Cerebral Perfusion and Cerebrovascular Reactivity Are Reduced in White Matter Hyperintensities

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Background and Purpose—There is growing evidence that white matter hyperintensities (WMH) should not be considered as benign age-dependent changes on MR images but indicate pathological changes with clinical consequences. Previous studies comparing subjects with WMH to normal controls have reported global reductions in cerebral blood flow (CBF) and cerebral vascular reactivity. In this study, we examined localized hemodynamic status to compare WMH to normal appearing white matter (NAWM).

Methods—A group of 21 normal 85-year-old subjects were studied using dynamic contrast-enhanced MRI together with administration of acetazolamide. From a combination of anatomic images with different signal weighting, regions of interest were generated corresponding to gray and white matter and WMH. Localized measurements of CBF and cerebral blood volume (CBV) and mean transit time were obtained directly within WMH and NAWM.

Results—When comparing WMH to NAWM, measurements showed significantly lower CBF \((P=0.004)\) and longer mean transit time \((P<0.001)\) in WMH but no significant difference in CBV \((P=0.846)\). The increases in CBF and CBV induced by acetazolamide were significantly smaller in WMH than in NAWM \((P=0.026, P<0.001)\).

Conclusion—These results show that a change in the hemodynamic status is present within the WMH, making these areas more likely to be exposed to transient ischemia inducing myelin rarefaction. In the future, MRI may be used to examine the effect of therapeutic strategies designed to prevent or normalize vascular changes. (Stroke. 2002;33:972-976.)

Key Words: hemodynamics ■ magnetic resonance imaging, perfusion-weighted ■ white matter

There is increasing evidence of an association between white matter hyperintensities (WMH), also described as leukoariosis,¹ and reduction in different cerebral functions, supporting the view that the presence of WMH represents pathological changes. WMH are related to impaired lower extremity function² and to both subjective and objective cognitive failure³,⁴ and are also associated with an age-related decline in cognitive functions.⁵ Changes in white matter tracts measured by diffusion-weighted MRI have been associated with degree of cognitive function.⁶ WMH are known to be highly related to age⁷,² but are also independently related to risk factors for cardiac and cerebral vascular disease.⁸–¹⁰ It is, however, unclear to what extent white matter changes are caused by pathology in the cerebral vessels. Myelin rarefaction and changes in the small penetrating arteries have been described in conjunction with changes in WMH,¹¹,¹² suggesting that ischemia contributes to lesion formation.¹ In support of this hypothesis, different techniques have shown that reduced cerebral blood flow (CBF)¹³,¹⁴ and cerebrovascular response to acetazolamide (ACZ) or CO₂ are both related to the degree of white matter changes.¹⁵–¹⁷ These studies, however, did not examine specifically the CBF or the cerebrovascular reactivity (CVR) within the WMH but measured global CBF or CVR and compared results from subjects with WMH to normal control subjects.

The purpose of this study was to examine the hemodynamics within WMH and compare it to the normal appearing white matter (NAWM) in a group of 85-year-old individuals from the Glostrup Population Studies.¹⁸ Hence, perfusion and CVR measurements within WMH, gray matter, and NAWM were performed using a combination of MR perfusion imaging and conventional anatomic MR imaging.

Methods

Subjects
Since 1964, a cohort of people born in 1914 and living in municipalities close to Copenhagen County General Hospital and the County Mental Hospital in Glostrup has participated in follow-up studies of their medical, social, and mental health status. Studies have been conducted in 1964, 1974, 1984, 1989, 1995, and 2000. In 2000, the study included physical and psychological examinations performed in the home of the participants. All 121 participants undergoing psychological examination were asked if they would...
Registered anatomic images (FLAIR, MPR, PD, T2W), parametric maps (CBF, CBV, MTT), and region of interest (ROI) map. The ROI set contains gray matter, white matter, and white matter hyper-intensity ROIs. Flair indicates FLAIR; MPR, MPRA GE; PD, proton density; T2W, T2-weighted; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time.

\[
\kappa_{\text{con}}C_{\text{im}}(t) = \Delta R_2(t) = -\frac{1}{TE} \ln \left( \frac{S_a(t)}{S_0} \right)
\]

where \(\Delta R_2\) is proportional to the concentration of contrast agent with the proportionality constant \(\kappa_{\text{con}}\) also known as the relaxivity. \(S_a(t)\) is the voxel signal at time \(t\), \(S_0\) is the baseline voxel signal before contrast arrival, and \(TE\) is the echo time. From the converted images, a voxel representing an arterial input curve was selected from voxels having maximal amplitude and short arrival time. CBF was set to the peak point of the solution to Equation 2.

