*Original Article*

# Brain Perfusion and Cognitive Function Changes in Hypertensive Patients

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**The aim of our study was to estimate brain perfusion and cognitive function (CF) in patients with arterial hypertension (AH) before and after hypotensive therapy. The study included 15 patients (mean age, 53.0±5.7years) with previously untreated or ineffectively treated essential hypertension of the second degree. All patients underwent brain single photon emission computed tomography (SPECT) scanning with $^{99m}$Tc-hexamethylpropylene amine oxime ($^{99m}$Tc-HMPAO) and comprehensive neuropsychological testing before and after 24 weeks of hypotensive therapy (angiotensin-converting enzyme [ACE] inhibitor or diuretics). The brain perfusion was significantly lower (15–22%) in all regions of AH patients. These patients showed a 25% decrease in attention and psychomotor speed as well as a 14% decrease in mentation. Six months of hypotensive therapy led to an increase in brain perfusion by an average of 7–11% in all brain regions. After treatment these patients demonstrated an average 11–18% improvements in attention and psychomotor speed, as well as an average 10% improvement in abstract mentation. Marked signs of brain hypoperfusion and impaired CF: decrease in attention, slowing psychomotor speed and mentation was found in hypertensive patients even without focal neurological symptomatology. Twenty-four weeks of hypotensive treatment with ACE inhibitors or diuretics had a positive effect on cerebral perfusion and led to CF improvement. (*Hypertens Res* 2008; 31: 673–678)**

***Key Words*: single photon emission computed tomography, brain perfusion, cognitive function, hypertension, hypotensive therapy**

## Introduction

Arterial hypertension (AH) is one of the major causes of chronic cerebrovascular insufficiency, cognitive function (CF) decline, and hemorrhagic and ischemic insults (*1*). Moreover, there is a relationship between AH and vascular dementia, the latter of which results in marked neurocognitive dysfunction and social disadaptation of patients. Studies of subjects with no or minor cognitive impairment have shown that neuropsychological tests can predict patients who are likely to proceed to dementia (*2*). Other studies have shown a link between midlife or later-life hypertension and subsequent cognitive impairment (*3–5*).

It is known that the main contributors to the development of vascular dementia are local or diffuse ischemic brain damages. However, only a few studies have directly investigated the cerebral perfusion status in patients with AH (*6–10*). Moreover, the efficacy of antihypertensive therapy to prevent vascular dementia in AH patients merits study in its own right. On the other hand, it has not been proven that decreases in arterial blood pressure (ABP) lead to a reduction of risk for vascular dementia. Finally, while two studies have shown that treatment of hypertension prevented cognitive dysfunction (*1*, *11*), other authors failed to establish such a correlation (*12*).

The aim of the present study was to estimate brain perfusion and CF in patients with arterial hypertension before and after hypotensive therapy.

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## Methods

### Patient Population

The study included 15 patients (11 men and 4 women; mean age, 53.0±5.7 years) with previously untreated or ineffectively treated essential hypertension of the second degree (systolic blood pressure [SBP] between 140 and 180 mmHg and diastolic blood pressure [DBP] between 90 and 110 mmHg). According to the diurnal blood pressure–monitoring data, the mean diurnal values of SBP and DBP were 151.6±10.3 mmHg and 97.6±6.2 mmHg, respectively. The average period of disease was 9.2±5.8 years.

The following criteria were used to exclude patients from this study: organic damage of target organs (including myocardial infarction, stroke and silent cerebral infarction, stenosed atherosclerosis of coronary and carotid arteries, or chronic renal insufficiency), psychiatric illnesses (including drug abuse and chronic alcoholism), a history of craniocerebral injury or neuroinfection, and serious concomitant diseases.

Eleven patients of similar age (10 men and 1 woman; mean age, 52.5±3.8 years) without angiographic signs of carotid atherosclerosis, coronary artery disease, AH, or neurological or psychiatric disorders were investigated as a control group.

