INTRODUCTION: Neurodegenerative diseases, a major public health problem, could have a vascular origin. Phase-contrast magnetic resonance imaging (PC-MRI) enables reliable, non-invasive, and rapid measurements of cerebrospinal fluid (CSF) and blood flows, and evaluation of the mechanical coupling between cerebral blood and CSF flows throughout the cardiac cycle (CC). OBJECTIVES: Our purpose was to evaluate the potential of PC-MRI to the study of cerebral blood and CSF flows in patients with neurodegenerative diseases such as Alzheimer’s disease (AD), Mild cognitive impairment with amnesic disorders (MCIa) and Vascular Dementia (VD). METHODS: The elderly population consisted of 20 AD (age: 80 ± 5 years); 12 AD patients with vascular cerebral lesions (ADvasc) (age: 81 ± 5 years), 10 MCIa patients (age: 80 ± 7 years), and 8 VD patients (age: 78 ± 7 years) were identified. They underwent the same PC-MRI protocol and were compared to 13 age-matched Healthy Elderly (HE) (age: 71 ± 9 years). Arterial blood pressure was analyzed to detect patients with hypertension. RESULTS: Significantly higher cerebral blood and CSF flows were observed in HE when compared to VD, AD and ADvasc, (p<0.05), but not MCIa patients who yielded the highest cerebral arterial and venous blood flows and stroke volumes compared to the other patients, (p<0.05). The highest oscillations of CSF were also detected in MCIa patients (p<0.05). CONCLUSION: Our preliminary data suggests an increase in cerebral arterial blood and CSF flows in MCIa. PC-MRI provides a new hydrodynamic view, which may help evaluate a potential role of cardiovascular alterations in neurodegenerative diseases. KEYWORDS: Magnetic Resonance Imaging/methods; neurodegenerative diseases; Elderly.
INTRODUCTION

Neurodegenerative diseases are a major public health problem. Alzheimer’s disease (AD) is a progressive neurodegenerative disorder, the main cause of disability in the elderly and the main reason for admission to an institution. It begins early before dementia symptoms, with the appearance of cognitive impairment affecting people in different ways, and it is possibly associated with behavioral disturbances. The disease can evolve over several years with the emergence of progressive dependence, inducing restriction of the activities of daily living, from instrumental (financial handling, transportation, ability to take medication and use phone) to basic activities (bathing, dressing, feeding etc.).

The evolution of clinical signs translates the development of biological anomalies. Brain damage of AD is often associated with vascular lesions.

Given that neuropathological investigations cannot be done in-vivo, AD has evolved into a predominantly clinical entity with a probabilistic diagnosis. The diagnosis of memory or cognitive complaints has been based on clinical analysis, biological tests and morphological imaging. More recent techniques have been increasingly used in memory clinics, such as hippocampal volumetry with magnetic resonance imaging (MRI), protein determination in cerebrospinal fluid (CSF) and positron emission tomography imaging with specific tracers (11C-PIB, 18F-AV-45). The last two techniques may help the clinician to identify a neuropathological pattern, but can be a potential source of confusion, particularly in light of the repeated reports that pathological changes (“Alzheimer’s pathology”) can exist without the concomitant clinical manifestations of AD. Despite increasing knowledge concerning amyloid pathology and the pathological cascade leading to neuronal death encountered in neurodegenerative diseases, the clinical diagnosis remains difficult without a gold-standard procedure. Further development of new tools to permit correct diagnosis is a challenge.

Many studies showed that several vascular risk factors are also those of AD. Methods for exploration of brain vascular and CSF hydrodynamics, based on our knowledge of risk factors for developing neurodegenerative diseases, especially vascular risk factors, could be a new approach to meet this challenge.

The bulk CSF circulation first described in cisternography studies relies on permanent transit of CSF from production to resorption sites and could be involved in normal pressure hydrocephalus (NPH) as well as in AD, suggesting that it can constitute a pathogenic factor of AD.

