Qualitative Assessment of Perfusion Maps Derived from Pulsed Arterial Spin Labeling Magnetic Resonance Imaging (PASL MRI) in Patients with Cognitive Disorders

Murat Dokdok 1, *, Meltem Hale Gokmen Alpsan 2, Kutlay Karaman 3, Oktay Karadeniz 3, Yasar Kutukcu 2 and Selcuk Gocmen 4

1 Radiology Department, Anadolu Medical Center, Gebze Kocaeli, Turkey
2 Neurology Department, Anadolu Medical Center, Gebze Kocaeli, Turkey
3 Radiology Department, Anadolu Medical Center, Gebze Kocaeli, Turkey
4 Neurosurgery Department, Anadolu Medical Center, Gebze Kocaeli, Turkey

*Corresponding author: Radiology Department, Anadolu Medical Center, Gebze Kocaeli, Turkey. Email: murat.dokdok@anadolusaglik.org

Received 2021 April 14; Revised 2021 December 11; Accepted 2021 December 13.

Abstract

Background: Dementia and its most common cause, Alzheimer’s disease (AD), are growing health problems worldwide. In the pathological process, before the emergence of symptoms, magnetic resonance imaging (MRI) may be used as a non-invasive method for measuring brain perfusion.

Objectives: This study aimed to investigate the feasibility and variability of brain perfusion maps derived from pulsed arterial spin labeling (PASL) MRI in a heterogeneous group of patients with cognitive disorders.

Patients and Methods: In this cross-sectional study, 85 out of 134 patients with cognitive disorders, including 23 cases of AD, 24 cases of mild cognitive impairment (MCI), 31 cases of depression, and seven cases of subjective memory impairment (SMI), were considered eligible for the study. All patients were evaluated qualitatively with 3D PASL sequences, using inline cerebral blood flow (CBF) maps. Mental examinations and neuropsychological tests were also performed beforehand.

Results: Based on the CBF maps, bilateral parietal hypoperfusion was significant in the AD and MCI groups (83 and 67%, respectively), compared to patients with depression or SMI (P < 0.01). However, it was significantly low in depressed patients (13%), and there was no hypoperfusion in the SMI group. There was a good interobserver agreement, based on the kappa coefficient in all groups (0.78%; 95% CI: 0.65 - 0.91).

Conclusion: The PASL MRI technique can be valuable for evaluating cognitive disorders, as it is non-invasive, rapid, and easily accessible. Besides, the qualitative assessment of CBF maps using this technique is reproducible and feasible in routine clinical practice.

Keywords: Dementia, Alzheimer’s Disease, Cerebral Perfusion, PASL MRI

1. Background

Today, dementia is one of the most important health-care challenges. In 2019, there were more than 50 million people living with dementia globally, as estimated by the Alzheimer’s Disease International (ADI). During the pathological process of Alzheimer’s disease (AD), beta-amyloid accumulation starts 10 to 15 years before the development of cognitive disorder, and there is no known treatment after complete neurodegeneration (1). Until recently, AD was diagnosed based on the criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA) published in 1984 (2). The sensitivity of these criteria was estimated at 81%, and they were revised in 2011 (3). Nevertheless, a definite diagnosis can be only made according to the postmortem or pathological studies of the brain. Besides the clinical criteria used by clinicians, research criteria and biomarkers, such as amyloid positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) measurements, may predict pathologies in the preclinical stage (4).

Cerebral blood flow (CBF) is associated with changes in an individual’s cognitive performance, as well as the risk of dementia, as reported in the literature (5). The arterial spinal labelling (ASL) magnetic resonance imaging (MRI) technique is alternatively used for CBF measurements in longitudinal studies (6). This technique has been effectively used to detect pathologies other than dementia (7),
including brain tumors (8), acute stroke (9), occlusive cerebrovascular diseases (10), and epilepsy (11). However, validation is needed in the clinical setting in future research on different pathological disorders (12).

2. Objectives

This study aimed to examine the feasibility and variability of perfusion maps derived from pulsed arterial spin labeling (PASL) MRI in a heterogeneous group of patients with cognitive disorders.

