ARTERIAL HYPERTENSION IMPACT ON CEREBRAL BLOOD FLOW IN PATIENTS WITH ALZHEIMER’S DISEASE

Impacto da hipertensão arterial sobre fluxo de sangue cerebral em pacientes com a doença de Alzheimer

Jadwiga Attier-Zmudkaab, Roger Bouzerarac, Catherine Gondryad, Frederique Couvillers, Bader Chaarani, Olivier Balédentac

ABSTRACT

BACKGROUND: Studies show the potential deterioration of brain vascularization and probable involvement of hypertension in Alzheimer disease (AD). OBJECTIVE: The objective was to evaluate the potential impact of hypertension on cerebral vascular flows in a sample of Alzheimer’s patients. METHODS: 19 patients with AD, including 10 with hypertension (aHT+) and 9 without hypertension (aHT-) were recruited. They underwent clinical evaluation and phase-contrast MRI protocol for flow assessment. Cerebral arterial flow distributions were evaluated using kurtosis and skewness indices at the intracranial and extracranial levels. RESULTS: No significant differences were found in the mean arterial flow, pulse flow and kurtosis between the levels in the AD aHT+ population. There was a significant difference in skewness between extra- and intracranial levels (p = 0.01). No significant differences were found in the mean arterial flow between the levels in the AD aHT- population. A significant difference was observed in the pulse flow (p = 0.03), kurtosis (p = 0.02) and skewness (p = 0.008) between the levels. At the extracranial level we did not find any significant differences in the mean arterial flow, pulse flow or skewness between aHT+ and aHT-. There was a significant difference in kurtosis at the extracranial level between the aHT+ and aHT- (p = 0.03). At the intracranial level, there were no significant differences in all parameters. CONCLUSION: Results showed a difference between cerebral vasculature in AD for aHT+ and aHT- groups. This is probably related to the loss of arterial compliance induced by the degradation of the vascular system.

KEYWORDS: aging; Alzheimer disease; hypertension; blood flow velocity; contrast media; magnetic resonance imaging.
INTRODUCTION

In 2004, Bateman demonstrated the key role of vascular risk factors in the development of neurodegenerative diseases, linking vascular pathophysiology and neurological effects on blood pulsation force sent into the arterial tree. The study showed that vascular pathophysiology is related to the strength of the pulse waves induced in the craniospinal cavity by the arterial vascular tree.\(^1\)

In 2009, Bell described the crucial role of vascular dysfunction in Alzheimer’s disease (AD). Recent data from brain imaging studies in humans and animal models suggest that cerebrovascular dysfunction can precede cognitive decline and the onset of neurodegenerative changes in AD. Cerebral hypoperfusion and impaired clearance of amyloid β across the blood-brain barrier (BBB) may contribute to the onset and progression of Alzheimer’s dementia. A decrease in cerebral blood flow adversely affects the synthesis of proteins required for memory and learning, and can eventually lead to neuronal injury and death. Inadequate clearance of Aβ in the brain by cells of the neurovascular unit can lead to its accumulation in the blood vessels and the brain parenchyma. The accumulation of Aβ in the cerebral blood vessels, known as cerebral amyloid angiopathy (CAA) is associated with cognitive decline and is one of the AD pathology characteristics.\(^3\)

A previous study showed both an increased average blood flow in the cerebral arteries and high arterial systolic peak in patients with amnestic mild cognitive impairment (MCI).\(^3\) Similarly, in 2009, Dai showed that average blood flow in cerebral arteries, average blood flow in cerebral veins and the oscillations of the cervical cerebrospinal fluid (CSF) were highest in patients with amnestic mild cognitive impairment.\(^4\) These results had come as a surprise as several authors have demonstrated a local decrease in blood flow in patients with amnestic mild cognitive impairment.\(^5\) Other studies have paradoxically showed that early on, cerebral blood flow is increased in the hippocampus and other regions in Alzheimer patients.\(^6\)

Various clinical, epidemiological and pathological studies suggest that AD is more frequently associated with stroke than expected; vascular brain lesions and those connected with AD are often related; β-amyloid plaques are more abundant in non-demented patients who have died from coronary artery disease than in those who have died from other causes. These findings suggest that vascular pathology and AD are directly related or at least share common determinants.\(^7\)

