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Possibilities of contrast-free magnetic resonance perfusion imaging for the detection of early brain damage in essential hypertension

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Arterial spin labeling (ASL) is a promising non-invasive method to assess cerebral perfusion, which identifies a decrease in cerebral blood flow (CBF).
Objective: *to assess cerebral perfusion in middle-aged untreated patients with uncomplicated grade 1–2 hypertension compared to same-age healthy controls.*
Patients and methods. *33 patients with essential hypertension and 40 healthy individuals (a control group) at the age of 40–59 years were examined. 24-hour blood pressure (BP) monitoring and brain magnetic resonance imaging were performed in different modes (T1 MPRAGE, T2 TSE, T2 FLAIR, DTI, and ASL).*
Results. *White matter hyperintensive changes were found in 7.5% of the healthy individuals and in 51.5% of the hypertensive patients ($p = 0.0002$). In hypertensive patients, CBF in the cortical plate of anterior frontal regions was significantly ($p < 0.001$) lower than that in the controls: right CBF, 39.1±5.6 and 45.8±3.2 ml/100 g/min, respectively; left CBF, 39.2±6.2 and 45.2±3.6 ml/100 g/min, respectively. In hypertensive patients with white matter hyperintensive changes, CBF was significantly lower than that in the controls: right CBF, 38.5±5.9 ml/100 g/min ($p = 0.0001$); left CBF, 39.2±6.7 ml/100 g/min ($p = 0.002$), and in those without these changes, right CBF was 39.5±5.1 ml/100 g/min ($p = 0.0002$); left CBF was 38.9±4.3 ml/100 g/min ($p = 0.00002$). Correlation analysis revealed significant inverse correlations of CBF with BP and systolic BP variability.*
Conclusion. *Lower cerebral perfusion occurs in middle-aged untreated patients with uncomplicated grade 1–2 hypertension even in the absence of white matter hyperintensity foci.*

Keywords: *hypertension; brain; target organ damage; middle age; magnetic resonance imaging; white matter lesion; arterial spin labeling; cerebral blood flow.*
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Arterial hypertension (AH) is one of the main risk factors for the development of stroke, dementia, myocardial infarction, chronic heart failure [1–4]. The risk of development of fatal and non-fatal cerebrovascular and cardiovascular complications in patients with AH is influenced not only by blood pressure (BP) level, but also by a variety of other factors, primarily including target organ damage (TOD) [1, 2], i.e. changes in organs and systems in the body selectively damaged by AH. These organs are first and foremost affected by elevated BP. Such target organs in AH include the brain, heart, kidneys and blood vessels[1, 2].Target organ brain damage in AH is detected by magnetic resonance imaging (MRI) [1, 2, 5]. White matter hyperintensities and/or "silent" infarctions, most of which are small in size and located in deep regions of the brain (lacunar infarcts), are considered to be the manifestations of brain damage due to AH [2]. Presence of white matter hyperintensities and silent cerebral infarctions enhances the risk of stroke, cognitive impairment and dementia [1, 2, 6, 7].

Nowadays, the search for new markers of an earlier target organ brain damage in AH (in patients who do not have white matter lesions) using routine MRI pulse sequences continues. Of particular interest are the results obtained using the Arterial Spin Labeling (ASL) pulse sequence. [5]. ASL is a promising noninvasive method for evaluating perfusion in a variety of neurological diseases [5]. Several indices are used to quantify perfusion, including cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT). ASL pulse sequence allows to measure CBF value.

The use of ASL MRI in patients with AH is presented in few studies [8–11]. However, in these studies the participants with AH were heterogeneous in age, presence of cerebral complications (stroke, transient ischemic attacks), concomitant diseases

(diabetes mellitus – DM, atrial fibrillation) which can influence the studied characteristics, presence or absence of antihypertensive therapy and achievement of target BP; moreover, control groups were not matched with study groups by age or presence of concomitant diseases. Besides, these studies did not examine the relationships between CBF and BP level assessed by 24-hour ambulatory blood pressure monitoring (24-hr ABPM), which is known to have stronger correlations with target organ brain damage in AH and stroke risk [1, 2], as well as 24-hour blood pressure variability.