3. Patients and Methods

3.1. Study Population

Individuals with a suspected cognitive disorder (reported by the person or a close family member) were included in this study. The exclusion criteria were as follows: contraindications for MRI; the presence of a known neurological disorder affecting cognitive functions; baseline MRI findings, indicating multi-infarct dementia, normal pressure hydrocephalus, or a brain tumor; history of psychotic disorders or major depression; alcohol or substance abuse; and abnormal laboratory findings interfering with the study.

Out of 134 patients with cognitive disorders, 85 patients (38 males and 47 females), admitted to the neurology and neuroradiology clinics of our hospital, were included. Thirty-one patients were diagnosed with depression, and seven patients were diagnosed with a subjective memory impairment (SMI) (patients without neuropsychological defects and normal mental examinations, but with complaints of cognitive disorders). The patients were classified into groups of mild cognitive impairment (MCI), AD, depression, and SMI, based on the clinical diagnosis before ASL MRI (Table 1).

This cross-sectional study was approved by the institutional ethics committee. Informed consent forms for routine MRI, including permission for using images pertaining to the patients anonymously, were obtained.

3.2. Neurological Examinations

All patients were evaluated by a neurologist in a mental examination, and a neuropsychological evaluation was performed by a psychologist. The standard neuropsychological test batteries included personal and general information, as well as orientation to time, place, and person, digit span performance, mental control, mathematical skills, abstract thinking, fluency, similarity tests, judgment testing, visual memory, clock drawing test, and verbal learning test for verbal memory. Also, mental examinations included the mini-mental state examination (MMSE) and either Addenbrooke’s cognitive examination-revised (ACE-R) or Montreal cognitive assessment (MoCA), based on the clinical decision.

The diagnoses of AD and MCI were established based on the clinical criteria, according to the results of mental examinations, clinical dementia rating (CDR), and neuropsychological tests. Depression was also screened using Beck’s Depression Inventory. The average MMSE score was calculated for each group and measured to be 28.4 for the MCI group, 26.3 for the AD group, and 29.5 for the depression and SMI groups. Besides, the patients underwent hemogram tests, liver panel tests, and thyroid function tests, and the levels of vitamin B12, cholesterol, folic acid, electrolytes, and vitamin D were measured.

3.3. MRI Technique and Examination

All MRI procedures were performed using a 3T Magnetom Skyra (Siemens AG Healthcare, Erlangen, Germany) with a 24- or 32-channel head coil. For morphological examinations, routine T1- and T2-weighted images were acquired in three orthogonal planes at a 1.0 mm isotropic resolution (1 mm slices), using a Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. Moreover, structural scales were used to measure atrophy and white matter density, including the global cortical atrophy (GCA) scale, Fazekas white matter scale, medial temporal lobe atrophy scale, Koedam parietal lobe scale, and the National Institute of Neurological Disorders and Stroke-Association International pour la Recherche et l’Enseignement en Neurosciences (NINDS-ARIEN) criteria for vascular infarcts and white matter lesions.

In this study, 3D PASL MRI images were acquired with flow-sensitive alternating inversion recovery (FAIR) labeling and QII saturation, combined with a 3D turbo gradient-and spin-echo (3DGRASE) readout, based on the following parameters: single TI, 1800 ms and bolus duration, 700 ms (one slab with 38 slices with 4-mm thickness in two measurements). Also, single-shot echo-planar imaging (EPI) was performed with an EPI factor of 21, a turbo factor of 18, a flip angle of 180, a bandwidth of 2,604 Hz/Px, echo spacing of 0.5, and TR/TE of 5000/15.72 ms, with no partial Fourier imaging and a three-minute acquisition time.