### Protocol Study

All patients underwent brain single photon emission computed tomography (SPECT) scanning with $^{99m}$Tc-hexamethylpropylene amine oxime ($^{99m}$Tc-HMPAO, Ceretec; Amersham, Buckinghamshire, UK) and comprehensive neuropsychological testing before and after 24 weeks of hypotensive therapy. The therapy included administration of the angiotensin-converting enzyme (ACE) inhibitor enalapril at a dose of 10–20 mg a day (5 patients) or diuretics (indapamide-retard) at a dose of 1.5 mg a day (10 patients). These drugs were administered after a control period of 10–14 d within which patients did not receive any hypotensive, vascular or nootropic therapy.

Informed consent was obtained from each patient. The study was approved by the Ethics Committee of Human Research of the Tomsk Institute of Cardiology.

### Brain SPECT

$^{99m}$Tc-HMPAO was prepared according to the manufacturer's instructions and used within 5 min after labeling. Perfusion brain SPECT was performed 10–12 min after the injection of $^{99m}$Tc-HMPAO at a dose of 740 MBq. SPECT examinations were performed using a rotating γ-camera (Omega 500; Technicare Corp., Solon, USA) equipped with a high-resolution low-energy collimator (140 keV) and interfaced with a dedicated computer system for scintigraphic data processing (Scinti; Gelmos, Moscow, Russia). Sixty-four, 20-s projections in a 64×64 matrix were acquired over 360°. Tomographic sections were obtained using a Parzen smoothing filter as a series of transverse 2 pixel slices.

**Table 1. Neuropsychological Tests Used to Assess Cognitive Deficits**

| Cognitive test | Purpose |
|---|---|
| The Rey Auditory Verbal Learning Test (AVLT) | Immediate verbal memory, delayed memory, learning, attention (trial 1) |
| Digit Span Test | Immediate verbal memory, attention |
| Token Test | Verbal comprehension |
| Digit Symbol Test | Psychomotor speed, attention, immediate non-verbal memory |
| The Bourdon-Wiersma Dot Cancellation Test (DCT) | Psychomotor speed, sustained and activity visual attention, concentration |
| The Trail Making Test (TMT) Parts A | Volume and sustained attention, psychomotor speed |
| The Trail Making Test (TMT) Parts B | Volume and shift attention, psychomotor speed, mental flexibility |
| The Complex Figure Test (CFT) | Visuoconstruction (copy), immediate visual memory, delayed memory |

### Data Analysis

Brain SPECT images were divided into 14 symmetrical (right and left) regions of interest per patient: the inferior and superior frontal lobes, the temporal, anterior and posterior parietal lobes, the occipital lobes, and the cerebellar hemispheres. To calculate regional cerebral blood flow (rCBF, mL/100 g/min), we used a three-component model of kinetics, $^{99m}$Tc-HMPAO, that was developed by Lassen *et al*. (*13*) and modified by Yonekura *et al*. (*14*).

### Neuropsychological Testing

We assessed the cognitive status of the patients by means of seven neuropsychological tests (Table 1) (*15*, *16*).

The Rey Auditory Verbal Learning Test (AVLT) assesses verbal memory. The measures retained are the total number of words immediately recalled over the first five trials and the delayed recall of the original list. Moreover, the immediate verbal recall was measured by means of the Digit Span Test, which requires subjects to repeat an orally presented series of numbers of increasing length, first forward and than backward.

