Analysis of MR Signal Dynamics during Carbogen Inhalation using a Combined Spin- And Gradient-Echo (SAGE) EPI Sequence

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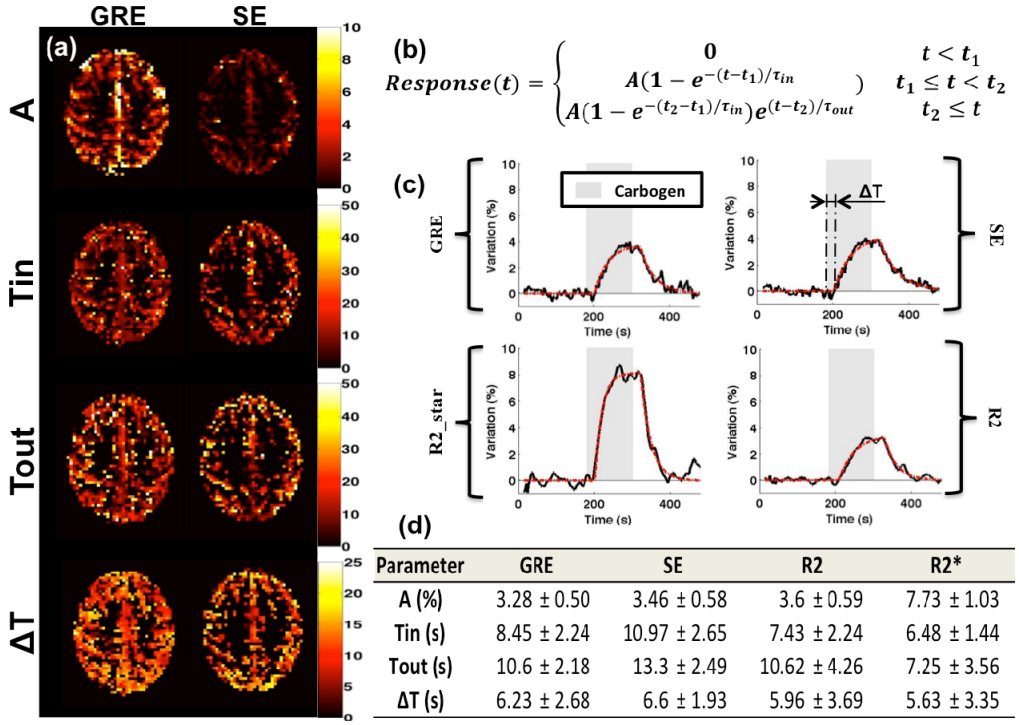
Introduction: The availability of a technique to image tissue oxygenation *in vivo* is of considerable interest. Such a tool may improve our knowledge about normal cerebral physiology during rest, sleep, or functional tasks. It may also improve diagnosis and therapeutic orientation in numerous pathologies including cancer or neurodegenerative diseases. MR methods have been proposed to assess the variations of brain oxygenation during respiratory challenges [1]. In particular, carbogen (95% O_2, 5% CO_2) challenges seem promising as they can induce up to 50% MR signal variations in lesions. Usually, the MR acquisitions are performed before and after the inhalation of the gas, and only the signal amplitude variations are computed. However, recent studies on stroke and tumor have suggested that the dynamics of the signal variations could be of particular interest [2,3]. The purpose of the present study was to analyze the dynamic changes in brain oxygenation induced by a carbogen respiratory challenge in normal human brain. Using a simple exponential model, maps of the amplitude, the wash-in and wash-out time constants, and the arrival time delay of the gas were computed.