High blood pressure and atherosclerosis are associated with an increased risk of AD.\(^7\) A history of hypertension is more frequent in patients with AD. Hypertension promotes the onset of leukoaraiosis, and stroke could also be a factor for AD. Raffaitin et al. demonstrated the impact of hypertension on cognitive decline.\(^12\) In 2005, Hanon et al. found that cognitive decline was more marked in AD patients who had a history of hypertension whereas there was no relationship with cognitive decline associated with a deterioration in autonomy in patients who reported their hypertension after the first signs of AD.\(^13\)

According to Kalaria et al., vascular diseases might be a cause of AD. Vascular risk factors such as hypertension, atherosclerosis, and diabetes can have an impact on the structure of vessels and, consequently, play a role in blood flow.\(^14\) There is a relationship between blood pressure and blood flow. The flow in an artery depends on the blood pressure at each
end of the vascular tree (the pressure change) and the resistance of the vascular tree to the flow of blood. Unfortunately, studies on the direct link between high blood pressure and cerebral blood flow are scarce. Toyoda et al. demonstrated in a population of spontaneously hypertensive rats that chronic hypertension alters cerebral autoregulation in the large arteries and arterioles by decreasing vessel dilation.  

Phase Contrast Magnetic Resonance Imaging (PC-MRI) is currently the only technique used to noninvasively quantify cerebral blood flows during the cardiac cycle, without the limitation of the skull barrier. In 2009, studying patients with dementia assumed to be AD, Henry-Feugeas routinely performed PC-MRI in addition to morphological MRI. The study discussed the role of the vascular component in the advanced stages of the disease. Many authors have demonstrated the potential impairment of cerebral vasculature in AD. Other studies show that hypertension may be involved in the pathophysiology of AD.

The hypothesis in the present study is that hypertension alters cerebral vascular blood flow in AD. The objective of this study was to evaluate the potential impact of hypertension on cerebral vascular flow in a population of Alzheimer’s patients.

**MATERIAL AND METHODS**

**Participants**

The subjects used in this study were elderly patients with memory disorders treated in the Geriatric Medicine and Neurology Department at the University Hospital of Amiens. The study protocol was approved by the local ethic committee (Comité de protection des personnes nord-ouest II CPP n° 2007/33; NCT 01815112). All participants received an explanation of the study’s objective and procedure. Written informed consents were obtained for all subjects to participate in the research.

Patients included in the study met the following criteria:

- Age greater than or equal to 65 years old;
- Memory complaint reported by the patient and/or their family;
- Dementia syndrome.

We have selected patients with mild AD, diagnosed according to both, the DSM-IV and NINCDS-ADRDA criteria with a Mini Mental State Examination (MMSE) score ≥ 15 out of 30.

A total of 19 patients with Alzheimer's like disease were recruited. After signing the informed consent, patients were hospitalized for neuropsychological assessment, MRI with flow sequence and clinical evaluation.

Blood pressure was measured three times a day, in the morning before taking medication, at noon and in the evening during hospitalization. The diagnosis of hypertension, was reported by general practitioners. The population was divided into two groups:

1. **aHT+** group: 10 subjects with controlled hypertension diagnosed by the general practitioner before the diagnosis of dementia. 7/10 of them were receiving antihypertensive therapy, 2 with Angiotensin converting enzyme (ACE inhibitors) inhibitors. Other antihypertensive drugs found in this group were calcium channel blockers, sartans, beta blockers, thiazide diuretics and central antihypertensive drugs;

2. **aHT−** group: 9 subjects without hypertension.

**Imaging**

Subjects were imaged on a 3 T scanner (Signa, GE Healthcare, WI). The protocol consisted of phase-contrast velocimetry sequences with retrospective cardiac gating (through a peripheral pulse sensor) performed as in previous studies. The main parameters were as follows: TE (echo time): 6-9 milliseconds (ms); TR (repetition time): 20 ms; the flip angle: 25°; the number of stages: 32; the field of view: 160 × 120 mm; the matrix: 256 × 128; slice thickness: 5 mm encoding speed (Venc): 80 cm/s for cervical and intracranial vascular flow. The acquisition planes were selected perpendicularly to the assumed direction of cervical and intracranial vascular flow with angiography sequence (Figure 1).

**Processing and data analysis**

An analysis of the images to calculate flow rates and associated curves was made using an open IDL based flow processing software (Figures 2A and 2B).

The cerebral arterial flow was defined as the summation of the internal carotid and vertebral arteries (at the extracranial level) and the internal carotid and basilar arteries (at the intracranial level). The pulse flow was defined as the difference between the peak systolic flow and the diastolic flow (Figure 2C).

Cerebral arterial flows and pulse flows were automatically calculated from the global arterial flow curves at the extracranial (cervical) and intracranial (cerebral) levels (Figure 2B).

