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Review Article

Gray matter contamination in arterial spin labeling white matter perfusion measurements in patients with dementia ☆

Henri J.M.M. Mutsaerts [a,*], Edo Richard [b], Dennis F.R. Heijtel [a], Matthias J.P. van Osch [c], Charles B.L.M. Majoie [a], Aart J. Nederveen [a]

[a] Department of Radiology, Academic Medical Center, Amsterdam, The Netherlands
[b] Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands
[c] C.J. Gorter Center for High Field MRI, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

Introduction: White matter (WM) perfusion measurements with arterial spin labeling can be severely contaminated by gray matter (GM) perfusion signal, especially in the elderly. The current study investigates the spatial extent of GM contamination by comparing perfusion signal measured in the WM with signal measured outside the brain.
Material and methods: Four minute 3T pseudo-continuous arterial spin labeling scans were performed in 41 elderly subjects with cognitive impairment. Outward and inward geodesic distance maps were created, based on dilations and erosions of GM and WM masks. For all outward and inward geodesic distances, the mean CBF was calculated and compared.
Results: GM contamination was mainly found in the first 3 subcortical WM voxels and had only minor influence on the deep WM signal (distances 4 to 7 voxels). Perfusion signal in the WM was significantly higher than perfusion signal outside the brain, indicating the presence of WM signal.
Conclusion: These findings indicate that WM perfusion signal can be measured unaffected by GM contamination in elderly patients with cognitive impairment. GM contamination can be avoided by the erosion of WM masks, removing subcortical WM voxels from the analysis. These results should be taken into account when exploring the use of WM perfusion as micro-vascular biomarker.

1. Introduction

White matter (WM) perfusion measured with arterial spin labeling (ASL) is a potential in vivo micro-vascular parameter to investigate the interplay between normal aging and degenerative and vascular pathology, such as small vessel disease (Brickman et al., 2009; Zhang et al., 2012). Data on WM perfusion are relatively scarce, because ASL has long been considered unsuitable to measure stable WM cerebral blood flow (CBF) (van Gelderen et al., 2008). Although recent technical advances have enabled these measurements, still a relatively long scan time (10–20 min) is required to capture single voxel WM CBF (van Osch et al., 2009).

Due to the often limited available scan time, clinical investigators either ignore WM perfusion or use it as a reference value (Firbank et al., 2011). Fortunately, voxel-wise comparison of WM perfusion is not always required. It may suffice to average the signal from all WM voxels to provide a single value for the hemodynamic status of the total WM region of interest (ROI). Perfusion signal from such a ROI has recently been shown to be reproducible in elderly patients with dementia (Zhang et al., 2012).

However, contamination of GM signal into WM voxels may seriously affect WM perfusion measurements, because the contrast between GM and WM CBF is large (Pohmann, 2010). Furthermore, changes and correlations are mainly found in GM CBF, while the WM CBF often remains relatively stable (Firbank et al., 2011; Parkes et al., 2004). Therefore, even a fraction of GM contamination may distort WM CBF measurements and its possible clinical correlations.

Main sources of GM contamination are the point spread function (PSF) of the ASL imaging readout module and partial volume (PV) voxels (Petr et al., 2013; van Gelderen et al., 2008). Both have a large effect in ASL due to its low imaging resolution, which is required to compensate for its low signal-to-noise ratio (SNR). Currently, PV voxels

Abbreviations: ASL, arterial spin labeling; CBF, cerebral blood flow; CSF, cerebrospinal fluid; GM, gray matter; PSF, point spread function; PV, partial volume; SNR, signal-to-noise ratio; WM, white matter.

* Corresponding author at: Department of Radiology, G1-230, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 56 63429; fax: +31 20 56 69119.
E-mail address: h.j.mutsaerts@amc.uva.nl (H.J.M.M. Mutsaerts).

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are excluded based on the segmentation of a high resolution anatomical scan (Bastos-Leite et al., 2008; Brickman et al., 2009; Zhang et al., 2012). However, simulations indicate that WM voxels without PV may still experience GM contamination due to the PSF (Pohmann, 2010).

Therefore, to correctly interpret perfusion signal averaged from a WM ROI, it is essential to investigate the spatial extent of GM contamination. Can perfusion signal originating from the WM be distinguished from signal blurred from the GM? With this knowledge a WM ROI could be constructed that experiences minimal GM contamination without excluding too many WM voxels. Constructing a WM ROI may be especially challenging in the elderly, because of the decreased T1 and ASL GM-WM contrast and WMH associated with aging (Brickman et al., 2009; Liu et al., 2012; Zhang et al., 2012). The current study investigates the spatial extent of GM contamination in elderly patients with dementia.

2. Material and methods

2.1. Subject recruitment

41 patients (19 men/22 women, mean age 74.9 ± 9.7 (SD) years) presenting to an outpatient memory clinic were included in this study. Main inclusion criteria were age higher than 18 years and score on the mini-mental state examination equal to or higher than 20. Main exclusion criteria were history of transient ischemic attack or stroke in the last two years or with cognitive decline within three months after the event, major depressive disorder, psychosis or schizophrenia, alcohol abuse, brain tumor, and epilepsy. All patients provided written informed consent and the study was approved by the VU University Medical Center and Academic Medical Center ethical review boards. Of the 41 enrolled participants, 18 fulfilled criteria for mild cognitive impairment and 23 fulfilled criteria for probable Alzheimer's Disease or mixed dementia (Winblad et al., 2004).

