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Cerebrovascular Hemodynamics in Alzheimer’s disease and Vascular Dementia

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Summary

Alteration in cerebrovascular hemodynamics has been reported in both ageing and dementia. However, it is still unclear whether this alteration follows similar pattern in ageing and in different dementia pathologies. The aim of this meta-analysis was to investigate changes in cerebral blood flow velocity and pulsatility index in two most common forms of dementia; Alzheimer’s disease and vascular dementia, using transcranial doppler studies. A literature search was conducted in Pubmed, EMBASE and Web of Science. After initial screening of 304 articles and removing duplicates, a total of 53 articles, published between 1980 and 2010, were reviewed. Finally 12 articles were included in the meta-analysis. For each study, effect sizes (ES) indicating the standardized mean differences of the hemodynamic measures between two groups were calculated. Using random effect models, pooled estimates of ES were measured. Patients with Alzheimer’s disease (ES=-1.09, 95% CI -1.77 - -0.44, p=0.004) and vascular dementia (ES=-1.62, 95% CI -2.26 - -0.98, p<0.001) had significantly lower cerebral blood flow velocity compared with healthy aged-matched controls. In addition, pulsatility index was significantly higher in both Alzheimer’s disease (ES =0.5, 95% CI 0.28 0.72, p<0.001) and vascular dementia patients (ES=2.34, 95% CI 1.39 3.29, p<0.001). Patients with Alzheimer’s disease had lower pulsatility index (ES = -1.22, 95% CI -1.98 0.46, P=0.002) compared to subjects with vascular type of dementia. Patients with Alzheimer’s disease and vascular dementia have a pronounced disturbance in their cerebrovascular hemodynamics. The severity of disturbances in cerebral hemodynamics is significantly lower in Alzheimer’s disease compared to vascular dementia.
Introduction

Over the decades, our knowledge regarding the pathogenic pathways behind dementia and its most common forms, Alzheimer’s disease and vascular dementia, has changed considerably. In contrast to previous thoughts about the pure neurodegenerative nature of Alzheimer’s disease, it is now well established that vascular dysfunction and hemodynamic disturbances play a role in both Alzheimer’s disease and vascular dementia. Several epidemiological studies have reported an association between vascular risk factors, such as hypertension, hyperlipidemia, diabetes mellitus type 2 and metabolic syndrome, and Alzheimer’s disease. Furthermore, pathologic investigations have shown that many autopsied brains of patients with Alzheimer’s disease contain cerebrovascular pathologies. In this setting, recently this pathologic condition was introduced as a vasocognopathy entity. Although recognition of Alzheimer’s disease as a vascular entity can have certain clinical, therapeutic and preventive implications, many issues regarding the mechanisms by which vascular risk factors initiate or promote cognitive impairment are still unknown.

While both ageing and Alzheimer’s pathology have been shown to affect neurovascular and metabolic regulation of cerebral blood flow, there are inconsistent findings on differences in cerebrovascular hemodynamics in patients with Alzheimer’s disease compared to healthy elderly subjects. Furthermore, it is not clear whether alterations in cerebrovascular hemodynamics follow similar patterns in different types of dementia. Transcranial doppler sonography is a non-invasive imaging technique widely used for the investigation of cerebrovascular hemodynamics in the major cerebral arteries. This technique provides two major hemodynamic measures: mean cerebral blood flow velocity and pulsatility index. While the mean cerebral blood flow velocity shows a relative measure of the integrity in arterial perfusion, the pulsatility index reflects cerebrovascular resistance and intracranial compliance.

By the introduction of transcranial doppler sonography, the number of investigations on the changes of cerebral hemodynamic status among demented patients has increased. However, this growing body of evidence on the cerebrovascular hemodynamic changes in Alzheimer’s disease and vascular dementia, if not demonstrated in a systematic way, might lead to complexity of interpretations. We conducted a systematic review and meta-analysis to investigate changes in the cerebral hemodynamics in patients with Alzheimer’s disease and vascular dementia in comparison with healthy aged match subjects. Furthermore, the differences in the cerebral hemodynamic measures were evaluated between Alzheimer’s disease and vascular dementia. Since the middle cerebral artery is the most commonly investigated vessel by transcranial doppler sonog-
raphy and supplies the main cognitive areas in brain, we focused on changes of cerebral blood flow velocity and pulsatility index in the middle cerebral arteries of the included studies participants.

