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Microbleeds, lacunar infarcts, white matter lesions and cerebrovascular reactivity — A 7 T study ☆

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ABSTRACT

The underlying pathology of lacunar infarcts, white matter lesions and also of microbleeds is poorly understood. We assessed whether the presence of lacunar infarcts, white matter lesions or microbleeds on MRI was associated with a decrease in cerebrovascular reactivity, and assessed whether this association was similar for lacunar infarcts, white matter lesions and microbleeds. BOLD-fMRI scan with breath-holding at 7 T and anatomical scans at 1.5 T were available in 49 patients with atherosclerotic disease from the Second Manifestations of ARTerial disease (SMART) study. Microbleeds and lacunar infarcts were scored visually and volumetric assessment of white matter lesions was performed on the 1.5 T scan. The percentage of voxels with a significant signal change on breath-holding and the whole brain signal change were calculated as measures of cerebrovascular reactivity. The mean percentage of voxels with a significant signal change was 25.1% (SD 6.6) and the mean percentage whole brain signal change was 1.20% (SD 0.51). Age, gender, and diastolic blood pressure were significantly associated with cerebrovascular reactivity. Cerebrovascular reactivity was lower with increasing age, lower in females compared to males and lower with lower diastolic blood pressure. ANCOVA showed that patients with microbleeds (n = 18) had a significantly lower whole brain signal change than patients without microbleeds, with a mean difference of −0.36% (95% CI −0.64 to 0.07), independent of age, sex, systolic and diastolic blood pressure and non-lacunar infarcts. No significant associations were found for presence of lacunar infarcts or white matter lesion volume with whole brain signal change or percentage of voxels with a significant signal change. The results show that presence of microbleeds is associated with an impaired cerebrovascular reactivity in patients with atherosclerotic disease, whereas no significant association was found for the presence of lacunar infarcts or white matter lesions in our study.

Introduction

Lacunar infarcts and white matter lesions (WML) are thought to result from changes in small vessels in the brain. Although the underlying pathology is poorly understood (Futrell, 2004; Norrving, 2004; O'Sullivan, 2008; Pantoni, 2002; Wardlaw, 2005), studies indicate that the vessel wall is involved in this process (Fisher, 1998; Lammie et al., 1997). There is increasing evidence that endothelial dysfunction plays a role (Hassan et al., 2003; Wardlaw et al., 2003, 2009). The increased permeability of the blood–brain barrier may lead to entry of serum components into the vessel wall, causing thickening, inflammation and disorganization of the vessel wall (Wardlaw et al., 2009). Microbleeds are associated with lacunar infarcts and WML and are also thought to result from changes in small vessels in the brain (Fazekas et al., 1999; Greenberg et al., 2009b). It has been suggested that microbleeds and lacunar infarcts have a similar vascular pathology (Wardlaw et al., 2006). The changes in the small vessels in lacunar infarcts and WML and possibly also in microbleeds may lead to stiffening of the vessel wall, resulting in impairment of the cerebrovascular reactivity (CVR).

CVR reflects the compensatory dilatory capacity of the cerebral vasculature to a dilatory stimulus such as carbon dioxide or acetazolamide (Molina et al., 1999). FMRI based on blood oxygenation level-dependent contrast (BOLD-fMRI) is a reliable and reproducible method to quantify CVR (Goode et al., 2009; Kassner et al., 2010). An advantage of BOLD-fMRI is that it assesses CVR at the tissue-level. Previous studies investigating CVR in relation to lacunar infarcts and WML often used

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transcranial Doppler ultrasonography (Bakker et al., 1999; Birns et al., 2009; Fu et al., 2006; Immink et al., 2005; Molina et al., 1999). However, transcranial Doppler ultrasonography measures blood flow velocity in the middle cerebral artery, whereas the BOLD-signal depends on reactivity of all vessels in the brain. A pilot study showed a reduction in CVR, measured with BOLD-fMRI at 3 T, between patients with WML and lacunar infarcts and healthy controls (Hund-Georgiadis et al., 2003). Changes in the acquisition strategies can affect the observed BOLD-signal. An important parameter in the acquisition is field strength. With increasing field strength, the specificity, sensitivity and contrast of the BOLD-response increase (Yacoub et al., 2001). This can be an advantage for the investigation of the relation between lesions thought to be caused by changes in small vessels and CVR. To our knowledge, the association between CVR and microbleeds has not yet been examined, and also BOLD-fMRI at 7 T has not yet been used to assess the association between CVR and lacunar infarcts and WML. We investigated associations of lacunar infarcts, WML and microbleeds with CVR using BOLD-fMRI at 7 T in patients with atherosclerosis.

Methods

Participants

Patients newly referred to our hospital with symptomatic and asymptomatic atherosclerotic disease from the Second Manifestations of ARTerial disease (SMART) study (Simons et al., 1999), without contraindications for 7 T MRI, were consecutively included for the 7 T study between July 2008 and February 2010. Atherosclerotic disease was defined as manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, or risk factors for atherosclerosis (e.g. hypertension, diabetes). The objectives and design of the SMART study have been described elsewhere (Simons et al., 1999). The SMART study and 7 T imaging were approved by the medical ethics committee of our institution. Written informed consent was given by all patients.