The labeling slap was located parallel to the morphological image planes. After acquiring two control and two tagged images, inline calculation of CBF maps (matrix size, $128 \times 128; 3.6 \times 3.6 \times 4$ mm) was performed automatically in the voxel plane using subtraction with a t-test. The qualitative perfusion images were first analyzed by optimal windowing and then co-registered with MPRAGE images on a Syngo workstation (Siemens AG, Berlin, Germany) for further evaluation. The color perfusion maps were inspected.
Table 1. The Patients’ Characteristics

| Diagnosis          | Male (n) | Female (n) | Average MMSE score | Mean age | Total (n) |
|--------------------|----------|------------|--------------------|----------|-----------|
| AD                 | 11       | 12         | 26.3               | 79       | 23        |
| MCI                | 13       | 11         | 28.4               | 62       | 24        |
| Depression & SMI   | 14       | 24         | 29.5               | 46.5     | 38        |

Abbreviations: AD, Alzheimer’s disease; MCI, mild cognitive impairment; Depression & SMI, depression and subjective memory impairment; MMSE, mini-mental state examination.

for all brain sections. All images were reviewed by two experienced neuroradiologists with the European Diploma in Neuroradiology. They were blinded to the ASL MRI indications of all patients and were asked to evaluate all lobes visually, particularly for the presence of hypoperfusion in the posterior parietal lobes, which is typical of AD. Next, the readers re-evaluated the images blindly long after the first evaluation (minimum of a two-year interval) to measure reproducibility. In this qualitative ASL MRI study, brain normalization methods with template images and correction of cortical atrophy were not needed, similar to CBF quantification studies.

### 3.4. Statistical Analysis

Statistical tests were performed to evaluate qualitative data on CBF maps after dichotomization of perfusion patterns, such as normal perfusion and hypoperfusion. Chi-square test was used to compare bilateral parietal hypoperfusion between the groups. The Minitab 17.2.1 software (LEADTOOLS© 1991-2002, Lead Technologies, Inc., USA) was used for data analysis. A 95% confidence interval (CI) was considered to represent the effect size. Moreover, Tukey’s post-hoc range test was used to evaluate observer agreement. The inter-observer agreement was expressed by kappa coefficients. The Fleiss’s kappa values were above 0.75, indicating an excellent agreement.

### 4. Results

Out of 134 individuals with cognitive disorders, 85 patients with cognitive tests and MRI results, including pulsed 3D ASL sequences, were included in this study (Figure 1). The patients were divided into groups according to the results of mental examination and neuropsychiatric tests, based on which a diagnosis was established. Structural MRI was performed to rule out other causes of memory problems (e.g., hydrocephalus, tumor, stroke, and vascular dementia) and support the diagnosis of AD according to structural clues, such as hippocampal or global atrophy. As shown in the flowchart (Figure 1), three patients with vascular dementia and 11 patients with hydrocephalus were excluded from the study based on the morphological assessments. All AD patients had medial temporal lobe atrophy (MTA) scores > 2, although it was not a specific finding for diagnosis. Regarding other morphological criteria, MTA was not evaluated, as it was out of the scope of this study.

The ASL control and tagged images were first evaluated for artifacts, such as motion and susceptibility, and then, inline calculation of CBF maps was performed (Figure 2). The ASL perfusion map results were classified as normal, hypoperfusion, and hyperperfusion. All hypoperfusion patterns were bilateral parietal hypoperfusion (in the parietal lobe and posterior cingulate gyrus). None of the maps indicated hyperperfusion, while 40 patients showed hypoperfusion. The patterns of hypoperfusion and normoperfusion were also compared between the groups (Figure 3).

The ratio of patients with bilateral parietal hypoperfusion was the highest in the AD group (83%) and the lowest in the depression group (13%), while it was null in the SMI group. The results showed that the corresponding ratio was significant in the AD and MCI groups (P < 0.01) as compared to patients with depression and SMI (95% CI: 61.22 - 95.05, 44.68 - 84.37, and 4.41 - 28.09, respectively). There was no significant difference between the AD and MCI groups regarding the rate of bilateral parietal hypoperfusion (67%). The depression and SMI groups had no cognitive deficits based on the neuropsychiatric tests (Table 2).

Complete agreement was found in 89% of the total population; the expected agreement was 0.50. Interobserver agreement was also determined by measuring the kappa coefficient (0.78; 95% CI: 0.65 - 0.91). The post-hoc test revealed that agreement was the highest in the depression + SMI group and the lowest in the MCI group (92 and 83%, respectively). The observed agreement was 88% in the AD group (Table 3).