**Methods**

*Search strategy*

Pubmed, EMBASE and Web of Science were searched with the key words representing Alzheimer’s disease, vascular dementia, transcranial doppler sonography, healthy ageing and cerebrovascular hemodynamics (see details in the appendix 1). The search was restricted to original articles published up to December of 2010 with English, German, French and Dutch languages (n=304). Two independent reviewers (BS and SJ) examined titles and abstracts to decide whether studies could be included. Then the full articles of included studies were checked for further determination. The reference lists of the key studies were reviewed for potential relevant articles. In order to avoid inclusion of repeated data, the whole final studies were checked for similar authors, patient characteristics and results. At the end, one study was excluded for this reason.

*Study selection/Data extraction*

Title and abstracts of 53 articles were screened initially and then a total of 23 studies were reviewed in detail. The following criteria were considered for eligibility of articles: (1) participants consisting of Alzheimer’s disease patients and/or vascular dementia diagnosed by NINCDS-ADRDA, NINCDS-AIREN, DSM-III-R or DSM-IV criteria (in those studies that used the term multi-infarct dementia, criteria were assessed to be compatible with the mentioned criteria for vascular dementia); (2) transcranial doppler sonography investigation as the main tool for measurement of cerebral hemodynamics; (3) healthy and age-matched control subjects who had no history of neurological or psychiatric disorders, substance abuse and chronic medical conditions such as anemia; and (4) assessment of cerebrovascular hemodynamics including cerebral blood flow velocity (cm/second) or pulsatility index measured in the middle cerebral artery. In those studies that provided cerebral blood flow velocity and pulsatility index values in both left and right middle cerebral arteries (n=5), left side measures were considered for the final analysis. Key information on demographic and cognitive status of participants, transcranial doppler sonography examina-
tion procedure and hemodynamic outcomes of each study were extracted by one reviewer (SJ) and were then checked by another reviewer (BS). When hemodynamic data were not reported in mean and standard deviation but in mean and confidence interval, the standard deviation was calculated. In one study where hemodynamic measures were presented separately in male and female groups, the mean and standard deviation of the hemodynamic parameters in men and women were combined.

Data analysis

For each study effect sizes were calculated by the Hedges method which can be interpreted as standardized mean difference of the hemodynamic measures between two groups. The larger the effect size, the greater the differences in the hemodynamic measures between the two groups. After calculation of the effect sizes for each study, the meta-analyses were performed by using a random effects model which computes the pooled effect size. The random effects model was applied since it takes into account the variability between studies. Furthermore, sensitivity analysis was performed to ensure that no single study biased the combined results by repeated excluding one study at a time and measuring of the combined effect size in the remaining studies. To assess heterogeneity, i.e., whether the differences between studies were greater than would be expected by chance alone, the Q method was used. Possible sources of for heterogeneity were explored by evaluating the differences in the characteristics of the included studies. The limited number of studies did not allow us to investigate source of heterogeneity further by meta-regression analysis. Using weighted regression and rank correlation methods, we assessed publication bias i.e., the phenomenon in which small studies with negative results are not published. All the statistical analyses were carried out using STATA version 10.

Results

Study population

Among 23 reviewed full-text articles, a total of 12 studies were included in the meta-analysis (Table 1). The studies included a total of 795 participants: 268 with Alzheimer’s disease, 200 with vascular dementia, and 327 controls. Females made 56%, 46% and 53% of the participants in Alzheimer’s disease, vascular dementia and control groups respectively. Average MMSE scores ranged from 13
to 25 in Alzheimer’s disease and from 12 to 23 in vascular dementia groups.

**Hemodynamic measures**

Hemodynamic measures from the individual studies are presented in the table 2. After pooling the data, in comparison with healthy aged-matched subjects, significantly lower cerebral blood flow velocity was observed in patients with Alzheimer’s disease (effect size=-1.09, p=0.004, figure 1-A) and vascular dementia (effect size=-1.62, p<0.001, figure 1-B). Pulsatility index was significantly higher in both Alzheimer’s disease (effect size=0.497, p=0.004, figure 2-A) and vascular dementia patients (effect size=2.34, p<0.001, figure 2-B). When we compared cerebral blood flow velocity between patients with Alzheimer’s disease and vascular dementia, there was no significant difference (effect size=0.24, p=0.56, figure 3-A). However sensitivity analysis revealed that the outlier study 3 biased the pooled estimate. After excluding the outlier study, patients with Alzheimer’s disease showed significant higher cerebral blood flow velocity (effect size=0.56, p=0.003). Compared to vascular dementia patients, patients with Alzheimer’s disease had significantly lower pulsatility index (effect size= -1.22, P=0.002, figure 3-B).