The second type of CSF flow is due to a rapid and dynamic cardiac pulsation. It is now well established that bidirectional oscillatory CSF movement occurs as a result of cardiac cycle-related cerebral blood volume variations. In addition to these transcranial CSF pulsatile dislocations, several recent studies have described intracranial CSF movement in response to cyclic blood flow, as well as the role of the brain itself. Similarly, the spinal circulation of CSF seems to be more complex than the simple bulk flow, moving downward posteriorly, and upward anteriorly. MRI studies have also suggested an active pulsatile spinal CSF flow, and a role of high compliance of the spinal compartment in regulating intracranial volumes and pressures exchanges. The role of pulsatile flow is to compensate the increase of intracranial volume (response to arterial inflow) before the venous outflow, to protect the cranial non-extensible box and the brain (Monro-Kellie doctrine). According to this doctrine, in physiological states, any volume increase in one of those compartments should be compensated by withdrawal of an equal volume in one of the two other compartments, in order to maintain a steady intracranial pressure (ICP). Each of these compartments can be characterized by its compliance, which corresponds to the pressure increase that occurs in the system when a volume is added to it.

A few works addressed the role of cerebrospinal hydrodynamics in the etiopathology of neurodegenerative diseases. Murphy et al. showed that Alzheimer’s pathology alters the mechanical properties of the brain by microstructural events that finally decrease brain stiffness. Another group of investigators suggested the presence of a compensatory process in mild cognitive impairment (MCI); they found a relationship between its functions and brain atrophy. Cerebral blood flow (CBF) is significantly elevated in the hippocampus and other regions early affected in AD. Silverberg, who explored the abnormalities of CSF production and turn-over, found an increase of intracranial CSF pressure in AD. The unifying concept in the pathogenesis of neurodegenerative diseases, based on alterations in CSF dynamics, was proposed by Chakravarty in 2004. Bateman went further and demonstrated the role of vascular risk factors as a common risk factor in neurodegenerative diseases, as vascular pathophysiology is related to the strength of the pulse waves induced in craniospinal cavity by the arterial vascular tree. Finally, Henry-Feugeas proposed to measure cerebral hemodynamics and to analyze the relationship between structural brain damage and cognitive decline, using phase-contrast magnetic resonance imaging (PC-MRI).

Many publications have discussed this brain-CSF dynamic organization, but earlier studies did not include flow assessment. In our previous study, we used this new hydrodynamic approach in a population of volunteers to define hydrodynamic...
MATERIALS AND METHODS

Participants

Fifty patients were recruited in the geriatric unit of the university hospital in Amiens and among outpatients with amnestic disorders. Patients were classified after a neuro-psychological and geriatric consultation. Dementia and AD were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria, respectively.35-36 VD was diagnosed according to NINDS-AIREN (National Institute of Neurological Disorders and Stroke and a European panel of experts). We selected patients with AD, MCI and VD using a mini-mental state examination (MMSE)37, with a score > or = 15 out of 30. The diagnostic criteria for patients with MCI were those published by Petersen et al.:38

- subjective memory complaint (i.e. reported by the patient or by their family);
- a documented, objective memory impairment adjusted for age and education;
- relatively normal general cognitive function;
- no dementia according to the DSM-IV criteria;
- generally preserved activities of daily living. Patients with a relevant neurological disease (stroke, tumor etc.) or cerebrovascular risk factors (except for arterial hypertension controlled by medication) were not included in the study.

The population with cognitive impairment consisted of 20 AD patients (age: 80 ± 5 years), 12 AD patients with vascular cerebral lesions (ADvasc) (age: 81 ± 5 years), 10 MCI patients with amnestic disorders (MCIs) (age: 80 ± 7 years), and 8 VD patients (age: 78 ± 7 years). All patients underwent the same PC-MRI imaging protocol. They were compared with a population (n=13) of age-matched healthy elderly (HE) (age: 71± 9 years) with normal neurological and neuropsychological screening results (notably a normal MMSE score for educational level) and no active psychiatric, neurological, cognitive disorders or cerebral lesions found with MRI.

Arterial blood pressure was also analyzed in our groups to detect patients with hypertension. 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. Among our AD patients, 45% (N=9) had hypertension, diagnosed by the general practitioner before the diagnosis of dementia. Seventy-seven percent (N=7) were receiving antihypertensive therapy, 2 with ACE (angiotensin-converting enzyme) inhibitors.

Among our ADvasc patients, 75% (N=9) had hypertension, diagnosed by the general practitioner before the diagnosis of dementia. All of them were receiving antihypertensive therapy, 55% (N=5) with ACE inhibitors.