### 5. Discussion

This study was conducted on patients with cognitive disorders, who had been provisionally diagnosed with AD, MCI, depression, or SMI, based on the mental examinations and neuropsychiatric tests performed by the neurologists.
All patients underwent PASL MRI. The CBF maps were visually evaluated by the neuroradiologists for brain perfusion. The results of the present study are twofold. First, bilateral parietal hypoperfusion on inline-calculated CBF maps, derived from 3D PASL MRI, was significant in the AD and MCI groups. The hypoperfusion rate was more remarkable in the AD group compared to the MCI group. On the other hand, the rate of hypoperfusion was significantly low in the depression group and even null in the SMI group. These results have been approved in many clinical and research studies, including a preliminary comparative prospective study by Johnson et al. (13).
Biomarkers, such as the CSF amyloid and tau levels, are used in research, and occasionally, for approving a clinical diagnosis. These methods require lumbar puncture, which can be challenging for the elderly and uncooperative patients. However, well-established non-invasive markers, including fluorodeoxyglucose (FDG) PET and PET with ligands that bind to fibrillar amyloid plaques are not readily available, affordable, or rapid methods. Although PET scan of amyloid-beta ligands and CSF biomarkers has high sensitivity for early AD (14), it shows limited sensitivity for clinical staging and disease progression follow-up (15). Since its application along with prodromal and clinical biomark-
ers of neurodegeneration for AD, FDG PET has shown a
great potential for early detection and monitoring of AD (16).
In a recent study, ASL was shown to be a reliable and
cost-effective alternative to 18F-FDG PET in clinical research (17).

ASL MRI, as a functional PET technique, uses magnetically
labeled blood protons as a tracer to measure brain
perfusion without exposure to ionizing radiation (18). In
this technique, there is no need for an exogeneous tracer
decaying in a specific period). ASL adds less than three
minutes to the routine structural MRI procedure for cogni-
tive disorders. The duration of the procedure was two min-
utes and five seconds for all patients in our daily practice.
There has been an approximately 0.50% decline per year in
CBF in healthy older individuals, as found in an ASL MRI
study (19). Likewise, by using CBF as a biomarker, we can
predict the future cognitive function of the elderly popu-
lation (20).

The cognitive changes in the elderly population may
be related to decreased CBF and reduced supply of oxygen
and nutrients in the cerebral gray matter during the ac-
cumulation of metabolic products (21). In ASL MRI of AD
patients, hypoperfusion is typically detected in the tem-
poroparietal cortex, posterior cingulate cortex, and pre-
cuneus; these cognitive areas are specific to memory (22).
The finding indicating a reduction in CBF agrees with pre-
vious metabolism studies using PET, which are more exten-
sive (23). Also, ASL MRI is a useful predictor of conversion
from MCI to AD (24). Studies show that ASL MRI is a sensi-
tive method, even in the preclinical stages of AD. Hypop-
erfusion in the posterior cingulate cortex was detected in
healthy elderly people with cognitive impairments in an
18-month period (25).

Similarly, FDG PET may be a strong predictor of conver-
sion from MCI to AD up to 24 months before the emergence
of clinical symptoms (26). Besides, ASL MRI, which appears
to be sensitive to disease progression, can be used as a mea-
sure of response to treatment (27). Based on the findings,
the more advanced the stage of AD is, the lower the level
of CBF will be in different stages of neurodegenerative dis-
eases in a wide spectrum ranging from normal cognition
to AD dementia (28). It seems that ASL MRI can help detect
MCI patients with an AD pathology by evaluating cognitive
deficits in very early phases and ruling out other cognitive
disorders, such as depression.

Additionally, another aspect of this study was the qual-
itative analysis of inline-calculated CBF maps derived from
3D PASL MRI, which demonstrated an excellent interob-
server agreement. The post-hoc analysis revealed that
agreement was more evident in the dominantly normop-
erfused depression and SMI groups, followed by the dom-
initely hypoperfused AD group. Overall, there are dif-
ferent available labeling methods, such as continuous,
pulsed, and velocity-selective ASL. In continuous ASL, a con-
stant gradient is applied in the direction of the flow along
with a constant radiofrequency (RF) pulse, while pseudo-
continuous ASL uses a long series of short RF and gradient
pulses. In PASL, a single RF pulse or a short train of pulses
is used to rapidly invert magnetization in a slab. Magne-
tization of blood is inverted proximal to the brain in the
former techniques, while in velocity-selective ASL, the la-
beling pulse lacks spatial selectivity and involves the whole
brain imaging volume.