**Source of heterogeneity**

Except for the set of studies on pulsatility index in patients with Alzheimer’s disease when compared to control subjects, all the other comparisons showed a significant heterogeneity (all p<0.001). Interstudy differences in gender distribution 2, 11 and prevalence of cardiovascular risk factors3, 6 in some of the included studies might be responsible for the observed heterogeneity. Furthermore differences in diagnostic criteria and presence of the mix pathologic states as well as differences in the applied methods to measure hemodynamic parameters might be considered as other potential sources for heterogeneity of findings among the studies.

**Publication Bias**

No indication of publication bias was found for the studies included in this meta-analysis except for the set of studies used for the comparison of cerebral blood flow velocity in Alzheimer’s disease patients and healthy controls. In this set of studies the funnel plot was asymmetric and there was borderline evidence of bias using weighted regression method (p value for bias 0.05).
Table 1. Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Groups</th>
<th>No Participants</th>
<th>Female (%)</th>
<th>Mean age (SD)</th>
<th>Mean MMSE (SD)</th>
<th>Diagnostic criteria</th>
<th>Measured parameters</th>
<th>Blinded TCD examiner</th>
<th>MAP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Beek A. et al (2010)</td>
<td>pr.AD</td>
<td>21</td>
<td>57</td>
<td>72.9 (5.7)</td>
<td>213 (4.6)</td>
<td>NINCDS-ADRDA</td>
<td>CBFV</td>
<td>n.s</td>
<td>93.8</td>
</tr>
<tr>
<td>Claasen J. et al (2009)</td>
<td>pr.AD</td>
<td>8</td>
<td>50</td>
<td>64.5 (5.0)</td>
<td>29 (0.5)</td>
<td>NINCDS-ADRDA</td>
<td>CBFV, PI</td>
<td>n.s</td>
<td>97</td>
</tr>
<tr>
<td>Vicenzini E. et al (2007)</td>
<td>pr.AD</td>
<td>60</td>
<td>51.7</td>
<td>70.7 (2.4)</td>
<td>19.9 (2.6)</td>
<td>NINCDS-ADRDA</td>
<td>CBFV, PI</td>
<td>+</td>
<td>n.s</td>
</tr>
<tr>
<td>Lee S et al (2007)</td>
<td>AD</td>
<td>17</td>
<td>58.8</td>
<td>67.1 (5.9)</td>
<td>22.1 (4.9)</td>
<td>NINDS-ADRDA</td>
<td>CBFV, PI</td>
<td>n.s</td>
<td>94.7</td>
</tr>
<tr>
<td>Döpp F. et al (2006)</td>
<td>pr.AD</td>
<td>20</td>
<td>70</td>
<td>66 (13)</td>
<td>18 (17)</td>
<td>NINDS-ADRDA</td>
<td>CBFV, PI</td>
<td>n.s</td>
<td>97.6</td>
</tr>
<tr>
<td>Marcos A. et al (1997)</td>
<td>pr.AD</td>
<td>36</td>
<td>66.7</td>
<td>70.4</td>
<td>-</td>
<td>NINDS-ADRDA</td>
<td>CBFV, PI</td>
<td>+</td>
<td>n.s</td>
</tr>
<tr>
<td>Biedert S. et al (1995)</td>
<td>pr.AD</td>
<td>23</td>
<td>50</td>
<td>65 (8)</td>
<td>-</td>
<td>NINDS-ADRDA</td>
<td>CBFV</td>
<td>n.s</td>
<td>94.3</td>
</tr>
<tr>
<td>Ries F. et al (1993)</td>
<td>pr.AD</td>
<td>24</td>
<td>58.4</td>
<td>65.8 (9)</td>
<td>183</td>
<td>Stroke-ADRDA</td>
<td>CBFV</td>
<td>+</td>
<td>n.s</td>
</tr>
<tr>
<td>Camaño J. et al (1993)</td>
<td>pr.AD</td>
<td>12</td>
<td>41.7</td>
<td>63.5 (6.6)</td>
<td>-</td>
<td>NINCDS-ADRDA</td>
<td>CBFV, PI</td>
<td>n.s</td>
<td>89.8</td>
</tr>
<tr>
<td>Provinciali L. et al (1990)</td>
<td>AD</td>
<td>12</td>
<td>75</td>
<td>72.8 (9.0)</td>
<td>-</td>
<td>DSM-III-R</td>
<td>CB</td>
<td>n.s</td>
<td>95.9</td>
</tr>
<tr>
<td>Foerstl H. et al (1989)</td>
<td>pr.AD</td>
<td>9</td>
<td>44.4</td>
<td>60-69</td>
<td>13</td>
<td>NINCDS-ADRDA</td>
<td>CBFV, PI</td>
<td>n.s</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 2. Hemodynamic measures in the individual studies included in this meta-analysis.