For this study, BOLD fMRI data were available for 58 patients. In 7 scans the BOLD-signal could not be calculated due to motion artifacts and two patients had a carotid artery stenosis >70%; these were excluded, leaving 49 patients for analysis (Table 1). The mean age of the study population was 58.9 years (SD 10.0, range 34 to 80). Seventeen of the 49 patients were included in the SMART-study with vascular risk factors (13 diabetes mellitus, 1 hypertension, 1 hyperlipidemia), 14 patients with a stroke, 4 patients with coronary artery disease, 11 patients with peripheral artery disease, and 1 patient with ischemic renal failure.

Magnetic resonance imaging 1.5 T

The MR protocol on the 1.5 T whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands) consisted of transverse T1-weighted (repetition time (TR)/echo time (TE): 235/2 ms), T2-weighted (TR/TE: 2200/11 ms and 2200/100 ms), fluid-attenuated inversion recovery (FLAIR) (TR/TE/inversion time (TI): 6000/100/2000 ms) and inversion recovery (IR) (TR/TE/TI: 2900/22/410 ms) sequences. Field of view was 230×230 mm, matrix size 180×256, slice thickness 4.0 mm, no gap, 38 slices.

Magnetic resonance imaging 7 T

On the same day as the 1.5 T scan the 7 Tesla scan was performed on a 7 T whole-body system (Philips Healthcare, Cleveland, OH, USA), using a volume transmit and 16-channel receive head coil (Nova Medical, Wilmington, MA, USA). A dual echo T2*-weighted scan (TR 20 ms, TE 2.5/15 ms, matrix size 508×399, resolution 0.35×0.4×0.6 mm^3, with flow compensation and acceleration factor 2.5) was made for visualization of microbleeds (Conijn et al., 2010).

Table 1
Baseline characteristics of study sample.

	Study sample (n = 49)	
Male gender*	38	(76%)
Age (years)†	58.9	± 10.0
Systolic blood pressure (mm Hg)†	135.9	± 16.3
Diastolic blood pressure (mm Hg)†	78.5	± 10.5
Hypertension*	33	(67%)
Diabetes*	20	(41%)
Anticoagulant medication use*	1	(2%)
Antihypertensive medication use*	29	(59%)
Brain infarcts present*	13	(27%)
Non-lacunar infarcts present*	7	(14%)
Lacunar infarcts present*	9	(18%)
Number of lacunar infarcts‡	0	(0–7)
Microbleeds present*	18	(37%)
Number of microbleeds‡	0	(0–6)
Intracranial volume (mL)**	1439	(1292–1597)
Total brain volume (mL)**	1115	(984–1264)
White matter lesion volume relative to total intracranial volume (mL)		
Total (n = 49)**	1.2	(0.4–8.0)
Upper quartile (n = 9)**	8.0	(5.0–28.0)
Lower three quartiles (n = 40)**	1.1	(0.3–3.1)

*Number (percentage), †mean ± SD, ‡median (range), one patient with >20 microbleeds was excluded from the analysis on the number of microbleeds, **median (10th and 90th percentile).

A BOLD-fMRI scan with breath-holding was made for all patients. The breath-holding paradigm consisted of 5 periods of breath-holding interleaved with 30 s of normal breathing. The first 4 breath-holding periods lasted 21 s, the last one 'as long as possible'. Data from the respiratory belt of the scanner was logged and used to evaluate task performance and the length of the 'as long as possible' condition. Single shot Echo Planar Imaging (EPI) with TR 3 s, TE 20 ms, 96 volumes, 45 slices with no gap, resolution 1.5×1.5×1.5 mm^3, SENSE factor 3.5 (resulting in an EPI readout train of 41), was used to measure the BOLD-effect induced by the breath-hold task. The use of thin slices helps to control the amount of through-slice dephasing due to susceptibility differences between air and tissue. Geometric distortions in the EPI images are limited by the application of SENSE. Multiple linear regression was applied to select activated voxels using a block model. The block was shifted by 5 volumes relative to the task to take into account the delayed BOLD-response to the task. A linear term was included in the model to account for scanner drift. The residual signal after regression was used to create a temporal Signal to Noise Ratio (tSNR) map by dividing the average signal over time by the standard deviation over time. This map reflects the quality of the data.

Estimated signal changes were used to create a T-map. From all the voxels in this map, the number of voxels that were activated by the breath-holding task was calculated by applying a threshold of 2 on the T-map. A whole brain mask was created by setting a threshold on the first EPI volume and smoothing and eroding the result. This whole brain mask was used to select the voxels within the brain, excluding the skull. The number of voxels with a significant signal change due to breath-holding was divided by the total number of voxels within the whole brain mask to obtain the percentage of activated voxels (CVR1).

$$CVR1 = (n/total) * 100\%,$$

where n is the number of voxels with a significant signal change due to breath-holding, and *total* is the total number of voxels within the whole brain mask. This measure was taken to compare the amount