arc on left. It is possible that the brachiocephalic trunk dampens the force of the heart beats, while this puffering-effect is missing on the left side. Every heart beat contributes to damaging the cerebral vessels and this effect is more prominent in patients with hypertension.

In the past 10 years several studies were performed to identify the possible correlation between the velocity rates measured with the TCD sonography and the CBF values calculated from PET or SPECT scans. In healthy people there is close correlation between the acetazolamide-induced velocity and the CBF increase, but in carotid stenosis this connection could not be proved. Our investigations revealed only slight correlation for which the possible explanation may be the following: the acetazolamide-induced increase in the flow velocity measured in the MCA represents the combined velocity rates of the smaller MCA branches in the surrounding area. Since hypertension affects each vessel differently, the regional vasodilatation may vary. The ROIs (region of interest) drawn for the evaluation of SPECT scans do not correlate completely with the anatomic region supplied by the selected vessel. Because of this, the ROIs may include areas from where no information can be gained regarding the collateral circulation or the Diamox-induced changes in the blood distribution. Moreover, hypertension causes inhomogeneous changes in the regional CBFs, therefore it is much more difficult to determine any correlation between the two parameters.

4.3. TCD sonography in hypertensive patients treated with cilazapril

Cilazapril is one of the longest lasting ACE-inhibitors, which effectively decreases the blood pressure in mild-to-severe hypertension. References in the literature suggest that it can normalize the CVRC, reduce the vascular hypertrophy and increase the outer diameter of the vessels. It may also support the endothelium function, has anti-atherosclerotic effects and inhibits the proliferation of the smooth-muscle cells.

After 12 months of cilazapril treatment the mean blood pressure levels and the systolic blood pressure levels dropped significantly. Diamox caused significant increase in the flow velocity in the medial cerebral arteries both before and 6 or 12 months after the cilazapril treatment. The change was most substantial after 12 months. The CVRC rates after on year of cilazapril treatment were higher than the ones prior to the investigation. However, the difference hasn’t reached the level of significance.

4.4. Investigation in subarachnoidal hemorrhage

4.4.1. Correlation between hypertension and vasospasm

The outcome of subarachnoidal bleedings caused by a ruptured aneurysm is predicted by the clinical condition of the patient upon admittance and the amount of blood in the subarachnoidal space. Beside these factors, the age of the patient and a previous history for

hypertension also contributes to a poor outcome. In patients with aneurysm the prevalence of hypertension is higher than in the normal population.

The high occurrence rate of hypertension demonstrates that this disease may have an important etiological role in the development of aneurysms. Moreover, the previously described vascular anomalies in hypertension occur frequently in patients with aneurysm. These factors may aggravate the complications (dominantly vasospasm and late ischemic injuries) of SAH.

Vasospasm is one of the most important complications of SAB. The most sensitive method in the detection of vasospasms is TCD sonography which reveals the impaired circulation in the circle of Willis in 70 percent of the cases.

Saveland found no difference in the outcome of SAH between patients with or without hypertension. However, several studies confirmed that hypertension increases the risk of this disease and therefore has a certain prognostic importance.

We found no significant correlation between the maximal velocity rates (that is, the severity of the vasospasm) and the hypertension. According to our data and previous multifactorial studies, development and frequency of the vasospasms correlates primarily with the severity of the bleeding and the clinical condition of the patient at the time of admittance to the ward. Other factors, like age, timing of the surgery, hypertension, hyperlipidemia may also affect the development of the vasospasm but this we could not prove with our investigations due to the complexity of the possible heterogeneity of the subjects. Our patients had hypertension but no accurate information was available regarding the duration of their hypertension or any possible organic damage. Thus, the severity of the hypertension could not be assessed.

It is possible however, that hypertension does not play an important role in the development of the vasospasm. Roganovic supports this theory by reporting no correlation between the spasm and the hypertension. Moreover, in vessels accustomed to hypertension the vasospasm may be less stressful.

4.4.2. TCD sonography + acetazolamide stimulus years after the SAH

Our results proved no difference either in the flow velocity rates before and after administering Diamox or in the cerebrovascular reserve capacity between patients with and without hypertension.