\[
C_i(t) = C_{BF}C_{t,i}(t) \odot (1 - H(t))
\]

where \(C_i\) is the tissue concentration, \(C_{t,i}\) is the concentration in the feeding artery, and \((1 - H(t))\) is the residue impulse response function. This solution was found by the singular value decomposition (SVD) method described by Sjöström et al., as well as by a least square fitting algorithm, fitting an exponential function as the residue impulse response function. CBF and MTT were then calculated from Equations 3 and 4, respectively.

\[
CBV = C_{BF} \int_0^\infty (1 - H(t)) dt
\]

\[
MTT = \frac{CBV}{C_{BF}}
\]

In our previous work, GE-EPI DSC-MRI studies on healthy volunteers with sequence acquisition parameters equal to this study gave absolute CBF and CBV values 6.5 times higher than positron emission tomography values in the literature, because of underestimation of the arterial input function. Consequently CBF and CBV values are therefore scaled by a factor of 1/6.5 in this study. The parametric maps were spatially transformed onto the FLAIR images, and the 6 anatomic slices corresponding to the perfusion maps were selected for semiautomatic region of interest (ROI) generation. This was performed by drawing reference regions in white matter, gray matter, cerebrospinal fluid, and WMH in all 6 slices. Pixels with signal intensities within \(\pm 2\) SD from the median signal intensity in the reference region on all anatomic image modalities were included in the corresponding ROI. ROIs with volume less than 40 mL for white and gray matter, 2 mL for cerebrospinal fluid, and 0.5 mL for WMH were excluded. To minimize partial volume effects, any voxel falling into more than 1 tissue type ROI was also excluded. By only generating regions in the 6 slices, no signal intensity changes due to field variation along the main magnetic field were present. This procedure resulted in region volumes of 102 ± 26 mL for gray matter, 92 ± 22 mL for white matter, and 7 ± 6 mL for WMH (see Figure). The generated ROI sets were visually inspected, and voxels included as WMH situated outside the area of white matter (eg, plexus choraeus) were excluded. The residual parametric maps measured before ACZ were subtracted from the maps measured after ACZ to create difference maps. Mean CBF, CBV, and MTT values before and after ACZ were compared.

Imaging Procedure

Imaging was performed using a 1.5 T MR scanner (Vision, Siemens Erlangen) utilizing a circularly polarized head coil. The imaging protocol consisted of a T1-weighted MPRA GE (TR/TE=11.4/4.4 ms, TI=100 ms, FA=8°, FOV=250 mm, matrix=224×256) with 1-mm isotropic voxels covering the entire head; a proton and T2-weighted double spin-echo (DSE) sequence (TR/TE=2880/20 and 80 ms, FA=90°, FOV=230 mm, matrix=256×256) with 60 slices of 2 mm measured interleaved using 2 separate acquisitions; and a T2-weighted FLAIR sequence (TR/TE=9000/110 ms, TI=2500 ms, FA=180°, FOV=230 mm, matrix=220×512) with 30 slices of 5 mm measured interleaved using 2 separate acquisitions. Perfusion-weighted MRI was performed as a dynamic susceptibility contrast (DSC)-MRI study using a \(T_2^*\)-sensitive gradient echo–echo planar imaging (GE-EPI) sequence (TR/TE=1000/66 ms, FA=60°, FOV=250 mm, matrix=128×128, 6 slices, 5 mm, 12 measurements). During the GE-EPI sequence, Gd-DTPA (Magnevist, Schering) was injected in an antecubital vein, using an MR-compatible double-syringe power injector (Spectris MR Injector, Medrad Inc). The Gd-DTPA (0.1 mmol/kg) injection was started at the 15th measurement with an injection rate of 3 mL/s, followed by 20 mL saline at 3 mL/s. Two DSC-MRI studies were performed before and after administering 1 g of ACZ (Diamox, Wyeth Lederle) injected manually over a period of 5 minutes. The second DSC-MRI study was performed at an average time of 19 (range, 16 to 27) minutes after ACZ injection. All images were axial, and the DSC, FLAIR, and DSC images were obtained in a plane parallel to the line through the anterior and the posterior commissure.