Among our VD patients, 37% (N=3) had hypertension, diagnosed by the general practitioner before the diagnosis of dementia. Sixty-six percent (N=2) were receiving antihypertensive therapy, 50% (N=1) with ACE inhibitors.

Among MCIs patients, 70% (N=7) had hypertension, diagnosed by the general practitioner before the appearance of cognitive impairment symptoms. Eighty-five percent (N=6) were receiving antihypertensive therapy, 42% (N=3) with ACE inhibitors.

Concerning HE, their blood pressure monitoring was normal. We had no information in their clinical history about hypertension and antihypertensive drugs.

All of the patients had controlled arterial blood pressure. The study protocol was approved by our independent ethics committee (CPP: SIRET 268 000 148 000 18/APE: 851 A). All participants were advised on study objectives and procedures and provided their written informed consent to participation.

Data acquisition

All MRI exams were performed with a standardized imaging protocol on a 1.5 or 3 Tesla (T) machine (Signa; General Electric Medical System, Milwaukee, WI, USA). Flow images were acquired with a 2D fast cine PC-MRI pulse sequence with retrospective peripheral gating, so that the 32 analyzed frames covered the entire CC. The MRI parameters were as follows: 2 views per segment; field-of-view...
(FOV): 14 × 14 mm²; matrix: 256 × 128; slice thickness: 5 mm; one excitation for the 3 T machine and two for the 1.5 T machine. Velocity (encoding) sensitization was set to 80 cm/s for the vessels, 10 or 20 cm/s for the aqueduct and 5 cm/s for the cervical subarachnoid space (SAS). A sagittal scout view was used as a localizer to select the anatomical levels for flow quantification. The selected acquisition planes were perpendicular to the presumed flow direction. Sections for each flow series are presented in Figure 1. The acquisition time for each flow series was about 90 s on the 3 T machine and 180 s on the 1.5 T machine, with slight variations that depended on the participant’s heart rate. The total additional examination time for these CSF and blood flow investigations was around 10 min.

Data analysis

PC-MRI images were analyzed using in-house image processing software. An optimized CSF and blood flow segmentation algorithm was used to automatically extract the region of interest (ROI) at each level (Figure 1).

In each ROI, flows were calculated for each of the 32 time frames in order to build a flow curve over the course of 32 points of the CC.

The right and left internal carotid arteries (ICAs) and vertebral arteries (VAs) were summed to generate the total arterial cerebral blood inflow curve (tCABF) during CC. The mean flow of tCABF was calculated (mCABF).

The right and left internal jugular veins were summed to generate the total jugular cerebral blood outflow curve (tCJBF) during CC. The mean flow of tCJBF was calculated (mCJBF).

The aqueductal and cervical (C2-C3) areas were also segmented to reconstruct CSF at aqueductal level (CSFaque) and CSF at cervical level (CSFcerv) curve flows during CC. CSF oscillates during CC, so it was not interesting to calculate mean flows — as we have done for blood —, since it

Figure 1 Phase-contrast magnetic resonance imaging data acquisition, curves corresponding to cerebral blood and cerebrospinal fluid flow.
would be of negligible value. Stroke volume (SV), the volume displaced through ROI during CC, was calculated as the mean of the integral of the positive and negative parts of the CSF flow during CC.

**Statistical analysis**

Shapiro-Wilk test was used to test for normality. CSF and blood flow parameters for the five groups (patients with AD, ADvasc, MCIa, VD and HE) were then compared using analysis of variance (ANOVA), followed by Tukey’s posthoc test for pairwise comparison. Age and gender were included as covariates in the analysis. Statistical analysis was performed using SPSS 17.0 software.

**RESULTS**

Table 1 summarizes our preliminary flow results for the arterial, venous and CSF compartments in the five study groups. In general, significantly higher CBF and CSF flow were observed in HE subjects when compared to VD, AD and ADvasc patients (p < 0.05), but not MCIa patients, who yielded the highest CBF and SV compared to the other patients (Figure 2).

MCIa patients showed significantly increased arterial blood flow and SVs when compared to the three other groups in the cervical compartment and to ADvasc and AD in the cerebral compartment (p < 0.05) (Figure 2). In addition, arterial cerebral SV was significantly decreased in ADvasc compared to AD (p < 0.05). Similarly, MCIa also showed significantly increased venous flow when compared to VD and ADvasc patients, in cervical and cerebral compartments (p < 0.05).