2.2. MRI protocol

All imaging was performed on a 3.0 T Intera with a SENSE-8-channel head coil and body coil transmission (Philips Healthcare, Best, The Netherlands). To restrict motion the subjects' head was stabilized with foamed material inside the head coils. An isotropic 1 mm 3D T1 weighted scan and 2D FLAIR scan with 3 mm slice thickness were collected using a routine clinical protocol. Added to this protocol was a gradient echo single shot echo-planar imaging pseudo-continuous ASL sequence with the following imaging parameters: resolution, $3 \times 3 \times 7$ mm^3; FOV, 240×240 mm^2; 17 continuous axial slices; TE/TR, 14/4000 ms; flip angle, 90°; SENSE, 2.5; labeling duration, 1650 ms; post-labeling delay, 1525 ms. Slices were acquired in sequential ascending order. 30 label and control pairs were acquired, resulting in a total scan time of 4 min. Background suppression was implemented with two inversion pulses 1680 and 2830 ms after a pre-labeling saturation pulse. The labeling plane was positioned parallel and 9 cm caudal to the center of the imaging volume (Aslan et al., 2010). For descriptive purposes of the presence of small vessel disease, the Fazekas WM hyperintensity severity scale and four-point global cortical atrophy score were assessed by a trained rater, blinded to the clinical information (Fazekas et al., 1987; Pasquier et al., 1996).

2.3. ASL post-processing

Matlab 7.12.0 (The MathWorks, Inc., Natick, MA USA) and the SPM8 toolbox (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK) were used for offline data processing with custom-built software. The label and control pairs were pair-wise subtracted after 3D realignment and subsequently averaged to generate perfusion weighted maps. These maps were converted to CBF based on a single compartment model, which assumes that the label remains in the vascular compartment (Wang et al., 2002):

$$CBF = \frac{6000\lambda\Delta M e^{(TE/T_{2a}^*)}}{M_{0a}2\alpha\alpha_{inv}T_{1a}\left[e^{-w/T_{1a}} - e^{-(w+\tau)/T_{1a}}\right]} \quad [mL/100g/min]$$

where λ is the brain–blood water partition coefficient (0.9 mL/g) (Herscovitch and Raichle, 1985), ΔM is the average difference between control and label for all 30 dynamics, TE is the echo time (14 ms), $T_2{}^*{}_a$ is the transverse relaxation time of arterial blood (50 ms) (St Lawrence and Wang, 2005), $M0_a$ is the equilibrium magnetization of arterial blood, of which an average scanner value was calculated ($4.12{}^*10^6$) according to previously described methods (Chalela et al., 2000), α is the assumed pseudo-continuous ASL labeling efficiency (0.85) (Aslan et al., 2010), α_{inv} is the correction for label loss due to background suppression pulses (0.83) (Garcia et al., 2005), T_{1a} is the T_1 relaxation time of arterial blood (1.650 s) (Zhang et al., 2013), w is the post-labeling delay (1.525 s), τ is the labeling duration (1.650 s). Post-labeling delay differences between slices due to the 2D readout were accounted for. No distinction was made between the quantification of GM and WM voxels. GM and WM probability maps were segmented from the 3D T1 weighted scan and transformed into ASL space by rigid registration of the GM probability map to the perfusion map. Default SPM8 settings were used for segmentation and registration except for the distance between sampling points, which was decreased to 1 mm for increased precision. All CBF maps were scaled such that the mean GM CBF (tissue probabilities >90%) of each patient matched the population mean (36.8 mL/100 g/min) for the slice used in the distance analysis. Negative values were not excluded. All data analyses were performed in native ASL space to avoid GM contamination due to interpolation.

2.4. Distance analysis

Two distance maps were constructed to compare the extent of inward and outward GM contamination. This method enables the comparison between perfusion signal measured in the WM to signal measured outside the brain. Outside the brain, where air or tissue types such as cerebrospinal fluid (CSF), meninges, bone and skin are located, no perfusion signal is expected except from outward GM contamination. This analysis was carried out in 2D and restricted to a single transversal slice (Fig. 1) located 2 slices (14 mm) superior to the basal ganglia. This slice contains a relatively large area of WM, has no central GM and does not experience much distortion or signal dropout as frequently observed anterior in echo-planar imaging. The procedures of the distance analysis are stepwise listed here, and visualized in Fig. 1.

1) The WM probability map (a) was converted into a WM mask (b), including tissue probabilities >10%. This low probability threshold avoids the exclusion of WM hyperintensity voxels, which are frequently misclassified as GM voxels. Subsequently, the GM probability map (A) was converted into a GM mask (B), including tissue probabilities >90%, which is complementary to the WM mask at the GM/WM boundary.
2) Any remaining regions inside the WM or GM masks (such as CSF) were masked as well (c and C), such that erosions or dilations affected the outer borders of the masks only.
3) Erosions were applied to the WM mask (d) and dilations to the GM mask (D), using a cross structural element with radius 1.
4) Inward (e) and outward (E) city-block geodesic distance maps were created by labeling each voxel for number of erosions required to remove this voxel from the WM mask (e) or for the number of dilations required to add this voxel to the GM mask (E).

Consequently, the resulting distance maps show for each WM voxel its shortest distance (in voxels) to the outer border of the WM mask