Quantification of the Cerebral Microvasculature using High-Resolution BOLD-Based Vessel Size Imaging at 3 Tesla

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TARGET AUDIENCE – Researchers with interest in quantification of the cerebral blood vessel system.

PURPOSE – *Vessel size imaging* (VSI)[1] allows quantitative mapping of the microvasculature by analyzing changes of the transverse relaxation rate, ΔR_2, and the effective transverse relaxation rate, ΔR_2^*, due to intravenous contrast agent injection.[1,2] Using intravenously administered contrast agents for the purpose of methodological development or for studies based on healthy subjects is, however, often ethically difficult to justify. To overcome this issue, the analysis of blood oxygenation level dependency (BOLD)-related signal changes provoked by inhalation of different gas mixtures (ambient air and carbogen [95 % CO_2, 5 % O_2]) has recently been suggested for characterizing the microvasculature with VSI.[3,4] So far, BOLD-based VSI has been applied with images that were acquired with a rather coarse spatial resolution of 3 mm and that were filtered with Gaussian smoothing kernels up to 8 mm full width at half maximum (FWHM) at 3T [4] and 7T [3] impeding clear assignment of the resulting VSI parameter maps to the underlying tissue structures. **In this contribution, we present an approach for mapping features of the microvasculature with substantially improved in-plane spatial resolution by employing *gradient echo sampling of FID and spin echo* (GESFIDE) with *periodically rotated overlapping parallel lines with enhanced reconstruction-echo planar imaging* (PROPELLER-EPI).**

METHODS – *Data Acquisition:* Twenty-three healthy subjects (age range: 20 – 25y) were measured with a *long-axis PROPELLER-EPI* sequence with a dual-echo gradient-echo and a spin-echo readout on a 3 T MRI system (TIM Trio Siemens Healthcare, Erlangen, Germany). Two gradient-echoes with echo times of 13 ms and 30 ms as well as one spin echo at 88 ms were sampled after a single excitation for each blade orientation. To cover *k*-space completely 12 blades were acquired with TR = 2183 ms per blade, radial field-of-view = 220 mm, acquisition matrix size = 192 × 192, in-plane resolution = 1.1 mm × 1.1 mm, 17 contiguous slices with 3 mm slice thickness, receiver bandwidth = 159 kHz, and 34 repetitions. The subjects were breathing room air and carbogen in an alternating fashion using a facial mask with a three-way valve. Each stimulation block lasted 3 minutes resulting in a breathing pattern of air – carbogen – air – carbogen – air and a total scan time of 15 min. Additionally, 3D whole-head T_1-weighted MRI data were collected for each subject with a magnetization prepared rapid gradient echo (MP-RAGE) sequence for automatic identification of gray and white matter regions using the following parameters: TE = 3.03 ms, TR = 2300 ms, TI = 900 ms, FA = 9°, and voxel size = 1 mm × 1 mm × 1 mm.

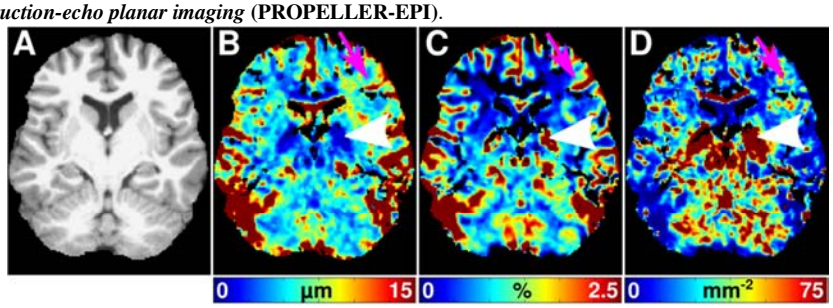

Fig. 1: *T_1-weighted image (A) and corresponding VSI parameter maps of a healthy subject. Maps of the vessel radius, deoxygenated blood volume, and mean vessel density are illustrated in B, C, and D, respectively. The pink arrow points to a pial vein that is clearly characterized by large vessel radii and low vessel density. The big arrow head marks the iron-laden basal ganglia that are characterized by a low vessel radius and high deoxygenated blood volume. Unreliable values in the parameter maps are indicated with black color.*