The objective of the present study is to assess cerebral perfusion using ASL pulse sequence in untreated middle-aged patients with uncomplicated grade 1–2 AH compared to healthy volunteers (control group), matched by age.

Patients and methods. The study design was approved by local ethics committee of Federal State Autonomous Educational Institution of Higher Education "I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University)" (First MSMU), protocol № 11–16 of 14.12.2016. All of the studies were carried out in accordance with the approved guidelines for conducting clinical trials of the First MSMU. All patients provided written informed consent.

Thirty three hypertensive patients aged 40–59 (at the enrollment) with AH, who met the inclusion criteria and signed the informed consent (13 men and 20 women, mean age – 50.2±6.2 years), and 40 almost healthy normotensive volunteers (15 men, 25 women, mean age – 49.1±4.4 years) (control group) were enrolled in the study, conducted in A. Ya. Kozhevnikov Clinic of Nervous Diseases.

Inclusion criteria for AH group: men and women aged 40–59 years; office systolic BP (SBP) – 140–179 mm Hg and/or diastolic BP (DBP) – 90–109 mm Hg; presence of at least one target organ damage (heart, blood vessels, kidneys); lack of antihypertensive treatment or irregular intake of antihypertensive medications for at least 12 weeks before enrollment; signing informed consent.

Inclusion criteria for control group: almost healthy men and women aged 40–59 years; absence of AH; signing informed consent.

Exclusion criteria: degree III obesity; age under 40 years old or over 60 years; pregnancy, lactation; office BP >180/110 mm Hg; clinically significant heart disease (myocardial infarction, degrees 2 and 3 atrio-ventricular block without artificial pacemaker, sinoatrial block, sick sinus syndrome, hypertrophic cardiomyopathy, aortic and mitral stenosis, chronic heart failure, angina pectoris), liver, kidneys (glomerular filtration rate – GFR – according to CKD-EPI <30 ml/min/1.73 m^2, hemodialysis, anuria), respiratory organs (including bronchial asthma and chronic obstructive pulmonary disease); clinically significant immunological disease; clinically significant endocrine disease (including DM); secondary AH, gout; mental illness and disorders, dementia, drug and alcohol abuse, severe peripheral vascular diseases (including Raynaud's syndrome); metabolic acidosis; refractory hypokalemia; clinically significant neurological diseases (including stroke and transient ischemic attack); surgical operation in the previous 3 months (excluding dental or plastic surgery); use of any medication (including regular intake of antihypertensive treatment) that may affect the results of the study for 12 weeks before enrollment, at the time of enrollment and until the end of the study.

Table 1. *Demographic and clinical characteristics of patients with AH and healthy volunteers (controls)*

Variable	Controls (n=40)	Patients with AH (n=33)
Men, n (%)	15 (37,5)	13 (39,4)
Women, n (%)	25 (62,2)	20 (60,6)
Age, years	49,1±4,4	50,2±6,2
AH grade 1/2, n (%)	_	30 (90,9)/3 (9,1)
AH duration, years	–	2,3+3,8
Newly diagnosed AH, n (%)	–	13 (39,4)
MoCa, points	29,2±1,0	28,1±1,7[a]
Smokers, n (%)	5 (12,5)	4 (12,1)
Quit smoking >1 year ago, n (%)	5 (12,5)	6 (18,2)
Office SBP, mm Hg	119,2+7,8	145,24+5,8[b]
Office DBP, mm Hg	76,6+4,9	91,76+4,6[b]
HR, bpm	70,0±7,0	72,6±8,2
Total cholesterol, mmol/l	5,6±1,0	5,6±0,8
GRF (CKD-EPI), mL/min/1,73 м^2	79,6±11,1	78,3±12,7
GRF (CKD-EPI) 30–60 ml/min/1.73 m^2, n (%)	0 (0)	2 (6,1)
Left ventricular hypertrophy, n (%)	0 (0)	17 (51,5%)

Note: – Values are expressed as mean ± SD (here and in table 2).
a – significant differences (p=0,002) compared to control group;
b – significant differences (p<0,001) compared to control group.
Abbreviations: MoCa – Montreal cognitive assessment, HR – heart rate, bpm – beats per minute.