In the last decade, many studies have been carried out
to assess the consistency and strength of ASL perfusion,
based on continuous or pulsed labeling methods. The re-
liability and reproducibility of ASL perfusion images have
been investigated in different centers, using different scan-
ers with different sequences and ASL methods (29-31). In
a multicenter reproducibility study of ASL, it was introduced
as a reliable perfusion method in routine clinical practice,
without the need for a research setting (29). PASL, as the
most common ASL method, is provided by many manu-
facturers, with instantaneous spatially selective saturation
or inversion pulse, echoplanar readout, and inline calcula-
tion of CBF maps (32, 33).

The reliability and reproducibility of ASL perfusion in
a healthy population are crucial for both diagnosis and
follow-up in the evaluation of disease progression. Jiang
et al. reported a good interrater agreement in cognitively
normal individuals using PASL MRI (6). Interestingly,
the reliability level decreased to moderate over a one-year
period, indicating the importance of proper slice positioning
and coregistration in longitudinal studies. Based on the
intra- and multicenter reproducibility analyses in healthy
individuals, all methods, but single inversion time (TI) PASL,
yielded comparable results (31). The 2D ASL EPI se-
quences might be used for the inline calculation of relative
CBF maps (in mL/g/min), which are derived from the blood
flow voxel by voxel over time. The quantitative estimation
of CBF might require advanced software programs, which
are not routinely supplied by manufacturers; for clinical
convenience and ease, no third-party software was used in
this study.

There are several limitations in this study, including
the small number of patients, selected from a single cen-
ter with no long-term follow-up. In this clinical study, no
healthy control group was included, whereas the depres-
sion and SMI groups were diagnosed with clinical tests;
these clinical tests were accepted as the reference standard
tests. Besides, the reviewing radiologists might not have
been completely blinded. When analyzing depression and
SMI patients as the control subjects, the reviewing radiol-
ogists could identify normal perfusion patterns, which in-
dicated the relatively young age of these patients. Also, the reproducibility and variations of test measurements, especially interobserver variability, might have been affected by the staff’s long-term collaboration with each other. The qualitative assessment and dichotomous statistical analysis were also some other limitations. However, the present study mainly aimed to propose a simple and practical clinical method for patients with a cognitive impairment. We also aim to provide further information about this group in a future longitudinal study.

In conclusion, PASL MRI may be a valuable method for evaluating patients with cognitive disorders, using a qualitative assessment of perfusion maps. ASL perfusion can be a non-invasive, rapid, and reliable biomarker to improve the diagnosis of patients with cognitive disorders. Although it was previously considered as a research tool, it has become easily accessible and feasible for clinical use owing to recent technological advances. However, translating ASL into clinical practice still requires the development and validation of standardized guidelines.

Footnotes

Authors’ Contribution: Study conception and design, M.D. and M.G.; Acquisition of data, M.D., M.G., K.K., Y.K., and S.G.; Analysis and interpretation of data, M.D., M.G., K.K., and O.K.; Drafting of the manuscript, M.D. and M.G.; Critical revision of the manuscript for important intellectual content, M.D., M.G., and S.G.; Statistical analysis, M.D. and M.G.; Administrative, technical, and material support, O.K. and Y.K.; and Study supervision, O.K., Y.K., and S.G.

Conflict of Interests: No conflict of interest was declared.

Data Reproducibility: The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

Ethical Approval: This cross-sectional study was approved by the institutional ethics committee (ASM-EK-20/31).

Funding/Support: None.

Informed Consent: In this retrospective study, the requirement for obtaining informed consent was waived. However, routine MRI informed consent forms, including permission for using images pertaining to the patient anonymously, were obtained.