The Token Test assesses verbal comprehension. The num-

**Table 2. Regional Cerebral Blood Flow (mL/100 g/min) in Patients with Arterial Hypertension**

| Brain regions | Control ($n$=11) | | AH patients ($n$=15) | |
|---|---|---|---|---|
| | Left hemisphere | Right hemisphere | Left hemisphere ($p$ value) | Right hemisphere ($p$ value) |
| Anterior parietal | 50.4±2.6 | 51.3±2.8 | 43.4±3.8 (0.034) | 42.6±3.2 (0.033) |
| Posterior parietal | 56.9±2.1 | 55.4±2.7 | 44.8±3.1 (0.009) | 44.3±3.5 (0.010) |
| Superior frontal | 52.3±2.6 | 53.4±2.5 | 42.0±3.5 (0.025) | 41.7±3.3 (0.024) |
| Inferior frontal | 54.5±2.8 | 55.4±2.4 | 46.2±3.7 (0.013) | 47.7±3.3 (0.021) |
| Temporal | 55.4±2.8 | 56.4±2.8 | 46.6±3.3 (0.011) | 47.4±3.6 (0.014) |
| Occipital | 58.4±2.9 | 58.1±2.7 | 45.4±3.0 (0.008) | 47.1±3.2 (0.009) |

Values are mean±SD. $p$, reliability of differences *vs*. control group. AH, arterial hypertension.

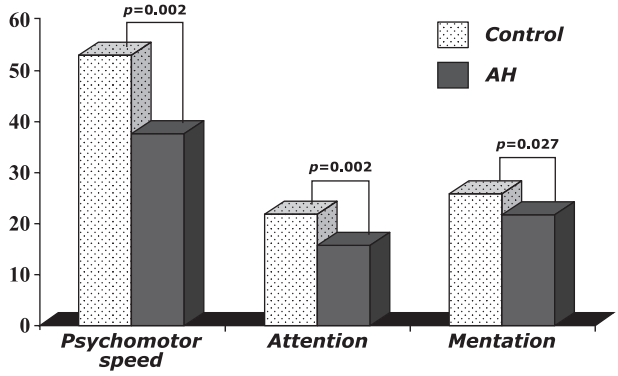


**Fig. 1.** *The cognitive status in AH patients. In patients with AH the parameters of cognitive function: attention, psychomotor speed and mentation were decreased as compared with a control group; p, reliability of differences vs. control group. AH, arterial hypertension.*

ber of correct responses is the measure taken.

The Digit Symbol Test is a task requiring sustained attention and visuomotor speed. The score was the number of correctly transcribed geometric symbols.

The Bourdon-Wiersma Dot Cancellation Test (DCT) assesses sustained visual attention. A concentration score that considers both speed and accuracy was derived.

The Trail Making Test (TMT Parts A and B) assesses visual searching speed, attention and mental flexibility. For both parts, the time to completion is the measure taken. Moreover, in TMT Part A the quantity of searching for signs over the 30 s was measured.

The Complex Figure Test (CFT) assesses nonverbal memory. This test requires patients to reproduce the points of geometric pattern in the order in which they are presented. The measures taken are the immediate and delayed recall scores.

To reduce the "test-retest" effects, different versions of neuropsychological tests were used.

### Statistical Analysis

The data received were processed by the method of variation statistics using the STATGRAF statistical package with *t*-Student parametric paired and non-paired criteria. Between-group comparisons were done using the Wilcoxon rank-sum test. Linear regression analysis was performed to calculate the relationship between rCBF and cognitive tests scores.

## Results

### Brain Perfusion and Cognitive Function in Hypertensive Patients

The results of $^{99m}$Tc-HMPAO SPECT showed that brain perfusion was significantly lower in all regions of AH patients compared with those of the control group (Table 2). The greatest rCBF decrease (21–22%) was revealed in the upper frontal, posterior parietal and occipital brain regions. Hypoperfusion was present to a lesser degree (15–16%) in the temporal, anterior parietal and inferior frontal cortex.

The results of neuropsychological testing showed a 25% decrease in attention (TMT A, score for 30 s) and psychomotor speed (Digit Symbol Test) ($p$=0.002) as well as a 14% decrease in mentation (Token Test) ($p$=0.027) in patients with AH as compared with the control group (Fig. 1). No significant difference in verbal or visual memory was found between these patients and the control group.