Study demographic and clinical characteristics are presented in Table 1.

There were no significant difference in sex, age and smoking status between healthy volunteers and patients with essential AH (Table 1). Office SBP and DBP values were significantly higher in patients with AH (p<0.001).

All subjects underwent triplex ultrasound of the extracranial divisions of the brachiocephalic arteries (no more than 4 weeks prior to entering the study). Atherosclerotic plaques were detected in 15 patients with AH, none of the patients had significant hemodynamic stenosis of the the extracranial divisions of the brachiocephalic arteries.

All subjects underwent clinical and neurological examination, 24-hr ABPM (BPLab monitoring system BP2005-01.04.00.2540, "Petr Telegin", Russia) according to European guidelines [12]. All patients underwent high-resolution brain MRI (MAGNETOM Skyra 3.0T, Siemens AG, Germany). MRI protocol included three-dimensional T1 anatomical pulse sequence (PS) MPRAGE with an isotropic 0.9 mm voxel in axial plane, field of view (FoV) of 280 mm, matrix 320×320, TR 2300 msec, TE 2.41 msec, number of excitations (NEX) 1, slice thickness 0.9 mm; T2 TSE pulse sequence in sagittal and axial plane, FoV 240 mm, matrix 384×384, TR 10000 ms, TE 100 ms, NEX 2, slice thickness 2mm and T2 FLAIR PS in axial plane, FoV 220 mm, matrix 320×320, TR 9000, TE 81, NEX 2, slice thickness 4 mm; diffusion tensor pulse sequence SE EPI in axial plane, FoV 220mm, matrix 128×128, TR 3700, TE 92, diffusion coefficient values b (0.1000 s/mm^2), 32 directions of diffusion gradients, NEX 1, slice thickness 4mm; Pulsed Arterial Spin Labeling (PASL), FoV 250mm, matrix 64×64, TR 2500, TE 12.0, NEX 1, slice thickness 8 mm, bolus duration 800ms, inversion time 1800ms; arterial time-of-flight angiography (TOF 3D) and venous time-of- flight angiography (TOF 2D).

Statistical analysis was performed with Microsoft Excel 2010 and SPSS Statistics 20 software packages on a PC running Windows 7. The normality of the distribution of the obtained parameters was estimated using the Kolmogorov–Smirnov test. Statistical evaluation was performed by analysis of variance (ANOVA) and contingency tables (Chi-square) for categorical variables. A nonparametric Mann–Whitney U-test and Wilcoxon signed-rank test were used for non-normally distributed variables. The strength of the linear relationship between paired continuous variables was estimated by correlation analysis. Correlation significance was estimated with confidence level of 95%. Data were expressed as mean and standard deviation (SD). P-values <0.05 were considered statistically significant for all analyses.

Results. Using routine MRI pulse sequences (_2 FSE, _2 FLAIR, _1 MPRAGE) white matter hyperintensities were found in 3 (7.5%) healthy volunteers (Fazekas 1) and in 17 (51.5%) patients with AH: Fazekas 1 – in 15 (45.5%) patients and Fazekas 2 – in 2 (6.1%) patients; p=0.0002.

Both right (39.1±5.6 vs. 45.8±3.2 ml/100 g/min, respectively) and left (39.2±6.2 vs. 45.2±3.6 ml/100 g/min respectively) CBF in the cortical plate of the frontal lobe measured by ASL in patients with AH was significantly (p<0.001) lower compared to controls.

CBF was significantly lower in hypertensive patients both with (right – 38.5±5.9 ml/100 g/min; p=0.0001, left – 39.2±6.7 ml/100 g/min; p=0.002) and without white matter hyperintensities (right – 39.5±5.1 ml/100 g/min; p=0.0002, left – 38.9±4.3 ml/100 g/min; p=0.00002).

Mean ABPM values are presented in Table 2. Patients with AH had significantly higher BP level and 24-hour BP variabiality (Table 2).