References

1. Ruan Q, D’Onofrio G, Sancarlo D, Bao Z, Greco A, Yu Z. Potential neuroimaging biomarkers of pathologic brain changes in Mild Cognitive Impairment and Alzheimer’s disease: A systematic review. BMC Geriatr. 2016;16:304. doi: 10.1186/s12877-016-0281-7. [PubMed: 27184250]. [PubMed Central: PMC4869390].

2. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer’s disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease. Neurology. 1984;34(7):939–44. doi: 10.1212/wnl.34.7.939. [PubMed: 660841].

3. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack C, Kawas CH, et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement. 2011;7(3):263–9. doi: 10.1016/j.jalz.2011.03.005. [PubMed: 2514256]. [PubMed Central: PMC3102424].

4. Scheltens P, Bollenkamp K, Breete MM, de Strooper B, Frisoni GB, Sal- loway S, et al. Alzheimer’s disease. Lancet. 2016;388(10043):505–17. doi: 10.1016/S0140-6736(15)00124-1. [PubMed: 2692134].

5. Wolters FJ, Zonneveld HI, Hofman A, van der Lugt A, Koudstaal PJ, Vernooij MW, et al. Cerebral Perfusion and the Risk of Dementia: A Population-Based Study. Circulation. 2017;136(6):719–28. doi: 10.1161/CIRCULATIONAHA.117.027448. [PubMed: 28588075].

6. Jiang L, Kim M, Chodkowski B, Donahue MJ, Pekar JJ, Van Zijl PC, et al. Reliability and reproducibility of perfusion MRI in cognitively normal subjects. Magn Reson Imaging. 2010;28(9):1283–9. doi: 10.1016/j.mri.2010.05.002. [PubMed: 20573464]. [PubMed Central: PMC2963675].

7. Du AT, Jahng GH, Hayasaka S, Kramer DH, Rosen HJ, Gorno-Tempini ML, et al. Hypoperfusion in frontotemporal dementia and Alzheimer disease as arterial spin labeling MRI. Neurology. 2006;67(7):1215–5. doi: 10.1212/01.wnl.0000238163.71349.78. [PubMed: 17030755]. [PubMed Central: PMC1779981].

8. Wolf RL, Wang J, Wang S, Melhem ER, O’Rourke DM, Judy KD, et al. Grading of CNS neoplasms using continuous arterial spin labeled perfusion MR imaging at 3 Tesla. J Magn Reson Imaging. 2005;22(4):475–82. doi: 10.1002/jmri.20415. [PubMed: 1616080].

9. Chalela JA, Alsop DC, Gonzalez-Atavales JB, Maldjian JA, Kasner SE, Detre JA. Magnetic resonance perfusion imaging in acute ischemic stroke using continuous arterial spin labeling. Stroke. 2000;31(3):680–7. doi: 10.1161/01.STR.31.3.680. [PubMed: 10700504].

10. Hendrikse J, van Osch MJ, Rutgers DR, Bakker CJ, Kappelle LJ, Golay X, et al. Internal carotid artery occlusion assessed at pulsed arterial spin-labeling perfusion MR imaging at multiple delay times. Radiology. 2004;233(3):899–904. doi: 10.1148/radiol.2333031276. [PubMed: 1548621].

11. Pende S, Wissmeyer M, Altrichter S, Vargas M, Delavelle J, Viallon M, et al. Interictal arterial spin-labeling MRI perfusion in intractable epilepsy. J Neuroradiol. 2010;37(1):60–3. doi: 10.1016/j.neurad.2009.05.006. [PubMed: 1967479].

12. Alsop DC, Detre JA, Golay X, Gunther M, Hendrikse J, Hernandez-Garcia L, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magn Reson Med. 2015;73(3):1022–6. doi: 10.1002/mrm.25197. [PubMed: 24754126]. [PubMed Central: PMC490038].

13. Johnson NA, Jahng GH, Weiner MW, Miller BL, Chui HC, Jagust WJ, et al. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: Initial experience. Radiology. 2005;234(3):853–9. doi: 10.1148/ra- diol.2343040997. [PubMed: 15754957]. [PubMed Central: PMC85934].