Image Analysis

All image data were transferred to a Linux-based PC system for post-processing. All images including the DSC-MRI images were coregistered to the FLAIR image (DSE in 3 cases) using a rigid-body registration (Figure 1). The registration algorithm is based on the principle of maximal mutual information in the combined histogram of the 2 images being registered. Parametric maps representing CBF, cerebral blood volume (CBV), and mean transit time (MTT) were calculated from the DSC-MRI images using a method described previously. In short, the images were converted into \(\Delta R_2\) maps by use of the relation in Equation 1.
Mean Values±SD of CBF, CBV, and MTT in Grey and White Matter and White Matter Hyperintensities From Images Before and After ACZ, and From the Calculated Difference Images

<table>
<thead>
<tr>
<th>ACZ ROI</th>
<th>CBF, ml/100 g min</th>
<th>CBV, ml/100 g</th>
<th>MTT, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>61.9±22.7</td>
<td>4.4±1.3</td>
<td>7.4±5.1</td>
</tr>
<tr>
<td>NAWM</td>
<td>31.4±12.4</td>
<td>2.7±0.8</td>
<td>7.3±4.7</td>
</tr>
<tr>
<td>WMH</td>
<td>24.5±12.0</td>
<td>2.9±1.2</td>
<td>10.8±6.2</td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>85.5±39.2</td>
<td>5.8±2.0</td>
<td>6.9±6.7</td>
</tr>
<tr>
<td>NAWM</td>
<td>49.9±25.2</td>
<td>3.5±1.1</td>
<td>6.6±6.3</td>
</tr>
<tr>
<td>WMH</td>
<td>32.9±15.6</td>
<td>3.3±1.4</td>
<td>9.2±6.4</td>
</tr>
<tr>
<td>Difference</td>
<td>23.0±25.4</td>
<td>1.6±2.0</td>
<td>0±4.6</td>
</tr>
<tr>
<td>NAWM</td>
<td>15.6±18.3</td>
<td>1.0±1.2</td>
<td>−0.2±4.0</td>
</tr>
<tr>
<td>WMH</td>
<td>8.0±12.3</td>
<td>0.5±1.1</td>
<td>−0.3±5.2</td>
</tr>
</tbody>
</table>

CBF, CBV, MTT, and difference values are calculated on a pixel basis before obtaining the mean regional values. ACZ indicates acetazolamide; ROI, region of interest; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; GM, grey matter; NAWM, normal appearing white matter; WMH, white matter hyperintensities.

and after ACZ as well as the difference for each parameter were calculated for each ROI.

Data Analysis

The data were analyzed statistically using the statistic program package R (http://cran.r-project.org). To examine the effect of ACZ, tissue region, and interaction between ACZ and region on CBF, CBV, and MTT values, a mixed model ANOVA was performed. Variation between subjects was handled as a random effect, whereas tissue region and ACZ were considered as fixed effects. To compare NAWM to WMH, mixed model analysis of variance was performed on the data after removal of gray matter values. NAWM and WMH region values of CBF, CBV, and MTT from the difference maps were compared using a paired t test. An F-test was used to test for significant difference in variance between the data from the two regions. Values of $P<0.05$ were considered statistically significant. No significant differences in variance between NAWM and WMH regions were found for any of the parameters.

Results

Values of CBF, CBV, and MTT before and after ACZ and values from the difference maps, measured in gray and white matter and WMH, are shown in the Table. To control the validity of the exponential function as kernel with a model-free method, both exponential fit and SVD were used solving Equation 2. The 2 methods gave comparable results, with an average difference of 6% and 0.4% in calculated CBF and CBV values, respectively. In our previous work, CBF calculated with exponential fit showed a higher correlation with carotid artery blood flow than SVD calculated values, hence values reported are calculated using the exponential fitting algorithm.

Overall, after adjusting for variation due to tissue region and subject, administration of ACZ results in a significant increase in CBF ($P=0.011$) and CBV ($P=0.022$), with no significant change in MTT ($P=0.70$). The percentage changes in CBF and CBV are 47±39 and 46±49% in grey matter, 52±48 and 44±54% in NAWM, and 45±41 and 30±38% in WMH, respectively.

When comparing WMH with NAWM, CBF is significantly lower in WMH ($P=0.004$), and the ANOVA analysis showed a strong tendency toward an interaction between the effect of ACZ on CBF and tissue region ($P=0.053$). When analyzing the difference maps, the change in CBF due to ACZ was significantly smaller in WMH than in NAWM ($P=0.026$). CBV in WMH and in NAWM was not significantly different ($P=0.846$), but there was a significant interaction between the effect of ACZ on CBV and tissue region ($P=0.002$). The difference maps showed a significantly smaller change in CBV ($P>0.001$) in the WMH than in the NAWM. MTT was significantly longer in WMH than in NAWM ($P<0.001$), but there was no significant interaction between ACZ effect and tissue region ($P=0.690$) and no difference in the change in MTT ($P=0.904$) between these regions.