The highest oscillations of CSF at both aqueductal and cervical levels were detected in MCIa patients. We noticed significantly higher cervical oscillations in MCIa group compared to ADvasc (p = 0.03). The CSF oscillations in the remaining groups were not significantly different; nevertheless, the lowest oscillations were found in ADvasc for cervical level.

**DISCUSSION**

In this original study, 50 patients with the most common cognitive disorders were enrolled. We compared the arterial and venous blood flows, as well as the CSF flow, in these patients with those in HE.

The main result indicated that the MCIa group had the highest mean arterial and venous blood flows and cervical CSF oscillations, which, surprisingly, conflicts with what many authors have already found, demonstrating less CBF in MCIa.39

In our study, CBF was measured directly in major cerebral arteries. We believe that the increase of CBF in major cerebral arteries measured by PC-MRI is associated with decreased brain perfusion in the capillary bed.

Alsop et al.23 demonstrated that CBF was significantly lower in the bilateral precuneus, parietal association cortex and the left inferior temporal lobe in AD population. However, after correction for grey matter loss, CBF was significantly elevated in the hippocampus and other medial temporal structures which are early affected in AD. These authors suggested the existence of compensatory or pathological elevation of neural activity, inflammation, or elevated production of vasodilators.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MCIa</th>
<th>AD</th>
<th>ADvasc</th>
<th>VD</th>
<th>HE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>80 ± 7</td>
<td>80 ± 5</td>
<td>81 ± 5</td>
<td>78 ± 7</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>MMSE</td>
<td>27 ± 2</td>
<td>20 ± 4</td>
<td>21 ± 4</td>
<td>23 ± 4</td>
<td>N</td>
</tr>
<tr>
<td>HT</td>
<td>7</td>
<td>11</td>
<td>9</td>
<td>3</td>
<td>N</td>
</tr>
<tr>
<td>mCABF (mL/min)</td>
<td>626 ± 175</td>
<td>512 ± 136</td>
<td>449 ± 99</td>
<td>553 ± 153</td>
<td>708 ± 145</td>
</tr>
<tr>
<td>mCJBF (mL/min)</td>
<td>355 ± 44</td>
<td>325 ± 83</td>
<td>278 ± 47</td>
<td>326 ± 79</td>
<td>382 ± 175</td>
</tr>
<tr>
<td>SVcerv (mL/CC)</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.4 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>SVaque (mL/CC)</td>
<td>0.07 ± 0.03</td>
<td>0.05 ± 0.03</td>
<td>0.05 ± 0.03</td>
<td>0.05 ± 0.02</td>
<td>0.07 ± 0.02</td>
</tr>
</tbody>
</table>

MCIa: mild cognitive impairment; AD: Alzheimer’s disease; ADvasc: Alzheimer’s disease with cerebral vascular lesions; VD: vascular dementia; HE: healthy elderly; MMSE: mini-mental state examination; HT: arterial hypertension; mCABF: mean arterial cerebral blood flow; mCJBF: mean jugular cerebral blood flow; SVcerv: cervical stroke volume; CC: cardiac cycle; SVaque: aqueductal stroke volume; N: normal value.
The existence of hyperdynamical arterial input in MCIa\textsuperscript{39} can be explained by the role of vascular risk factors in the development of neurodegenerative diseases.

As mentioned before, we measured arterial blood pressure in our patients. In our MCIa group (ten patients), the majority (seven patients) suffered from arterial hypertension. The role of hypertension in dementia is still a challenge.\textsuperscript{40–42} Several authors have demonstrated the role of potential vascular risk factors in the development of neurodegenerative diseases.\textsuperscript{43–45} A recent study has already shown the association between augmentation of the mean arterial inflow and high systolic arterial peak flows in MCIa patients.\textsuperscript{39}

With regard to the Monro–Kellie doctrine, as the cranium is a rigid, closed box in adults, a volume increase must be compensated, otherwise there is a risk of augmentation of ICP and damage to the brain.\textsuperscript{12,17,18} Compliance is a pressure increase in the system in response to an increase of the volume. We can hypothesize that a constant high systolic peak flow can cause mechanical stress on the brain parenchyma, which could lead to degenerative process in the brain tissue such as damage to the choroid plexus — and, consequently, alteration of CSF turn-over — and conditions which could favor deposition of beta-amyloid.\textsuperscript{11,46}