14. Shaw LM, Vanderstichte H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Cerebrospinal fluid biomarker signature in Alzheimer’s disease neuroimaging initiative subjects. Ann Neurol. 2009;65(4):403–13. doi: 10.1002/ana.21610. [PubMed: 19295504]. [PubMed Central: PMC2669350].
15. Jack CR, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer’s disease: Implications for sequence of pathological events in Alzheimer’s disease. Brain. 2009;132(Pt 5):1535-55. doi: 10.1093/brain awp062. [PubMed: 19392553]. [PubMed Central: PMC267798].

16. Arnaiz E, Jelic V, Almkvist O, Wahlund LO, Winblad B, Valind S, et al. Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. Neuroreport. 2001;12(4):851-5. doi: 10.1097/00001756-200103260-00045. [PubMed: 11775595].

17. Dolui S, Li Z, Nasrallah IM, Detre JA, Wolk DA. Arterial spin labeling versus (18)F-FDG-PET to identify mild cognitive impairment. Neuroimage. 2020;215:116050. doi: 10.1016/j.neuroimage.2020.116050. [PubMed: 31951403]. [PubMed Central: PMC6957781].

18. De Vis JB, Peng SL, Chen X, Li Y, Liu P, Sur S, et al. Regional Cerebral Blood Flow in Mild Cognit-...

19. Zhang N, Gordon ML, Goldberg TE. Cerebral blood flow measured by arterial spin labeling MRI at resting state in normal aging and Alzheimer’s disease. Neurosci Biobehav Rev. 2017;72:168-75. doi: 10.1016/j.neubiorev.2016.11.021. [PubMed: 27908711].

20. De Vis JB, Peng SL, Chen X, Li Y, Liu P, Sur S, et al. Arterial-spin-labeling (ASL) perfusion MRI predicts cognitive function in elderly individuals: A 4-year longitudinal study. Magn Reson Imaging. 2018;48(2):449-58. doi: 10.1016/j.mrmi.2018.05.006. [PubMed: 29290549]. [PubMed Central: PMC6028323].

21. De Vis JB, Hendriksje, Bhogal A, Adams A, Kappelle LJ, Petersen ET. Age-related changes in brain hemodynamics: A calibrated MRI study hum. Brain Mapp. 2015;36(10):3973-87. doi: 10.1002/hbm.22891. [PubMed: 26777724]. [PubMed Central: PMC4869092].

22. Sierra-Marcos A. Regional Cerebral Blood Flow in Mild Cognitive Impairment and Alzheimer’s Disease Measured with Arterial Spin Labeling Magnetic Resonance Imaging. Int J Alzheimers Dis. 2017;2017:5479597. doi: 10.1155/2017/5479597. [PubMed: 28573062]. [PubMed Central: PMC5442339].

23. Alsop DC, Dai W, Grossman M, Detre JA. Arterial spin labeling blood flow MRI: Its role in the early characterization of Alzheimer’s disease. J Alzheimers Dis. 2010;20(3):871-80. doi: 10.3233/JAD-2010-096999. [PubMed: 20418854]. [PubMed Central: PMC3618820].

24. Chao LL, Buckley ST, Kornak J, Schuff N, Madison C, Yaffe K, et al. ASL perfusion MRI predicts cognitive decline and conversion from MCI to dementia. Alzheimer Dis Assoc. Disord. 2010;24(1):319-27. doi: 10.1097/WAD.0b013e3181b4f73e. [PubMed: 20220321]. [PubMed Central: PMC2865220].

25. Xekardaki A, Rodriguez C, Montandon ML, Toma S, Tombere E, Hermann FR, et al. Arterial spin labeling may contribute to the prediction of cognitive deterioration in healthy elderly individuals. Radiology. 2015;274(2):490-9. doi: 10.1148/radiol.14140680. [PubMed: 25294548].

26. Cabral C, Morgado PM, Campos Costa D, Silveira M; Alzheimer’s Disease Neuroimaging Initiative. Predicting conversion from MCI to AD with FDG-PET brain images at different prodromal stages. Comput Biol Med. 2015;58:301-9. doi: 10.1016/j.compbiomed.2015.01.001. [PubMed: 25625689].