Material and Methods: Imaging was performed at 3T using a GE Signa 750 whole-body scanner (GE Healthcare, Waukesha, WI) and an 8-channel head coil. The study was approved by the IRB and all subjects signed written informed consent. Five subjects were scanned using the following protocol:
MR acquisitions were performed using one spin- and four gradient-echoes (SAGE) [4] EPI sequence (TR=3000ms, TE= 13.1, 24, (gradient echoes) 48.2, 59.1 (asymmetric spin echo) and 70.0 (spin echo) ms, 9 slices with voxel-size: 3.34x3.34x5 mm, spacing: 2mm). During the experiment, the volunteers were breathing spontaneously through an adult non-rebreathing mask (Hudson RCI, Durham, NC). Our paradigm consisted of 2 minutes carbogen breathing, preceded and followed by 3 minutes of medical air breathing, manually introduced into the breathing circuit at a rate of 10 L/min.
For each voxel of the SAGE sequence, an air baseline was computed from the average of the first 3 minutes of air breathing. Similarly, a carbogen baseline was computed from the average of the signal acquired during the last 30 seconds of the carbogen breathing block. From the baseline values, activation maps were created. Voxels with signal variation lower than twice the noise variance were excluded from the analysis. T2 and T2* relaxation maps using the multiple echoes were created following the method presented by Ma and Werli [5]. To model the signal evolution, we created a part exponential function, with 4 parameters (cf. Fig.1b): the amplitude A, a wash-in time constant Tin, a wash-out time constant Tout, the time delay between the carbogen introduced into the breathing circuit and the observed effect ΔT. t1 and t2 represent respectively the time when the carbogen is on and the time when it is off. A first order polynomial fit was first used to obtain an initial estimate of the time constants in each voxel. The results of this approximation were then used to initialize a non-linear mean-square Levenberg-Marquardt fitting algorithm. New parametrical maps were eventually created using either the signal amplitude of the gradient- and spin-echoes or the relaxation rates.



Parameter	GRE	SE	R2	R2*
A (%)	3.28 ± 0.50	3.46 ± 0.58	3.6 ± 0.59	7.73 ± 1.03
Tin (s)	8.45 ± 2.24	10.97 ± 2.65	7.43 ± 2.24	6.48 ± 1.44
Tout (s)	10.6 ± 2.18	13.3 ± 2.49	10.62 ± 4.26	7.25 ± 3.56
ΔT (s)	6.23 ± 2.68	6.6 ± 1.93	5.96 ± 3.69	5.63 ± 3.35

Results: Overall, 90% of the voxels within the brain showed a response to carbogen. However a smaller fraction resulted in sufficient SNR for a correct application of the fitting procedure, especially in white matter (WM). Parametrical maps of one volunteer are presented in Fig.1a. The relative homogeneity of Tin, Tout, and ΔT maps can be observed. According to Fig.1c, the mono-exponential model (cf. Fig.1b) appears to be appropriate to describe the response to carbogen inhalation. R2* also exhibits a better sensitivity to the carbogen challenge than R2 or the individual echoes. The values in Fig.1d highlight the reproducibility of the measurements throughout the 5 volunteers. The wash-out time constant appears to be slightly longer than the wash-in process.

Legend: *(a) Maps of the parameters in one subject. (b) Part exponential function used for our model. (c) Average signal over the brain for different echoes and relaxation time (black) and corresponding fits (red). (d) Estimates of the 4 parameters averaged over all 5 volunteers.*

Conclusion: This study suggests that maps representing the dynamics of the BOLD signal during a carbogen respiratory challenge can be created in the healthy brain from a simple mathematical model. The parameters seem to be homogeneous and the values remain stable across subjects. Improvement in SNR and spatial resolution may help to increase the amount of converging voxels, particularly in WM. This may be facilitated by using blood pool contrast agents, such as ferumoxytol [6]. This method is well adapted to study pathologies such as cancer, where high blood volume regions are present.

References: [1] Robinson et al., NMR in biomed, 1999 [2] Muller et al., Eur Rad, 2010. [3] Dani et al., Annals of Neurology, 2010. [4] Schmiedeskamp et al., MRM, 2011 [5] Ma and Wherli, J Magn Reson B, 1996. [6] Neuwelt et al., Neurosurgery 2007.

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