Increase of the systolic arterial peak flow provokes rapid variation of blood volume in the brain. ICP is a function of the volume increase and cranial compliance. To preserve constant ICP, in the case of increased arterial volume, either the venous volume or the volume of CSF, or both, must be reduced.\textsuperscript{24} In this way we could explain progression from MCIa non-dementia state to AD. It is noteworthy that around 30% of the patients with MCIa will develop AD.\textsuperscript{47,48}

A protective factor in most MCIa patients could be a good compliance of the skull or rather the well-developed vascular venous tree.\textsuperscript{49} Thus, it would be interesting to analyze brain hydrodynamics in our AD patients. We did not observe the hyperdynamics of blood and CSF flows in AD patients, as we did with the MCIa group. We did not find significant differences in blood flow between AD and HE patients, either. While keeping in mind the theory of progression from MCI to AD, MCI patients had an increased arterial blood inflow, which was never compensated for by venous outflow (poor venous tree), which finally resulted in the decreased turn-over rate of CSF, damage to the choroid plexus and, consequently, beta amyloid deposition and progression to the AD state.\textsuperscript{56}

![Figure 2 Blood and cerebrospinal fluid flow results in the arterial, venous and cerebrospinal fluid compartments in patients with vascular dementia, Alzheimer’s disease, Alzheimer’s disease with cerebral vascular lesions, mild cognitive impairment and in the healthy elderly.](Image)

**Figure 2** Blood and cerebrospinal fluid flow results in the arterial, venous and cerebrospinal fluid compartments in patients with vascular dementia, Alzheimer’s disease, Alzheimer’s disease with cerebral vascular lesions, mild cognitive impairment and in the healthy elderly. Brackets indicate a significant pairwise comparison with p < 0.05.
The atrophy of cerebral tissue makes a place for the brain in the rigid skull box and, consequently, leads to a decrease of CBF and pulsatility.

Contrary to the theory of MCIa-AD progression, concerning blood flow values, we did not find any differences between HE and AD. Does it mean that the flows returned to normal ranges or were always normal? It is well known that CBF decreases with age.28 Our healthy aging population is ten years younger than the pathologic one. It is extremely difficult to find the “real” HE; even if neuropsychological assessment is correct, morphological MRI shows a majority of vascular or other cerebral tissue lesions.29 From this observation, it would be interesting to have a younger control group. We can suppose that older healthy subjects should present lower CBF than AD group in the present study.

We must not forget that blood flow does not equal blood pressure; flow rate increases with increasing pressure, but 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, in the elderly, hypertension (mainly systolic) will damage the vessels.30 Without the knowledge of whether or not our patients and HE had been receiving effective antihypertensive treatment and for how long, we can only suppose that patients presenting with MCIa were in “a state of fight” in which an increase in CBF 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.20 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 (AD and HE) is effective treatment or proper choice of medication — ACE protects the walls, so there is no influence on blood flow. Among AD patients, 7/9 were receiving treatment, 2 with ACE inhibitors, which improve endothelial function and reduce left ventricular and arterial hypertrophy more effectively than other antihypertensive drugs.32 We may not have seen any differences in CBF between AD and HE patients due to the fact that most of the AD subjects were taking antihypertensive treatment, and no complications of high blood pressure were found.

PC-MRI can also measure CSF oscillations. The highest oscillations were in MCIa group, both at the cervical and aqueduct level. CSF oscillations confirm that an increase of pressure stress in the brain during CC may exist in MCIa population in accordance with the increase of arterial blood flow measured in the main cerebral arteries. CSF measured in the aqueduct could reflect an increase of pulsatility of the choroid plexus present in the ventricles.

CONCLUSION

Our data suggest an increase in cerebral arterial blood and CSF flow in MCIa.

PC-MRI allows safe, reliable and rapid measurements of vascular and CSF flow oscillations during CC. It provides a new hydrodynamic view, which may help evaluating the potential role of cardiovascular alterations in neurodegenerative diseases.

REFERENCES