27. Chen Y, Wan HJ, O’Reardon JP, Wang DJ, Wang Z, Korczynski M, et al. Quantification of cerebral blood flow as biomarker of drug effect: arterial spin labeling phMRI after a single dose of oral citalopram. Clin Pharmacol Ther. 2011;89(2):251-8. doi: 10.1038/clpt.2010.296. [PubMed: 2191380].

28. Binnewijzend MA, Benedictus MR, Kuiper JP, van der Flier WM, Teunissen CE, Prins ND, et al. Cerebral perfusion in the predementia stages of Alzheimer’s disease. Eur Radiol. 2016;26(2):506-14. doi: 10.1007/s00339-015-3834-9. [PubMed: 26040547]. [PubMed Central: PMC4712241].

29. Petersen ET, Mouridsen K, Golay X. The QUASAR reproducibility study. Part II: Results from a multi-center Arterial Spin Labeling test-retest study. Neuroimage. 2010;49(1):104-13. doi: 10.1016/j.neuroimage.2009.07.068. [PubMed: 19660557]. [PubMed Central: PMC2788325].

30. Mutsaerts HJ, van Osch MJ, Zelaya FO, Wang DJ, Nordhoy W, Wang Y, et al. Multi-vendor reliability of arterial spin labeling perfusion MRI using a near-identical sequence: Implications for multi-center studies. Neuroimage. 2015;113:443-52. doi: 10.1016/j.neuroimage.2015.03.043. [PubMed: 25818685].

31. Gevers S, van Osch MJ, Zelaya FO, Wang DJ, Nordhoy W, Wang Y, et al. Multi-vendor reliability of arterial spin labeling perfusion MRI using a near-identical sequence: Implications for multi-center studies. Neuroimage. 2015;113:443-52. doi: 10.1016/j.neuroimage.2015.03.043. [PubMed: 25818685].

32. Gevers S, van Osch MJ, Bokkers RP, Kies DA, Teweswisse WM, Majoie CB, et al. Intra- and multicenter reproducibility of pulsed, continuous and pseudo-continuous arterial spin labeling methods for measuring cerebral perfusion. J Cereb Blood Flow Metab. 2011;31(4):707-15. doi: 10.1038/jcbfm.2011.10. [PubMed: 21304555]. [PubMed Central: PMC3170917].

33. Gevers S, van Osch MJ, Bokkers RP, Kies DA, Teweswisse WM, Majoie CB, et al. Intra- and multicenter reproducibility of pulsed, continuous and pseudo-continuous arterial spin labeling methods for measuring cerebral perfusion. J Cereb Blood Flow Metab. 2011;31(4):707-15. doi: 10.1038/jcbfm.2011.10. [PubMed: 21304555]. [PubMed Central: PMC3170917].

34. Gevers S, van Osch MJ, Bokkers RP, Kies DA, Teweswisse WM, Majoie CB, et al. Intra- and multicenter reproducibility of pulsed, continuous and pseudo-continuous arterial spin labeling methods for measuring cerebral perfusion. J Cereb Blood Flow Metab. 2011;31(4):707-15. doi: 10.1038/jcbfm.2011.10. [PubMed: 21304555]. [PubMed Central: PMC3170917].

35. Gevers S, van Osch MJ, Bokkers RP, Kies DA, Teweswisse WM, Majoie CB, et al. Intra- and multicenter reproducibility of pulsed, continuous and pseudo-continuous arterial spin labeling methods for measuring cerebral perfusion. J Cereb Blood Flow Metab. 2011;31(4):707-15. doi: 10.1038/jcbfm.2011.10. [PubMed: 21304555]. [PubMed Central: PMC3170917].

36. Gevers S, van Osch MJ, Bokkers RP, Kies DA, Teweswisse WM, Majoie CB, et al. Intra- and multicenter reproducibility of pulsed, continuous and pseudo-continuous arterial spin labeling methods for measuring cerebral perfusion. J Cereb Blood Flow Metab. 2011;31(4):707-15. doi: 10.1038/jcbfm.2011.10. [PubMed: 21304555]. [PubMed Central: PMC3170917].