Flow distribution during a cardiac cycle can be assessed through kurtosis (flattening) and skewness (asymmetry) coefficients of the data at the intra- and extracranial levels (refer to appendix).

**Statistical analysis**

Results are expressed as (mean ± SD).
A non-parametric Wilcoxon test was used to evaluate the variability of the parameters describing arterial flow curves between the two populations aHT + and aHT- and between the intra- and extracranial levels. The values of skewness and kurtosis between each group were compared using the Mann-Whitney test. A p-value of 0.05 was taken as statistically significant.

RESULTS

Participants

The mean age of the AD population in the present study was 79 ± 5 (aHT+: 79 ± 6 and aHT-: 79 ± 5, p = 0.96).

For aHT+ group (9 females and 1 male), the mean MMSE score was 20 ± 6.
For aHT- group (3 females and 6 males), the mean MMSE score was 18 ± 8.

Intra-group comparison: aHT+ extracranial versus intracranial level (Figures 3A and 3B).

Mean cerebral blood flow curves over time are depicted in Figure 3C.

No significant differences were found in the mean arterial flow, pulse flow and kurtosis between the levels in the AD aHT+ population. However, there was a significant difference in skewness between extra- and intracranial levels (p = 0.01, extracranial level: 0.73 ± 0.15 vs. intracranial level: 0.64 ± 0.17) (Table 1).

### Table 1 aHT+ and aHT- groups: extracranial and intracranial levels comparison.

<table>
<thead>
<tr>
<th></th>
<th>Extracranial level</th>
<th>Intracranial level</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>aHT+ group</strong></td>
<td></td>
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<tr>
<td>mean arterial flow (mL/min)</td>
<td>485 ± 74</td>
<td>515 ± 165</td>
<td>0.63</td>
</tr>
<tr>
<td>pulse flow (mm³/s)</td>
<td>11320 ± 2517</td>
<td>11029 ± 4319</td>
<td>0.92</td>
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<td>kurtosis</td>
<td>-1.11 ± 0.31</td>
<td>-1.07 ± 0.3</td>
<td>0.84</td>
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<td>skewness</td>
<td>0.73 ± 0.15</td>
<td>0.64 ± 0.17</td>
<td>0.01</td>
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<tr>
<td><strong>aHT- group</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>mean arterial flow (mL/min)</td>
<td>508 ± 94</td>
<td>509 ± 103</td>
<td>0.9</td>
</tr>
<tr>
<td>pulse flow (mm³/s)</td>
<td>11636 ± 3185</td>
<td>9941 ± 2574</td>
<td>0.03</td>
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<tr>
<td>kurtosis</td>
<td>-0.78 ± 0.39</td>
<td>-1.02 ± 0.18</td>
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<tr>
<td>skewness</td>
<td>0.88 ± 0.16</td>
<td>0.69 ± 0.07</td>
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<td><strong>Comparison aHT+ vs aHT-</strong></td>
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<tr>
<td>mean arterial flow (mL/min)</td>
<td>P = 0.2</td>
<td>P = 0.88</td>
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<tr>
<td>pulse flow (mm³/s)</td>
<td>P = 0.78</td>
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<td>skewness</td>
<td>P = 0.095</td>
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</table>

Data expressed as mean ± SD; Bold value indicates statistical significance; Wilcoxon or Mann-Whitney’s tests were used for P-value calculation.
Intra-group comparisons:
aHT+ extracranial versus intracranial level
Mean cerebral blood flow curves over time are depicted in Figure 3D.
An example of individual cerebral blood flow curves of aHT- subject, at intra- and extracranial levels, is depicted in Figure 4.
No significant differences were found in the mean arterial flow between the levels.
A significant difference was seen in the pulse flow between the levels (p = 0.03, extracranial level: 11636 ± 3185 mm/sec vs. intracranial level: 9941 ± 2574 mm/sec), “kurtosis” (p = 0.02, extracranial level: -0.78 ± 0.39 vs. intracranial level: -1.02 ± 0.18), “skewness” (p = 0.008, extracranial level: 0.88 ± 0.16 vs. intracranial level: 0.69 ± 0.07) (Table 1).

Comparison between aHT+ and aHT- groups at extracranial vs. extracranial level
Mean cerebral blood flow curves over time are depicted in Figure 3A.
At the extracranial level we did not find any significant differences in the mean arterial flow, pulse flow or “skewness” between aHT+ and aHT- groups. There was a significant difference in the kurtosis at the extracranial level between the two groups (p = 0.035, aHT+: -1.11 ± 0.31 vs aHT-: -0.78 ± 0.39) (Table 1).