Table 2. *Mean ABPM values (mm Hg) in patients with AH and healthy volunteers (controls)*

Variable	Healthy volunteers (n=40)	Patients with AH (n=33)
24-hour SBP	113,4±8,3	144,5±16,3[a]
24-hour DBP	74,6±6,2	90,1±11,1[a]
Daytime SBP	117,05±8,9	149±17,2[a]
Daytime DBP	77,4±6,6	93,9±11,6[a]
Nighttime SBP	102,5±8,7	132,4±16,9[a]
Nighttime DBP	66,07±6,06	80,2±12,2[a]
24-hour SBP variability (SD)	14,6±3,5	18,5±4,1[a]
24-hour DBP variability (SD)	11,3±2,2	13,8±3,7[a]
Daytime SBP variability (SD)	13,5±3,6	17,03±4,1[a]
Daytime DBP variability (SD)	10,45±2,6	13,2±2,8[a]
Nighttime SBP variability (SD)	10,6±3,04	14,1±3,99[a]
Nighttime DBP variability (SD)	8,5±2,4	10,1±3,3[b]

Note: – Significant differences compared to control group: a – p<0.001; b – p=0.02.

Results of correlation analysis are shown in Table 3. Significant correlations were found between CBF and SBP and DBP according to office and ABPM measurements and SBP variability according to ABPM data for all analyzed time intervals (diurnal, daytime, nighttime; Table 3). CBF index had a stronger correlation with SBP level compared to DBP (according to office and ABPM measurements) as well as with daytime SBP and DBP than nighttime and diurnal SBP and DPB, and with SBP level compared to SBP variability (Table 3).

No significant correlation was found between CBF and DBP variability, disease duration, total cholesterol level.

Discussion. White matter hyperintensities are known to be the most typical manifestations of brain damage due to AH [2]. They are detected in almost all elderly hypertensive individuals [2]. At the same time, their prevalence in younger patients at the earliest stages of AH has been analyzed only by C. Sierra et al. [13], who examined 60 untreated patients with essential AH aged 50–60 years (mean age – 54.4+3.8 years) without TOD. Brain MRI obtained on 1.5 T scanner revealed cerebral white matter hyperintensities in 38% of patients. As there was no age comparable healthy control group, the question of the frequency of cerebral white matter abnormalities in the healthy individuals of the same age remains unclear. We also examined untreated patients with uncomplicated hypertension without DM of the same age (mean age 50.2±6.2 years) and found cerebral white matter hyperintensities in 52% of cases, which significantly exceeded their incidence in healthy subjects with normal BP (7.5%). Higher prevalence of white matter changes in our study, despite the inclusion of younger patients, may be due to the fact that we performed an MRI scan on a 3.0 T scanner, while S. Sierra et al. on a 1.5 T scanner. Furthermore, approximately a half of the patients (52%) in our study had a TOD (heart – left ventricle hypertrophy – and kidneys – GRF value 30–60 ml/min/1.73 m^2), which indicated longer AH duration.

Table 3. *CBF (ml/100 g/min) in the cortical plate of the frontal lobes correlations with BP levels and variability (mm Hg)*

Variable	CBF Cortical plate of the frontal lobe	
	left	right
Office SBP	r=-,529 p<0,0001	r=-,537 p<0,0001
Office DBP	r=-,468 p<0,0001	r=-,503 p<0,0001
24-hour SBP	r=-,399 p<0,0001	r=-,401 p<0,0001
24-hour DBP	r=-,303 p=0,009	r=-,326 p=0,005
Daytime SBP	r=-,411 p=<0,0001	r=-,412 p<0,0001
Daytime DBP	r=-,308 p=0,008	r=-,335 p=0,004
Nightime SBP	r=-,362 p=0,002	r=-,358, p=0,002
Nightime DBP	r=-,286 p=0,014	r=-,286 p=0,014
24-hour SBP variability (SD)	r=-,324 p=0,005	r=-,299 p=0,010
Daytime SBP variability (SD)	r=-,284 p=0,015	r=-,270 p=0,021
Nighttime SBP variability (SD)	r=-,290 p=0,013	r=-,229 p=0,052

Note: – Pearson's correlation coefficients are presented.