<table>
<thead>
<tr>
<th>Authors (Years)</th>
<th>CBFV cm/sec (SD)</th>
<th>PI (SD)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alzheimer's Disease</td>
<td>Vascular dementia</td>
<td>Control</td>
<td>Alzheimer's Disease</td>
<td>Vascular dementia</td>
<td>Control</td>
</tr>
<tr>
<td>Van Beek et al (2010)</td>
<td>34.4 (13)</td>
<td>-</td>
<td>39.5 (10.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Claasen et al (2010)</td>
<td>38 (7.1)</td>
<td>-</td>
<td>55 (19)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lee et al (2007)</td>
<td>56.3 (12.2)</td>
<td>-</td>
<td>57.7 (15.4)</td>
<td>0.92 (0.18)</td>
<td>-</td>
<td>0.88 (0.12)</td>
</tr>
<tr>
<td>Vicenzini et al (2007)</td>
<td>38.7 (2.9)</td>
<td>46.3 (3.1)</td>
<td>54.9 (3)</td>
<td>1.08 (0.05)</td>
<td>1.1 (0.5)</td>
<td>0.91 (0.5)</td>
</tr>
<tr>
<td>Doepp et al (2007)</td>
<td>43 (13)</td>
<td>36 (8)</td>
<td>59 (13)</td>
<td>1 (0.2)</td>
<td>1.1 (0.2)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>Biedert et al (1995)</td>
<td>45.5 (8.8)</td>
<td>38.2 (9.5)</td>
<td>50.4 (1.2)</td>
<td>0.85 (12)</td>
<td>1.27 (0.15)</td>
<td>0.82 (0.13)</td>
</tr>
<tr>
<td>Caamano et al (1990)</td>
<td>42.7 (7.2)</td>
<td>38.6 (13.7)</td>
<td>57.5 (8.47)</td>
<td>0.93 (0.27)</td>
<td>1.5 (0.22)</td>
<td>0.78 (0.15)</td>
</tr>
<tr>
<td>Ries et al (1993)</td>
<td>46.7 (10.6)</td>
<td>41.9 (8)</td>
<td>53.1 (13.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Biedet et al (1990)</td>
<td>47.6 (9.8)</td>
<td>39.1 (10.2)</td>
<td>50.7 (1.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Proviciali et al (1990)</td>
<td>56.3 (11.6)</td>
<td>41.8 (13.9)</td>
<td>53.7 (5.8)</td>
<td>0.88 (0.14)</td>
<td>1.06 (0.13)</td>
<td>0.73 (0.15)</td>
</tr>
<tr>
<td>Marcos et al (1997)</td>
<td>40.7 (7.5)</td>
<td>42.2 (9.7)</td>
<td>45.5 (8.13)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Forestel et al (1989)</td>
<td>47.6 (9.8)</td>
<td>39.1 (10.2)</td>
<td>50.7 (1.3)</td>
<td>0.95 (0.13)</td>
<td>1.27 (0.17)</td>
<td>0.86 (0.17)</td>
</tr>
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</table>

Abbreviations: CBFV: cerebral blood flow velocity, PI: pulsatility index, SD: standard deviation.
Figure 1. (A) Forest plot of cerebral blood flow velocity in patients with Alzheimer’s disease compared to control subjects. (B) Forest plot of cerebral blood flow velocity in patients with vascular dementia compared to control subjects.
Figure 2. (A) Pulsatility index in patients with Alzheimer's disease compared to control subjects. (B) Pulsatility index in patients with vascular dementia compared to control subjects.
Figure 3. (A) Forest plot comparing cerebral blood flow velocity in patients with Alzheimer’s disease and vascular dementia. (B) Forest plot comparing pulsatility index in patients with Alzheimer’s disease and vascular dementia.
Discussion

This meta-analysis shows that patients with Alzheimer’s disease and vascular dementia, in comparison with healthy aged matched subjects, have a pronounced disturbance in their cerebrovascular hemodynamics. The severity of disturbances in cerebral hemodynamics is significantly lower in Alzheimer’s disease compared to vascular dementia.

Recently, the cerebrovascular hypothesis of dementia has received considerable attention. This hypothesis implies that chronic cerebral hypoperfusion, in the presence of vascular risk factors leading to vascular and metabolic damages of the brain, is the main drive of neuronal dysfunction and cell death with consequent cognitive disability. While the most common form of dementia, Alzheimer’s disease, was first introduced as a primary neurodegenerative disorder, there is ongoing debate whether this entity should be recognized as a primary vascular disorder. By the introduction of various neuroimaging techniques, a large number of studies have assessed whether Alzheimer’s disease and vascular dementia have different patterns of vascular and hemodynamic characteristics.