Discussion

This study has demonstrated that both CBF and CVR are reduced and MTT is increased in areas with WMH as compared with NAWM. Although several previous reports support our findings of altered hemodynamics in relation to WMH, to our knowledge this is the first study demonstrating this by using high-resolution perfusion-weighted MR. Previous studies have not measured the hemodynamic status specifically within the WMH and compared it to surrounding NAWM, but have compared CBF in global white matter in individuals with WMH to individuals without WMH. Reduced CBF in global white matter associated with WMH has been shown by positron emission tomography, single-photon emission computed tomography, and Xe-CT. In addition, using transcranial Doppler sonography (TCD), Tzourio et al found the degree of WMH to be associated with a reduction in MCA blood flow velocity. Because of the absence of a control group, it cannot be excluded that CBF in NAWM is itself reduced in our study population compared with CBF in NAWM in subjects without WMH. Hatazawa et al found a global white matter CBF reduction of 14%, whereas the reduction in CBF between WMH and NAWM in this study was 29%, suggesting that the measured reduction in global white matter CBF reflects local changes in WMH. Our finding of a reduced CVR within WMH is in accord with previous findings. Oishi and Mochizuki, using Xe-CT, found a significantly reduced CVR in patients with leukoariosis compared with controls. Isaka et al measured cortical CVR using a surface detector system and Xe clearance and found a significant negative correlation between CVR and the severity of periventricular hyperintensities. Reduction in CVR measured by CO2-enhanced TCD has also been associated with the extent of WMH. However, Ture et al were unable to find any significant reduction in CVR in the white matter of subjects with leukoariosis compared with normals. As pointed out by that group, the limited resolution in their CBF images with subsequent partial volume effects between tissue compartments could explain why no differences were detected.

Our results are a strong indication of an altered hemodynamic status within the WMH compared with the surrounding tissue and of WMH representing a pathological vascular state. Several histological studies report vascular changes in relation to WMH as well as varying degrees of ischemic injury. It would be expected that reduction in CVR...
would render the tissue more sensitive to alterations in perfusion pressure, and it is noted that WMH have been associated with orthostatic hypotension. The association between hypertension\textsuperscript{9,10,29} as well as atherosclerosis\textsuperscript{3} and WMH supports the theory of vessel disease causing these lesions. Sander et al\textsuperscript{30} found a relationship between elevated nighttime systolic blood pressure and WMH, whereas Schmidt et al\textsuperscript{31} found that the LL PON1 genotype, which has been associated with small-vessel disease retinopathy, influenced the progression of WMH. The altered hemodynamics due to induced vessel changes could cause rarefaction of the myelin sheaths as consistently found in histological studies of WMH.\textsuperscript{1}

Our results were obtained in a selected group of 85-year-old subjects with an expected high prevalence of WMH. Whether other age groups exhibit the same hemodynamic changes in WMH as found in this study needs to be established.

Regional differences in vasculature and histopathological changes suggest a distinction between deep and periventricular WMH.\textsuperscript{11} Our ROI-generating program selected regions with regard to signal intensities, and not anatomical location, on the basis of manually drawn reference regions, and by combining the information from several images with different signal weighting. Partial volume effects were reduced by excluding voxels selected for more than 1 tissue, thereby obtaining ROIs specific to the different tissue types. The WMH ROIs could potentially have been stratified based on their location in deep and periventricular regions, but our data set was not large enough for such a stratification. To perform this stratification in a greater population as well as combining the hemodynamic information with information from MR diffusion and spectroscopic measurements would be of interest and is the aim of future studies.

In the group of 85-year-old volunteers, ACZ induced a significant increase in both CBF and CBV, smaller than the increase measured in our previous study of a group of younger healthy volunteers,\textsuperscript{21} and suggests a possible reduction in CBF with age. To confirm this, measurements from more individuals with identical imaging protocols are required. An age-dependent reduction in CBF has been demonstrated in studies using TCD. Matteis et al\textsuperscript{32} showed an age-dependent reduction in CBF in both sexes using a breath-holding technique, whereas Kastrup et al\textsuperscript{33} using CO\textsubscript{2} inhalation as a stimulus, showed a reduction in CBF, only in women between the 4th and 5th decade.

Using our approach, we have demonstrated that it is possible from the absolute values to measure significant ACZ-induced changes. The measured data were scaled by a numerical factor derived from a previous study\textsuperscript{21} because of a known underestimation of the measured input function. Since all subjects and measurements have been scaled by the same numerical factor, this procedure does not influence any of the results of the statistical analysis, and the conclusions drawn from the study are the same independent of this procedure. There is need for a more optimized calibration method of the absolute values measured. One approach used by Ostergaard et al\textsuperscript{34} is to scale the area under the arterial input function by the given dose of contrast agent and then use a common conversion factor to get absolute CBF.

**Conclusion**

We have shown for the first time that perfusion and CVR are reduced within WMH in comparison to the NAWM in a group of normal elderly. Furthermore, we suggest that this approach could be a step toward examining the effect of therapies designed to prevent or normalize vascular changes.

**Acknowledgments**

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**References**

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