White matter hyperintensities occur due to chronic cerebral hypoperfusion, which causes insufficiency of the mechanisms of compensation and energy supply, resulting in such morphological lesions of the brain tissue [14]. Contradictory data exist for reduction of CBF in AH which was measured by transcranial doppler or radioisotope techniques (the absolute majority of studies included elderly patients with multiple concomitant diseases and complications) [14]. Further studies evaluating cerebral perfusion at the early stages of essential AH, including middle-aged patients, especially without white matter hyperintensities, are necessary. The question remains about the cerebral perfusion measurement techniques, in particular, the non-invasive ones. That is why ASL pulse sequence being a non-invasive technique for quantifying cerebral perfusion has drawn great attention recently.

Using ASL pulse sequence we detected a significant reduction in CBF in the cortical plate of the frontal lobes in untreated middle-aged patients with uncomplicated AH compared to age-comparable normotensive healthy controls. At the same time, significantly lower CBF values in our study were found in hypertensive patients both with and without white matter hyperintensities (visualized using routine MRI pulse sequences) compared to controls. Similar results were shown in a recently published paper by T. Wang et al. [8] who also used ASL to study hemodynamic changes in normal-appearing white matter in middle-aged patients with AH. Thirty two healthy volunteers (mean age – 46,6±8,4 years) and 41 hypertensive patients (mean age – 47,9±8,3 years, mean BP – 155±21/98±11 mm Hg), of whom 80.5% received antihypertensive treatment were included in the study. Hypertensive patients we divided in two subgroups depending on the grade of the AH (grade 1 or 2). MRI scans were obtained using 3T scanner; MRI protocol included T1, T2, FLAIR, DWI, pCASL. Hypertensive patients had significantly lower CBF values in the centrum semiovale, anterior and posterior horns of the periventricular white matter, the splenium of the corpus callosum, compared to healthy volunteers. Patients with grade 2 AH had significantly lower CBF values in all regions of interest compared to controls. Unlike our study, T. Wang et al. [8] included patients who received antihypertensive treatment, which affected their results. The authors did not assess CBF in hypertensive patients with and without white matter hyperintensities, as it was an exclusion criterion.

Interesting results were also obtained in CARDIA brain MRI study [9], in which 680 subjects (mean age – 50.3±3.5 years) underwent brain MRI on a 3 T scanner using T1, T2, MPRAGE, FLAIR, DTI, pCASL pulse sequences. Among the participants in this sub-study 32.2% had AH. At the enrollment in CARDIA Brain MRI study the patients in the main group had normal mean BP values (118+15/74+11 mm Hg), 10,2% of patients had DM. The authors found that middle-aged hypertensive patients had significantly lower total cerebral perfusion, compared to the control group; however, the assessment of cerebral blood flow in AH patients, depending on the presence of white matter hyperintensities was not performed.

Possible interactions between white matter lesions and cerebral perfusion in AH using ASL were examined in two studies [10, 11]. J.W. van Dalen et al. (sub-study preDIVA-M, preDIVA-MR imaging [10]) examined older patients with concomitant cerebrovascular and cardiovascular pathology. Brain MRI protocol included T1, T2, FLAIR, PCASL (Intera scanner 3T). The study included 181 patients (mean age – 77±2 years) with SBP >140 mm hg (mean BP – 148/81 mm Hg), 60% of patients received antihypertensive treatment, 26% had controlled AH. Grade 1 hypertension was revealed in 41% of patients, grade 2 hypertension – in 21%, and grade 3 hypertension – in 11% of patients; 11% had a history of stroke/transient ischemic attack, 11% had DM, 23% – cardiovascular diseases (coronary arteries disease, history of myocardial infarction, peripheral artery disease. The mean CBF in the normal-appearing white matter was significantly higher than the mean CBF in the regions with white matter hyperintensities (22.5±7.7 vs. 10.6±6.3 mL/100 g/min, p<0.001). However, a control group was absent in the study, thus, it is impossible to assess whether the values obtained differ from those in healthy elderly individuals without AH.