There was a direct correlation between rCBF and CF parameters in the patient group. Thus, a positive correlation was revealed between mentation and perfusion in the upper ($r^2$=0.214; $p$=0.008) and inferior ($r^2$=0.434; $p$=0.0004) frontal regions. Deterioration of attention correlated with a decrease in rCBF in the upper frontal ($r^2$=0.173; $p$=0.018), anterior parietal ($r^2$=0.206; $p$=0.009) and temporal ($r^2$=0.194; $p$=0.012) regions. Moreover, the decrease in psychomotor speed was associated with perfusion impairment in the frontal ($r^2$=0.436; $p$=0.003), anterior parietal ($r^2$=0.346; $p$=0.003) and temporal ($r^2$=0.189; $p$=0.002) regions.

**Table 3. Regional Cerebral Blood Flow (mL/100 g/min) in Patients with Arterial Hypertension ($n$=15) before and after Hypotensive Therapy**

| Brain regions | Before treatment | | After treatment | |
|---|---|---|---|---|
| | Left hemisphere | Right hemisphere | Left hemisphere ($p$ value) | Right hemisphere ($p$ value) |
| Anterior parietal | 43.4±3.8 | 42.6±3.2 | 47.3±3.7 (0.010) | 46.9±3.3 (0.019) |
| Posterior parietal | 44.8±3.1 | 44.3±3.5 | 48.3±3.1 (0.023) | 47.1±3.4 (0.033) |
| Superior frontal | 42.0±3.5 | 41.7±3.3 | 44.8±3.1 (0.044) | 43.9±3.8 (0.046) |
| Inferior frontal | 46.2±3.7 | 47.7±3.3 | 49.3±2.9 (0.037) | 50.6±3.1 (0.041) |
| Temporal | 46.6±3.3 | 47.4±3.6 | 49.0±3.1 (0.031) | 49.9±3.8 (0.045) |
| Occipital | 45.4±3.0 | 47.1±3.2 | 50.7±2.9 (0.013) | 51.2±3.2 (0.018) |

Values are mean±SD. $p$, reliability of differences *vs*. before treatment.

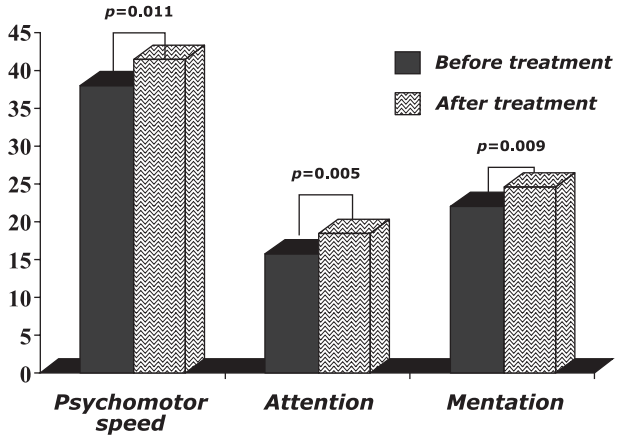


**Fig. 2.** *The change in cognitive status in AH patients after hyponensive therapy. After treatment AH patients demonstrated improvement in psychomotor speed, attention and abstract mentation; p, reliability of differences vs. before treatment. AH, arterial hypertension.*

## Changes in Brain Perfusion and Cognitive Function after Hypotensive Therapy

After 6 months of hypotensive therapy, there was a mean decrease in the diurnal values of SBP and DBP of 133.2±9.3 mmHg ($p$=0.002) and 85.6±6.8 mmHg ($p$=0.010), respectively, in the AH patients.

Antihypertensive treatment led to an improvement in brain perfusion in all patients. Thus, rCBF significantly increased by an average of 10–11% in the anterior parietal, 8–10% in the occipital, 7% in the posterior parietal, 5–7% in the superior frontal, 4–7% in the inferior frontal and 4–6% in the temporal cortex (Table 3). There was no significant difference in the increase in cerebral perfusion after treatment between the two groups of drugs (ACE inhibitors and diuretics) ($p$=0.256–0.834).