Cerebral blood flow velocity, detected by ultrasound, has been used extensively as a proxy for cerebral blood flow. Our results are in line with previous findings showing a state of cerebral hypoperfusion in dementia. However, comparison of patients with Alzheimer’s disease and vascular dementia revealed that Alzheimer’s disease patients have significantly less impairment in their cerebral perfusion than vascular dementia patients, suggesting a potential spectrum of hemodynamic disturbances in different types of dementia. This difference between Alzheimer’s disease and vascular dementia may be a reflection of differences in type, load or even location of vascular pathology. For instance, histological investigations have shown that amyloid angiopathy is the main vascular pathology in Alzheimer’s disease, whereas atherosclerosis with consequent micro and macro vascular infarcts are the major pathologic features of vascular damage in vascular dementia. In addition to the type of vascular damage, the severity of vascular changes might underlie this difference. For instance, although it was shown that patients with Alzheimer’s disease have cerebral white matter lesions and microbleeds, as signs of small vessel disease, the severity of these pathologies are reported to be significantly higher in vascular dementia. Finally, different locations of vascular changes in the brains of patients with Alzheimer’s disease and vascular dementia might contribute to variation of cerebrovascular hemodynamics in these two types of dementia. In a large autopsy series of demented patients, evaluation of topographic patterns of brain vascular lesions showed that subjects with pure vascular dementia had
higher frequency of small subcortical lesions while cases with a definite diagnosis of Alzheimer’s disease with vascular encephalopathy showed more lobar and cortical infarcts.

Significant increase in pulsatility index in both Alzheimer’s disease and vascular dementia patients indicate a remarkable increase in cerebrovascular stiffness associated with decline in intracranial vascular compliance. A diffuse injury to micro-vascular structure imposed by atherosclerosis and amyloid angiopathy can be a potential explanation for this phenomenon. However, most of the included studies in this meta-analysis have not provided detailed information on vascular pathologies proximal or distal to the middle cerebral artery. Furthermore, increased cerebrovascular resistance might highlight the role of chronic cerebral hypoperfusion not only as a consequence of neuronal loss and lower metabolic demand but also as the primary factor in development and promotion of dementia. The combination of high level of vascular resistance and low perfusion state suggests a global vascular pathology which could start from small vessel disease in both types of dementia and extend to larger vessels in the vascular type of dementia. Collectively, it seems that hemodynamic disturbances and neurodegeneration act in concert in development and progression of dementia and no single mechanism can fully explain common mixed pathologic findings in the brains of patients with dementia.

Although dementia is a slowly progressing medical condition and pathogenic mechanisms may start working decades before apparent clinical symptoms, there is a limited data on hemodynamic changes in pre-clinical stages of dementia and mild cognitive impairment. Sun et al investigated the mean cerebral blood flow velocity in mild cognitive impairment patients and demonstrated that those patients had significantly lower cerebral blood flow velocity compared to age-matched controls. While decrease in cerebral blood flow velocity and increase in pulsatility index are well-described phenomenon in ageing, the findings of our review highlight the intensified disturbances of cerebrovascular hemodynamics in aged people with dementia.

This meta-analysis has certain limitations. First, we could only include outcomes measured in the middle cerebral artery. Even though middle cerebral artery is the main vessel responsible for perfusion of parietotemporal areas in brain, there might be regional variations in hemodynamic disturbances through development and progression of dementia which we could not address. Nevertheless, recent studies among demented patients confirm that most of intracranial arteries follow similar hemodynamic pattern we presented for the middle cerebral artery. Second, the studies were small and despite statistical analysis, there is concern of publication bias as small negative studies were unlikely to be published because of a lack of power compared to small positive studies. Finally,
transcranial doppler sonography cannot provide any estimation on the extent of brain atrophy. Therefore, neuronal loss and decrease in metabolic demand can be considered as an alternative explanation for reduction of cerebral blood flow in patients with dementia in comparison with healthy elderly. In this setting, interpretation of cerebral hemodynamic parameters before correction for the level of brain atrophy needs caution.

Regulations of cerebral blood flow and other hemodynamic measure follows complex mechanisms\textsuperscript{29}. Though great achievement has been made in recognition of these mechanisms in physiologic states, our knowledge concerning the impairment of regulatory pathways in dementia is limited and needs further investigation. In future work, using pooled data of other hemodynamic indexes such as cerebral autoregulation and vasomotor reactivity measured at a regional level, more details on hemodynamic disturbances in different types of dementia might be revealed.
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