Comparison between aHT+ and aHT- groups intracranial versus intracranial level
Mean cerebral blood flow curves over time are depicted in Figure 3B.
At the intracranial level there were no significant differences in the mean arterial flow, pulse flow, “kurtosis” or “skewness” between aHT+ and aHT- groups (Table 1).

DISCUSSION
The question we initially posed was whether or not hypertension would have an impact on cerebral vascular flow. The primary discovery of our research was the flattening of the blood curve in the aHT- patients, which is not preserved in aHT+ patients. The present findings do not show statistically significant differences in the mean arterial or pulse flow between the aHT+ and aHT- patients. The phenomenon occurs in a rigid box, so compliance must intervene to compensate for the rigidity. The difference in kurtosis is due to the deleterious effect of hypertension on compliance by the stiffening of vessels.

Age, sex and the covariates of study participants
The mean age in the present study was 79 ± 5. Because the average age of our Alzheimer’s patients was similar for both groups with and without hypertension, the groups were easily comparable. Age is a major risk factor for AD,29 hypertension29 and cerebrovascular changes develop with age30,31, influencing the results of blood flow. With age, arterial changes appear: intimal thickening, the destruction of endothelial cells, and smooth muscle cells losing their contractile phenotype to a secretory phenotype. The calcification of arterial walls occurs, contributing to high blood pressure and increasing the risk of stroke, which is often associated with increased morbidity and mortality in patients with chronic kidney disease. The arterial system becomes less compliant due to the alteration of the elastic fibers and the rigidification of collagen. Increased arterial stiffness leads to an increase in systolic and pulse blood pressure. The ability of the endothelium to relax the smooth muscle cells of the arterial wall is then impaired, limiting the possibilities of arterial vasomotoricity in physiological or pathological conditions.32,33

In 2007, Stoquart-El Sankari confirmed that cerebral blood flow decreases with age regardless of the study technique30,31. She observed a decrease in the cerebral blood flow in the elderly with preserved compliance. Flow measurements were made using MRI to compare 19 young subjects (mean age 27 ± 4 years old) with 12 elderly patients (mean age 71 ± 9 years old). The mean cerebral blood flow in the young and elderly subjects was 688 ± 115 ml/min and 509 ± 103 ml/min, respectively.34 In our aHT-population, consisting of 9 patients, the mean cerebral blood flow was 508 ± 94 ml/min at extracranial level and 509 ± 103 ml/min at intracranial level. The mean age of our aHT-population was 79 ± 5 years old, which is older than the population in the study of Stoquart-El Sankari. On the other hand, the mean cerebral blood flow in the aHT+ population was 485 ± 74 ml/min at extracranial level, i.e., lower than in...
the elderly studied by Stoquart-El Sankari. In contrast, the mean intracranial cerebral blood flow was 515 ± 165 ml/min, much higher than among the elderly in the cited study. Physiological brain aging has an impact on vascular flow, the impact of AD on blood flow was demonstrated by the same authors in 2011. They found increased cerebral blood flow in patients with amnestic MCI and decreased blood flow (even standardization) in Alzheimer patients. Unfortunately, we note an imbalance of genders in the groups (aHT+ : 9 females and 1 male and aHT- : 3 females and 6 males), which could influence the results.

We didn’t include vascular risk factors such as cigarette consumption, body mass index, cholesterol levels, diabetes mellitus, stroke, cardiovascular disease or apolipoprotein genotype in statistical analyses, which is a limitation of this study.

Passage from the extracranial to the intracranial level

Arterial flow propagation conditions are not the same at cervical and cerebral levels. We must not forget that the skull (intracranial = cerebral level) is rigid and non-extendable. In order to observe vascular flow and to obtain the most accurate measurements, we are interested in two scanning levels, the extra- and the intracranial ones. Cerebral blood flow at the extracranial level (cervical) is estimated by using the sum of flow in the internal carotid and vertebral arteries, whereas at the intracranial level (cerebral) it is estimated using the sum of flow in the basilar and internal carotid arteries. In our aHT- and aHT+ population, the mean arterial flow remained unchanged during the passage from the extra- to the intracranial level.