Data Processing and Data Analysis: Images were processed and analyzed using MATLAB, SPM8 (http://www.fil.ion.u-cl.ac.uk/spm) and the Freesurfer software package (http://surfer.nmr.mgh.harvard.edu/). The magnitude PROPELLER-EPI images were reconstructed from *k*-space data using sliding-window reconstruction as described by Krämer et al.[5] and the reconstructed images were realigned to match the space of the data of the first repetition. To estimate robustly changes of R_2 and R_2^* image denoising with the spatial adaptive nonlocal means technique [6] and filtering with a 2 mm FWHM 2D Gaussian smoothing kernel was applied to the MR images of each repetition. Based on these pre-processed images, baseline correction, ΔR_2, ΔR_2^*, and the ratio $q \equiv \Delta R_2^*/\Delta R_2$ were computed as described by Jochimsen et al.[3] The *q*-values were transferred into vessel radii using a transfer function obtained by Monte-Carlo simulations that took into account assumptions of signal change due to gas inhalation and MRI acquisition parameters.[3,7] Additionally, maps of deoxygenated blood volume and mean venous vessel density were computed.[3] Using Freesurfer's automatic processing of T_1-weighted data, subject-specific voxel-based atlases of gray matter (GM) and white matter (WM) structures were generated for each subject.[8] The individual T_1-weighted data were co-registered to the mean of the spin-echo PROPELLER-EPI data and the resulting registration matrix was applied to the voxel-based atlases to enable automated analysis of anatomical regions of the VSI parameter maps.

RESULTS – Figure 1 shows representative maps of the vessel radius (B), deoxygenated blood volume (C), and venous vessel density (D). These VSI parameter maps clearly provide anatomic depiction of tissue structures (e.g., cortical GM, globus pallidus, red nucleus). The radius and deoxygenated blood volume maps (B,C), for instance, enable identification of large pial veins (see arrow in Figs. 1B and 1C). Interestingly, low vessel radii are observed in regions with high tissue iron concentration (see arrow head in Fig. 1B). In these anatomical regions high deoxygenated blood volumes occur (arrow in Fig. 1C) that yield high venous vessel densities (arrow in Fig. 1D). Average values of the vascular parameters across 23 subjects obtained with BOLD-VSI are summarized in Table 1.

	q	r_v [µm]	DBV [%]	N_v [mm^{-2}]
white matter	2.9 ± 0.3	7.3 ± 0.7	0.6 ± 0.1	36 ± 8
cortical gray matter	4.1 ± 0.3	12.7 ± 1.0	1.4 ± 0.2	30 ± 6
hippocampus	3.4 ± 0.4	10.1 ± 1.9	1.0 ± 0.2	32 ± 10
globus pallidus	1.41 ± 0.2	2.8 ± 0.6	1.2 ± 0.4	225 ± 72

Tab. 1: *Mean values and standard deviations of $q=\Delta R_2^*/\Delta R_2$, vessel radius ($r_v$), deoxygenated blood volume (DBV), and mean vessel density (N_v) across both hemispheres of 23 healthy subjects are shown for selected anatomical regions.*

DISCUSSION – We have presented a non-invasive approach for vessel size imaging with an effective in-plane resolution of 2 mm (after Gaussian smoothing) at the clinical field strength of 3T. The calculated maps facilitate depiction of anatomical structures and, thus, enable studying vascular features of smaller structures than before such as deep GM nuclei or hippocampus. In literature, mean vessel radii in GM (cortical and deep GM) and WM have already been determined using BOLD-VSI at 3T [GM: (7.3 ± 0.3) µm, WM: (6.6 ± 0.5) µm] [4] and at 7T [GM: (13.4 ± 1.7) µm, WM: (13.7 ± 2.1) µm].[3] In contrast to these studies, we measured vessel radii in cortical GM and deep GM separately and obtained substantially larger mean vessel radii in cortical GM than in WM (Tab. 1). The larger mean radius of vessels observed in cortical GM compared to WM agrees with the fact that the proportion of veins in cortical GM is larger than in WM. With confocal laser microscopy of *ex vivo* samples of the human brain microvascular radii ranging from 3.4 to 3.9 µm were measured.[9] Although this value is smaller than the radii in this study, one has to take into account that the *ex vivo* approach likely underestimates the vessel radii due to shrinkage of the anatomical specimen. The values obtained for deoxygenated venous blood volume are similar to the values that were measured by analysing the gradient-echo signal decay [GM: (1.75 ± 0.13) %, WM: (0.58 ± 0:09) %].[10]

CONCLUSION – GESFIDE-PROPELLER-EPI acquisition during inhalation of different gas mixtures enables characterization of the microvasculature with an effective in-plane resolution of 2 mm at 3T. In future, animal experiments are required to validate the BOLD-VSI technique by relating the computed vascular measures to histological examinations of the same sample.

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