Our findings may be explained by the fact that proliferative vasculopathy is completely regressing after recovering from SAH. After a certain amount of time (in our case 1-8 years)

the harmful effects of the vasospasm cannot be detected, thus it does not affect the resting flow velocity and the reserve capacity.

4.5. Investigating patients with migraine and hypertension using TCD sonography

We found no substantial difference in the base flow parameters measured with TCD sonography between the control group and patients with migraine and hypertension.

The combined occurrence of migraine and hypertension is much more frequent and troublesome in the older age-groups. The parallel occurrence of mild-to-medium hypertension and migraine is most probably coincidental. Untreated hypertension may increase the frequency or severity of the migrainous attacks.

Some authors believe that there is no real difference in the MCA flow velocity rates between patients with migraine and healthy people. Others detected higher base flow velocities or reported instability in the velocity rates. The elevated velocity rates may be explained either by the decreased diameter of the irradiated vessel segment or the altered regional blood flow due to the changes occurred at the level of the arterioles. In several instances higher pulsatility indices were found which may be a result of the vasoconstriction. Since the headache in some patients with migraine occurs always on the same side, there may be a difference in the velocity rates between the two hemispheres. Several work-groups confirmed that headaches tend to occur on the side with a higher flow velocity, but again, other authors found no difference in the flow velocity rates between the two hemispheres.

Since only 4 of our patients with migraine reported their headaches to present only on one side, we didn't expect to find any differences between the two sides. Similarly no difference was found in the pulsatility indices of the two sides. In our patients hypertension was a complicating factor. As described previously, resting velocity rates were basically the same in patients with hypertension and in healthy people. However, during one of our investigation slower values were detected and another work-group also proved this. Based on these findings, the following explanations can be given:

- The flow velocity is in the normal range because the hypertensive vascular malformations compensate for the higher velocity rates, that is, the flexible, reactive vessels often observed in patients with migraine become more rigid. As a consequence, "normal" flow velocities are detected instead of the elevated rates. We must be aware that these findings are abnormal.

- However, it is still possible that the velocity rates in these patients were indeed in the normal range because hypertension has not yet damaged – or at least not to a detectable extent – the vascularity, so the results are not abnormal.

5 CONCLUSION, POSSIBLE CLINICAL ADAPTATIONS OF OUR RESULTS

Patients with hypertension require regular, complex medical examinations due to the increased risk of stroke. During our investigations we collected all the information that can be gained from SPECT and TCD sonography. With the help of SPECT scans adequate regional data can be gained but the regular use of this method is limited by a) the ionizing radiation b) the relatively poor temporal resolution c) its inability to continuously monitor the hemodynamic processes d) the high costs. TCD sonography also has its benefits (good temporal resolution, low costs, easy usage, ability to monitor continuously and the infinite repeatability) and hindrances (unusable with thick temporal bone, depends on the experience of the examiner). It can be used to detect and follow the vascular malformations in various diseases (like hypertension, diabetes or hyperlipidemia).

Since stroke still has no definitive therapy, special emphasis should be laid on prevention. Patients with hypertension have to undergo medical examination as soon as possible, and proper treatment has to be started if necessary. We should choose a drug that improves cerebral autoregulation whenever possible. Hypertensive patients with increased risk of stroke (presence of migraine, previously impaired cerebral circulation, hyperlipidemia, smoking, use of oral anticoncipients, etc.) should be screened at regular intervals.

One of the most promising investigation methods is transcranial Doppler sonography. It can be used as a part of the everyday diagnostic routine but it can play an important role in the prevention of stroke (regular screening and evaluating hemodynamic parameters). Well planned, prospective studies with a hard end-point can be carried out with the help of TCD sonography. Monitoring the efficiency of an antihypertensive therapy is also possible or we can investigate the effects of different drugs on the cerebral vessels. Another advantage of TCD sonography is that it can be easily combined with other methods like PET, SPECT or various neuropsychological examinations. Since hypertension tends to damage cognitive functions first, properly planned neuropsychological investigations have to be carried out in the affected group of patients. Due to the effect of hypertension on the cerebral vessels, we

should combine the neuropsychological examinations with TCD sonography or – if morphologic abnormalities are suspected – other imaging methods.