Apart from the loss of a small part of arterial blood flow related to cerebellar irrigation, which represents 10% of the cerebral vasculature, there was no significant reduction in the mean cerebral blood flow, taking into account the fact that the precision of the measurement was within the magnitude of decrease. We expected a potential difference in the peak flow, which is logically slightly delayed between the levels and represents the flow propagation in the arterial tree. This small phase shift causes a difference in skewness coefficient (asymmetry), which is slightly but significantly different for aHT- and aHT+ subjects. This is related to a significant drop in pulse flow (11,636 mm3/sec vs. 9,941 mm3/sec, p = 0.03) among aHT- patients, which translates into the flattening. As for the kurtosis coefficient, the pulse flow is not modified in the aHT+ patients. This flattening of the flow distribution can be explained by the compliance of the vascular system in AD patients who are not affected by hypertension. In aHT+ group, compliance is modified due to impairment of the vascular wall leading to the failure of protective mechanisms because of the stiffening effect.

aHT- vs. aHT+

Hypertension is a cardiovascular risk factor often found in Alzheimer patients. Given that our results, in particular the mean blood flow in the aHT— subjects at the extra- and intracranial levels — were similar to the elderly population studied by Stoquart-El Sankari et al. in 2007 but different from the aHT+ population, suggests the impact of hypertension on vascular blood flow. A study by Kuyumcu et al. showed conflicting results. The prevalence of hypertension was lower in AD patients than in those with normal cognitive function in the study population. In the present study, 7 out of 10 aHT+ patients were given treatment, including two who received ACE inhibitors (angiotensin converting enzyme). The protective influence of ACE inhibitors and calcium channel blockers on the vascular wall has been previously demonstrated in the literature. There were no significant differences between blood flow in the aHT+ and aHT- groups, but there were major standard deviations. The aHT+ and aHT- populations did not behave in the same way when observing the passage from the extra- to the intracranial compartment. The lack of statistical significance in kurtosis in the aHT+ patients could be due to the hardening of vessels affected by the process related to hypertension. Similarly, the lack of a loss of pulse flow in the same population (11,320 mm3/sec at the extracranial level and 11,029 mm3/sec at the intracranial level) could be linked to the non-compliance of vessels damaged by hypertension. The loss of flow is well marked in the aHT+ population in the passage from extra- to the intracranial level (11,636 mm3/sec at the extracranial vs. 9,941 mm3/sec at the intracranial level for p = 0.03).

No clear impact on the curves was observed; however, on an individual basis, aHT+ patients showed no significant differences across the extra- and intracranial levels, demonstrating the lack of vascular compliance most likely related to vascular stiffness (vascular remodeling).

We must not forget that blood flow does not equal blood pressure, flow rate increases with increasing pressure, but it depends on vascular resistance. Therefore, special attention must be given to the parameters of resistance (viscosity, calcifications, rigidity etc.) modifiable by ACE treatment. The hypothesis here is that among elderly, hypertension (mainly systolic) will damage the vessels. Without the knowledge of whether or not our patients had been receiving effective antihypertensive treatment and for how long, we can only suppose that patients presenting MCI were in...
“a state of fight”, where an increase in cerebral blood flow was followed by its fall back to normal levels (or pseudo return to balance). This might be associated with vascular adaptation (deterioration) in hypertension, which was deactivated due to hypertension-induced vascular changes.\(^3\) This phenomenon would lead to a failure of self-regulatory system of the brain.

Another explanation for the lack of differences between the two groups is effective treatment or proper choice of medication (ACE protects the walls, so there is no influence on blood flow). Among aHT+ patients (whose hypertension was discovered by general practitioner more than 10 years before cognitive decline and is well controlled), 7 were receiving treatment, 2 with ACE inhibitors (angiotensin converting enzyme). ACE inhibitors improve endothelial function and reduce left ventricular and arterial hypertrophy more effectively than other antihypertensive drugs.\(^40\) We may not have seen any differences in the mean pulse flow between aHT+ and aHT- patients due to the fact that most of aHT+ subjects were taking antihypertensive treatment, and no complications of high blood pressure were found. We also note a significant difference in MMSE score for participants in the aHT+(20±6) and aHT-(18±8). It is surprising that hypertensives performed better on this test.

**CONCLUSION**

Results showed a difference between cerebral vasculature in AD for aHT+ and aHT- groups. Our hypothesis is that there is a linear and evolutionary relationship between arterial hypertension and AD. In at least both hypertension and Alzheimer’s disease, we see a degradation of the vascular system, more precisely a modification in the characteristics of the vessel function (vasoreactivity). As a result, we witness a failure of the self-regulatory system of the brain, and an amplification of the phenomenon in the final stage.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**REFERENCES**