

Neuroimaging

Lower cerebral blood flow in subjects with Alzheimer's dementia, mild cognitive impairment, and subjective cognitive decline using two-dimensional phase-contrast magnetic resonance imaging

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Abstract

Introduction: In this cross-sectional study, we aimed to detect differences in cerebral blood flow (CBF) between subjects with Alzheimer's disease (AD), mild cognitive impairment (MCI), and subjective cognitive decline (SCD), using two-dimensional phase-contrast magnetic resonance imaging.

Methods: We included 74 AD patients (67 years, 51% female), 36 MCI patients (66 years, 33% female), and 62 patients with SCD (60 years, 32% female) from the Amsterdam Dementia Cohort. Patients with SCD are those who visited the memory clinic with subjective cognitive complaints without objective cognitive impairment. Whole-brain CBF (mL/100 g/min) was calculated using total volume flow measured with two-dimensional phase-contrast magnetic resonance imaging and normalized for brain volume.

Results: Mean CBF values (SD) were lower in AD compared to SCD (age and sex adjusted 70 ± 26 vs. 82 ± 24 mL/100 g/min, $P < .05$). Mean CBF values of MCI were comparable to AD. Across clinical groups, lower CBF was associated with lower scores on the Mini-Mental State Examination (age and sex adjusted $\text{st}\beta = 0.19$ per mL/100 g/min; $P = .02$).

Discussion: Lower whole-brain CBF is seen in AD patients compared to SCD patients and is associated with worse cognitive function.

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Keywords:

Two-dimensional phase-contrast MRI; Cerebral blood flow; Alzheimer's disease; Neurodegeneration; Cognition

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease caused by accumulation of amyloid plaques and neurofibrillary tangles, eventually leading to brain atrophy [1]. Accumulating evidence shows that patients with AD not only have brain atrophy but also have lower cerebral blood flow (CBF) compared to those with subjective cognitive

decline (SCD). It is possible that neurodegeneration and small vessel disease (SVD) independently contribute to lower CBF in subjects with AD and that CBF may reflect total disease burden in AD [2,3].

Several techniques can be used to measure CBF in subjects: single-photon emission computed tomography, positron emission tomography (PET), and arterial spin-labeling (ASL) magnetic resonance imaging (MRI) [2,4-9]. However, these techniques have several disadvantages. Single-photon emission computed tomography and PET are invasive, and ASL is very sensitive to measurement variability [8].

The authors have declared that no conflict of interest exists.

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<https://doi.org/10.1016/j.dadm.2017.10.001>

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Two-dimensional phase-contrast (2D PC) imaging may be a promising alternative. This is a noninvasive, relatively fast, and cheap technique that measures the average flow in the carotid and basilar arteries. Furthermore, 2D PC imaging is an accurate and reproducible method to assess whole-brain CBF [10]. Two small studies and one larger study showed that 2D PC imaging is capable of measuring whole-brain CBF, which can be used to differentiate between subjects with SCD and with AD [6,11,12]. However, those studies did not adjust for brain volume. This is an important limitation because brain volume may be a confounder in the relationship between cerebral perfusion and cognition [13]. Two studies that did adjust for brain volume were performed in the general population and in subjects with diabetes mellitus, showing contradictory results for the association of CBF with cognition [13,14].

We used 2D PC MRI to investigate differences in CBF, normalized for brain volume, in a large sample of subjects with AD, mild cognitive impairment (MCI), and SCD. In addition, we studied the association between CBF and cognitive function.

2. Methods

2.1. Subjects

In this cross-sectional study, 231 subjects were selected from the memory clinic-based Amsterdam Dementia Cohort. All subjects visited the memory clinic between October 2010 and May 2011 and underwent an extensive dementia screening, including medical history, neurological and physical examination, cognitive assessment, and brain MRI including 2D PC MRI [15]. The 2D PC image could not be used for the calculation of CBF when the lumen of (one of) the vessel(s) was not distinguishable from the static tissue (e.g., due to movement or artifacts). This led to the exclusion of 59 subjects.

In total, 172 subjects were included in the present study: 74 patients with AD, 36 patients with MCI, and 62 patients with SCD [16,17]. We found no difference in demographics between the study subjects and the subjects who were excluded because of their 2D PC MRI. The excluded patients were evenly distributed over the diagnostic groups.

AD diagnosis according to the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [18,19] and MCI diagnosis according to the Petersen criteria [20,21] were made based on the consensus of a multidisciplinary team [15]. Subjects with SCD were those who visited our memory clinic with subjective cognitive complaints, but for them, clinical examination and neuropsychological tests were normal (i.e., criteria for MCI, dementia, or any other neurological or psychiatric disease that might cause cognitive decline were not met).

We collected information on presence of hypertension, hypercholesterolemia, and diabetes mellitus based on self-reported medical history and medication use. We dichotomized smoking into current and never/former smoking.

The other cardiovascular risk factors were also dichotomized into present or absent. Mini-Mental State Examination (MMSE) scores were used as a measure of cognitive function.

The ethical review board of the VU University Medical Center approved the study. All subjects gave written informed consent to use their clinical information for research purpose.

2.2. MRI acquisition

All subjects underwent brain MRI imaging on a 3.0 T whole-body MRI scanner (Signa HDxt, General Electric Medical Systems, Milwaukee, WI, USA) using an eight-coil-channel head coil. The scan protocol has been described elsewhere more extensively [4].

The MRI protocol included a three-dimensional T1-weighted sequence (repetition time [TR] = 7.8 ms, echo time [TE] = 3 ms, inversion time = 450 ms, flip angle = 12°, and voxel size = 1.0 × 0.9 × 0.9 mm); a sagittal three-dimensional fluid-attenuated inversion recovery (TR = 8000 ms, TE = 123.6 ms, inversion time = 2350 ms, and voxel size = 1.0 × 1.0 × 1.0 mm); an axial 2D T2* gradient echo with an echo-planar read-out (TR = 5300 ms, TE = 25 ms, and voxel size = 1.0 × 0.5 × 0.5 mm); and an axial 2D proton density/T2-weighted (PD-T2) fast spin echo (TE = 20/112 ms, TR = 8680 ms, and voxel size = 1.0 × 0.5 × 0.5 mm). All scans were checked by neuroradiologists for gross abnormalities.

Medial temporal lobe atrophy (MTA) was rated on the coronal reconstructions of the T1-weighted images with scores ranging from 0 to 4 [22]. For analyses, we used the mean of left and right MTA scores and dichotomized this into low (<1.5) or high (>1.5). White matter hyperintensities (WMHs) were rated using the Fazekas scale, with scores ranging from 0 to 3, on the fluid-attenuated inversion recovery images [23]. The Fazekas score was dichotomized into low (0–1) and high (2–3). Microbleeds were defined as small round hypointense foci on T2*-weighted images, with a maximum diameter of 10 mm located in brain parenchyma. Lacunes were defined as deep lesions (3–15 mm) with cerebral spinal fluid (CSF)-like signal on all sequences. Microbleeds and lacunes were counted and for the analyses dichotomized into present or absent. The rater was blinded to the subjects' clinical data [2].

For the estimation of brain volume, not normalized by head size, T1 images were used. Preprocessing using FSL (version 5.0, www.fsl.fmrib.ox.ac.uk/fsl) included non-brain tissue removal [24], linear registration to standard space [25], and tissue segmentation [26], as previously described [4].

2.3. 2D PC MRI

For flow measurement, nongated 2D PC imaging was performed. A transverse 2D PC image was made in a plane perpendicular to the internal carotids and basilar artery at the base of the skull (TR = 23.0 ms, TE = 7.2 ms, field of

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