A.J. Bastos-Leite et al. [11] analyzed perfusion measurements depending on the grade of white matter hyperintensities. The study included 21 subjects (mean age – 76±5 years) from a prospective longitudinal Leukoaraiosis and Disability (LADIS) study, 16 patients received antihypertensive treatment, 2 had Alzheimer's disease, 1 – vascular dementia. All subjects underwent brain MRI at 1.5 T scanner (Sonata; Siemens, Erlangen, Germany), including FLAIR and PASL. The values of total, cortical and subcortical CBF were calculated. The patients were divided into two groups depending on the grade of white matter hyperintensities: 1st group – Fazekas 1 and 2 (n=14), 2nd group – Fazekas 3 (n=7). The patients in the 2nd group had a significantly lower total, cortical and subcortical CBF, compared to the 1st group.

Hypertension-related cerebral small vessel disease is the main cause of white matter abnormalities [15]. The observed perfusion deficiency in AH may indicate a potential mechanism of white matter lesions and leukoaraiosis which may be associated with hemodynamics. It is well known that cerebral blood flow is directly related to cerebral perfusion pressure and inversely – to cerebral vascular resistance [16]. Medial smooth muscles (media) hypertrophy and intima thickening in the cerebral arteries <1 mm in diameter and arterioles in response to chronically elevated BP lead to a reduction of lumen diameter. Later, degeneration of vascular smooth muscle cells develops, and fibrin and hyaline deposition occur in the vascular wall. Those adaptive and degenerative structural changes in the wall of resistance arteries account for the main feature of cerebral circulation of patients with AH – elevated cerebral vascular resistance, which causes reduction in CBF. As the narrowing of the lumen of the arteries progresses, perfusion of the capillaries also decreases, which can subsequently lead to ischemia and lacunar infarctions [17]. In addition, a periodic rapid decrease of BP in patients with arteriolosclerosis may cause a significant reduction of blood flow due to inability of sclerotic vessels to expand [18]. It has been shown that oligodendrocytes are the most sensitive to ischemia white matter cells, mass death of which is a prerequisite for the development of extensive demyelination [19, 20]. In the case of periventricular white matter lesions, lacunar infarctions, spongiosis, "incomplete" infarctions, extensive regions of demyelination and loss of axons are very frequent findings. Multiple disseminated small areas of changes in signal intensity in deep white matter regions (so-called “punctate” subcortical leukoaraiosis) are usually caused by lacunar infarctions, small foci of gliosis, angioectasias, expansion of perivascular spaces.

According to our findings, significant correlations were observed between CBF and office and ABPM (daytime measurements mainly) BP levels (especially SBP), as well as SBP variability (diurnal, daytime, nighttime) in untreated middle-aged patients with uncomplicated AH. Relationships between a decrease in CBF measured by ASL and diurnal BP variability has not been studied so far, and BP level was assessed only in few studies [8–10] and only with office BP measurements. Thus, in the previously described CARDIA study, an increase in DBP (but not SBP) was associated with a decrease in CBF in the gray matter of the brain (p=0.01). T. Wang et al. [8] found significant differences in CBF in the genu of the corpus callosum when comparing patients with grade 1 and 2 AH. J.W. van Dalen et al. [10], on the contrary, found no correlation between the level of both the SBP and the DBP with the CBF.

Conclusions. The data obtained in this study indicate a decrease in cerebral perfusion at the earliest stages of essential AH (short disease duration, grade 1–2 AH, lack of complications) even in middle-aged patients, which distinguishes them from healthy individuals of the same age. According to the fact that CBF reduction was found even in patients without white matter hyperintensities, ASL technique used in addition to the routine MRI, can be considered as an informative method for early evaluation of target-organ brain damage in AH. Taking into account the available data on the multidirectional influence of antihypertensive drugs on brain perfusion [2], it can be assumed that the use of this MRI pulse sequence will allow to evaluate the effectiveness of antihypertensive therapy in preventing the development and/or progression of white matter lesions.

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