**Blood Water Volume Fraction of White Matter Hyperintensities**

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**Introduction:** White matter (WM) hyperintensities are commonly observed in the elderly brain on T₂-weighted MRI and may contribute to the cognitive decline of Alzheimer’s disease. Two types of hyperintensities are generally recognized: small, focal lesions in the deep WM (dWMHs) and lesions that lie along the ventricles (pWMHs). Although their etiology remains poorly understood, it is likely that ischemic–vascular injury plays an important role in pWMHs, while demyelinating, gliotic processes may contribute more to dWMH pathology.¹ Longitudinal water proton (¹H₂O) relaxation rate constants (R₁) are strongly associated with macromolecular volume fraction² and, combined with an intravascular contrast agent, can be a powerful probe of vascular integrity. The purpose of this study is to quantify the intravascular water volume fraction (pₚ) in periventricular and deep WMHs in the elderly human brain using a low molecular weight gadolinium contrast reagent.

**Methods:** 15 elderly subjects (10 male, 5 female; 70 ± 6 yrs) with no history of vascular disease provided informed consent and were enrolled. MR data were obtained on a 7T Siemens MAGNETOM instrument. 3D inversion recovery (IR) T₁-weighted (MPRAGE; TR/TE/TI/FA 2300 ms/ 2.8 ms/ 57 min post contrast (gadoteridol) injection (0.11 mmol/kg; 2 mL/s). ¹H₂O R₁ maps were prepared after registration of all images and voxelwise evaluation of the Bloch equations for each variable TI dataset accounting for all RF pulses and delays and assuming monoexponential IR recovery.²

¹H₂O R₁ maps and FLAIR images were co-registered to the anatomic MPRAGE images (Fig. 1).¹ Intravascular water volume maps were obtained by voxelwise fitting of tissue and blood ¹H₂O R₁ maps to an equation for two-site (transendothelial) water exchange.³ A fixed intravascular ¹H₂O lifetime (τᵢ= 300 ms)⁶ and Kᵦ=0 were assumed. Blood ¹H₂O R₁ values were determined from an ROI placed entirely within the sagittal sinus.

WM hyperintensity pₚ was determined by semi-automatic segmentation of FLAIR images (Seg3D)⁵ and application of masks to pₚ maps (thresholded to values > 0). The pₚ of normal appearing white matter (NAWM) was obtained similarly, after 3-class segmentation⁶ of anatomic MPRAGE images. Statistical analyses were performed in Stata (College Station, TX).

**Results and Discussion:** Figure 2 shows several slices from the pₚ map of a healthy 66 year old female. Histograms of global white and gray matter are also shown. Mean pₚ in NAWM was 2.1 ± 0.2%, in reasonable agreement with the 1.5 ± 0.3% measured recently using DSC-MRI⁴. Hyperintensities were present in periventricular and deep WM in 14/15 and 12/15 subjects, respectively (Fig. 3). The mean pₚ in all WMHs was 1.9 ± 0.3% and was not significantly different from the pₚ of NAWM (P= 0.13; repeated measures ANOVA). Comparison of WMH pₚ values (Table 1) reveals significant increases in pWMHs compared to dWMHs (repeated measures ANOVA; P= 0.04). These results are consistent with increased disturbances in microvascular water permeability in periventricular compared to deep WMHs, and suggest that the etiology of lesions in periventricular and deep WM may be different. DCE-MRI studies with increased dynamic range of R₁ values and decreased pharmacokinetic sampling time will be necessary to validate the assumptions of the pharmacokinetic model and substantiate these results.

**Figure 1.** R₁ maps and FLAIR images are co-registered to the anatomic MPRAGE images.

**Figure 2.** (Top) pₚ map of a 66 year old female. (Bottom) Histograms of gray and white matter reveal the expected increase in gray matter pₚ.

**Figure 3.** (Left) FLAIR image from a 74 year old male shows good suppression of the cerebrospinal fluid. Both periventricular and more focal, deep lesions are identified (orange). In-plane area of WMHs ranged from 17-147 mm². (Right) pₚ map with magnification of the periventricular WMH indicated by arrow (inset).

**Table 1.** WMH blood water volume fraction

<table>
<thead>
<tr>
<th>White Matter Hyperintensity</th>
<th>pₚ (%)</th>
<th>WMH - NAWM (%)</th>
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<tbody>
<tr>
<td>Deep</td>
<td>2.1 ± 0.5</td>
<td>+ 4</td>
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<tr>
<td>Periventricular</td>
<td>2.6 ± 0.6</td>
<td>+ 28</td>
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