Six months of hypotensive therapy had a positive effect on CF in all of our patients with AH. These patients demonstrated improvements in attention and psychomotor speed, as evidenced by the average 16% increase in the score of the 30 s test (TMT Part A) ($p$=0.005), the average 11% decrease in the time test of TMT Part A ($p$=0.002), the average 18% decrease in the time test of TMT Part B ($p$=0.017), and the average 9% improvement in performance in the Digital Symbol Test ($p$=0.011). Moreover, we observed an average 10% improvement in abstract mentation (Token Test) ($p$=0.009) (Fig. 2).

There were direct correlations between the improvement in mentation and the increase in rCBF in the superior frontal ($r^2$=0.469; $p$=0.003), inferior frontal ($r^2$=0.435; $p$=0.003), anterior parietal ($r^2$=0.341; $p$=0.017), posterior parietal ($r^2$=0.393; $p$=0.009), temporal ($r^2$=0.501; $p$=0.002) and occipital ($r^2$=0.284; $p$=0.033) brain regions. Moreover, positive correlations were observed between the dynamics of psychomotor speed and the changes in temporal perfusion ($r^2$=0.364; $p$=0.013), as well as between the improvement in attention and the increase in rCBF in the inferior frontal ($r^2$=0.365; $p$=0.014) and anterior parietal ($r^2$=0.206; $p$=0.009) cerebral regions.

## Discussion

In spite of the wide use of brain SPECT to diagnose cerebrovascular diseases, only a few studies have investigated the cerebral perfusion status in patients with AH (*6–10*).

The results of the present investigation showed that brain perfusion was significantly decreased in all regions of AH patients in comparison with the control group. In patients with hypertension, pathological changes in microcirculation may be attributable to any of three different causes. First, there may be damage to the mechanisms for regulating vasomotor tone, which would lead to enhanced vasoconstriction or reduced vasodilator responses (*17*). Second, there may be anatomic alterations in the structure of individual precapillary resistance vessels, including hypertrophy of the smooth muscles and accumulation of elastic fibers. Finally, there may be changes at the level of the microvascular network, perhaps involving a reduction in the density (rarefaction) of arterioles

or capillaries within a given vascular bed (*18*, *19*).

Our findings are in agreement with the results of Chazova *et al*. (*6*) and Mychka *et al*. (*9*), who reported similar decreases in brain perfusion in the parietal, parietooccipital, frontoparietal and temporoparietal regions in AH patients. In two other studies, the most marked brain perfusion abnormalities in hypertensive patients were observed in the frontal and temporal lobes (*8*, *10*). In these two studies, the observed hypoperfusions in the frontal and temporal regions were probably caused by damage to the cortico-medullar arteries, which supply these segments with blood and are particularly prone to changes as a result of hypertension.

At present, initiating adequate hypertension treatment before the development of irreversible organic change is one of the most important clinical challenges (*20*). At the same time, it will be important to estimate the efficacy of treatment not only in terms of arterial pressure decrease but also in terms of the effect on the target organs. However, in the literature there are very few studies on the effects of hypotensive therapy on the cerebral microcirculation in patients with AH, and their findings are polysemantic. Two studies have shown that short-term treatment with β-blockers led to a decrease in brain perfusion in conjunction with a decrease in cardiac output (*21*, *22*). In other investigations it was established that the use of this group of drugs led to either no effect or a slight improvement on cerebral circulation (*9*, *23*). Oku *et al*. reported that was no statistically significant difference in rCBF or cerebral perfusion reserve in hypertensive patients between before and after treatment with angiotensin II receptor blockers (*24*).

In our investigation, 6 months of hypotensive therapy (ACE inhibitors or diuretics) led to an improvement in brain perfusion in AH patients. These data are in accord with the results of Chazova *et al*., who observed an improvement in brain perfusion in AH patients after 6 months of treatment with perindopril (*6*). Moreover, the experimental investigations of Frohlich (*25*) demonstrated that modern antihypertensive drugs, including ACE inhibitors, were able to reverse the pathophysiological disorders observed in hypertension by improving the circulation and vascular reserve. Although there is no direct evidence that hypotensive therapy has a positive effect on the remodeling of the cerebral arteries in hypertensive patients, some investigations have shown that antihypertensive drugs, especially ACE inhibitors, are able to regress the media hypertrophy of peripheral arteries and increase their luminal diameter (*18*).

The main limitation of our study was that cerebellar blood flow was used as a reference to estimate the rCBF. However, the drug therapies could have influenced the blood flow not only in the cerebral hemisphere but also in the cerebellum, which could have affected the rCBF measurement.

It is known that all cerebrovascular disorders, including those caused by atherosclerosis and AH, can lead to dementia development (*26*). The results of the present investigation showed disturbance of CF: decreases in attention, psychomotor speed and mentation in hypertensive patients compared with controls.

In a previously published study patients with long-term AH demonstrated memory impairment, mentation disturbance, perception mistakes and instability of attention (*27*).

There are several possible mechanisms through which hypertension might directly impair CF. AH leads to alterations in the vascular walls (lipogialinos), mainly in microcirculation vessels. These changes lead to the development of arteriolosclerosis, which in turn causes cerebrovascular reactivity changes.

Moreover, it has been hypothesized that neurocognitive dysfunction in hypertensive patients may be the result of cerebrovascular autoregulation and brain perfusion damages (*10*). Our finding of a direct correlation between the rCBF in various brain regions and CF parameters lends credence to this idea. That is, there was a positive correlation between mentation and frontal perfusion in our investigation. It is known that marked mentation disturbances develop when the frontal lobes are damaged. In the present study, deterioration of attention and decrease in psychomotor speed in hypertensive patients were caused by disorders of microcirculation in the frontal, parietal and temporal regions. At the same time, a clear dependence between perfusion abnormalities in fixed brain regions and alterations in one or more higher brain functions were not found in these patients. The given phenomenon can be obviously explained by the fact that carrying-out the majority of neuropsychological tests needs a great number of cognitive operations connected with functioning of not only brain cortex but of many other brain regions, subcortical regions and brain stem, in particular. Therefore, it is impossible to associate these brain functions with particular cortex centers, the damage to which would be specific with respect to the parameters' dynamics of either test.

Six months of hypotensive therapy had a positive effect on CF in AH patients. Thus, these patients demonstrated improvements in attention and abstract mentation, as well as increases in psychomotor speed.

A number of studies have revealed the positive effect of antihypertensive therapy on neurocognitive dysfunction. For example, Birkenhäger *et al*. showed that the actions taken to decrease arterial blood pressure also reduced the development of cognitive deficits and vascular dementia (*1*). Kalra *et al*. reported improvements in tests of attention and psychomotor speed after hypotensive treatment (*28*). Other investigators have also concluded that decreases in arterial blood pressure in patients with long-term hypertension lead to improvements in CF (*3*, *29*, *30*).

It has not been determined how decreases in ABP can decrease the risk of dementia. It is likely that antihypertensive treatment reduces the frequency of small (silent) insults (*11*). It is possible that hypotensive therapy improves CF through its positive effect on cerebral perfusion. And indeed, in our study a direct correlation was established between the improvement in mentation and the increase in rCBF in

numerous brain regions, with the closest correlation being observed in the frontal and temporal lobes. Moreover, a positive correlation was demonstrated between the dynamics of psychomotor speed and the changes in temporal perfusion, as well as between the improvement in attention and increase in rCBF in the inferior frontal and anterior parietal cerebral regions.

## Conclusion

We conclude that hypertensive patients even without focal neurological symptomatology have marked signs of brain hypoperfusion and impaired CF: decrease in attention, slowing of psychomotor speed and mentation. Twenty-four weeks of hypotensive treatment with ACE inhibitors or diuretics had a positive effect on cerebral perfusion and led to CF improvement.

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