A Mathematical Model to Evaluate Quantitative BOLD MRI for the Measurement of the Cerebrovascular Reserve Capacity during Hypercapnia

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INTRODUCTION The most commonly used method for the evaluation of cerebrovascular reserve capacity (CVC) in patients with neuro-vascular disease is transcranial Doppler sonography (TCD) prior and during inhalation of a CO_2-air mixture. This method does not provide information on tissue perfusion but measures the flow and its increase in a few large arteries of the brain instead. Alternatively, BOLD-based MRI imaging during the inhalation of a CO_2-air mixture provides information on the tissue perfusion reserve. We developed a new method based on a mathematical description of the CO_2 enrichment of the blood in the alveoles that characterizes the change of the MR-signal during hypercapnia and compared the results with TCD measurements.

METHODS 27 patients with uni- or bilateral high-grade stenosis or occlusion of the common or internal carotid artery were included in the study. Both middle cerebral arteries (MCA) were insonated through the temporal bone window for the TCD measurements.
The MR-protocol consisted of T_1- and T_2-weighted imaging, time-of flight MR angiography (TOF-MRA), phase contrast flow measurements (PC-MRA) [1], and multi-slice single-shot multi-echo EPI imaging (4 echo images, matrix size 64×64, FOV 22 cm, slthck 5 mm, 20 slices, TR = 3000 ms, TE = 17/44/71/98 ms) [2] performed on a 1.5T scanner (MAGNETOM Sonata, Siemens Medical Systems, Erlangen). The total examination time was 15-20 minutes. The BOLD measurement took 5 minutes (100 scans) and the patients were breathing the 7% CO_2-air mixture during minutes two and three (see Fig. 1). Quantitative I_0- and T_2*-values were determined pixel-wise using a mono-exponential model. The maps were motion corrected in SPM99 [3]. The T_2*-maps were spatially filtered with a three-dimensional Gaussian filter (FWHM = 10 mm) and the T_2* time courses were filtered with a median filter (kernel size 5). A pixel-wise least square fit of a model function to the T_2*-time course was performed. The reference function is based on a mathematical model, which is described as

$$T_2^*(t)=\begin{cases} y_1 & : 0<t<t_1 \\ y_1+y_{diff}\cdot(1-\exp(-(t-t_1)/\tau_1)) & : t_1<t<t_2 \\ y_2+\left[\left[y_1+y_{diff}\cdot(1-\exp(-(t_2-t_1)/\tau_1))\right]-y_2\right]\cdot\exp(-(t-t_2)/\tau_2) & : t_2<t \end{cases} \quad (1)$$

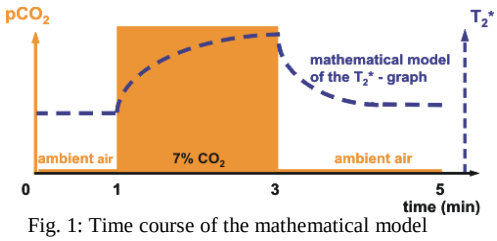

Fig. 1: Time course of the mathematical model during the inhalation of 7% CO_2-air mixture.

The transition of the 7% CO_2-air mixture from the alveoles to the capillaries of the blood system can be described by a compartment model. The increase in the concentration of the partial CO_2-pressure (pCO_2) in the blood is described as a mono-exponential rise. The increasing pCO_2 causes a vasodilation of the arteries in the brain, which results in a higher cerebral blood flow (CBF). The increase of CBF between ambient and 7% CO_2-air mixture is nearly linear [4]. The amount of deoxygenated haemoglobin decreases with constant oxygen consumption and higher CBF leading to a prolongation of the T_2*-relaxation time (BOLD-effect). The relationship between the given conditions is also nearly linear. This yields to the mathematical model, which describes the time course of the T_2*-time while breathing the air mixture (see Eq. 1), as shown in Fig. 1. The time course could be described for each individual pixel with 7 parameters (y_1, y_2, y_{diff}, τ_1, τ_2, t_1, t_2). In addition, the parameters $T_2^*_{base}$ [$(y_1+y_2)/2$], $T_2^*_{max}$ [$y_1+ y_{diff}(1-\exp(-(t_2-t_1)/\tau_1))$], ΔT_2^* [$T_2^*_{max}- T_2^*_{base}$] and relative ΔT_2^* [$(T_2^*_{max}/ T_2^*_{base})-1$] were derived from the fitted time course and all 11 parameters were available for display as parameter maps. These maps were evaluated by visual inspection by an experienced neuroradiologist.

RESULTS Quantitative BOLD MRI was successfully acquired in and well tolerated by all patients. Each patient dataset required about 5 minutes calculating time. The T_2* time course of an individual cortical pixel, before and after the pixel fit is shown in Fig. 2. E.g. ΔT_2* maps of one patient with normal BOLD response and one patient with a decreased BOLD response in one hemisphere are shown in Fig. 2 and Fig. 3.
7/27 patients could not be evaluated by TCD due to an insufficient bone window. 9/10 patients with bilaterally normal CVC in TCD showed symmetrically distributed normal BOLD response on color parameter maps. One patient with occlusion of the left carotid artery showed normal CVC in TCD, but the BOLD effect was clearly reduced in the corresponding territory. 6/7 patients with a decreased CVC in TCD in one hemisphere and 3/3 patients with a decreased CVC in TCD in both hemispheres showed reduced BOLD responses in the corresponding hemispheres. One patient with unilateral impairment of CVC in TCD showed a normal BOLD response.

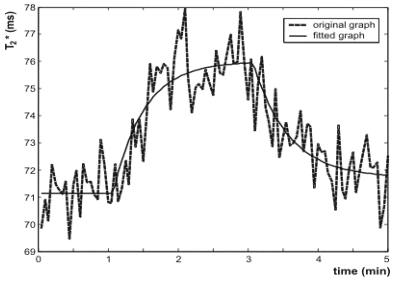

Fig. 2: T_2* time course of an individual cortical pixel (original and fitted time course).

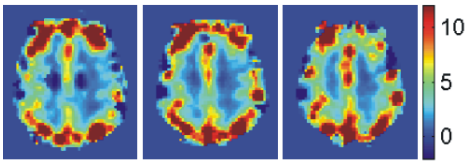

Fig. 3: ΔT_2*-maps in a patient with right-sided high-grade carotid artery stenosis with normal CO_2 induced BOLD effect. Color bar shows ΔT_2 in ms.

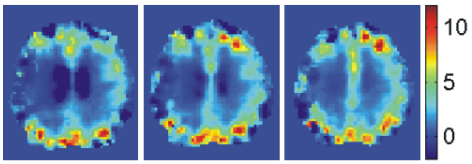

Fig. 4: ΔT_2*-maps in a patient with right-sided high-grade carotid artery stenosis. Clearly reduced BOLD effect in the right middle cerebral artery territory. Pathological result also in TCD.

DISCUSSION The mathematical model of the T_2* time course is a fast and robust tool to evaluate the behavior of a BOLD contrast MR-signal during hypercapnia. The advantages of the parameter maps are, that every individual parameter could be analyzed, e.g. the time delay in the start of CO_2 administration (t_1), time constant of the exponential increase (τ_1), or the magnitude of the BOLD effect (ΔT_2*, relative ΔT_2*).
Quantitative BOLD MRI is able to diagnose patients with impaired CO_2-reactivity and appears highly correlated with TCD results. The method is mature and can easily be included in a routine MRI exam. The results of TCD and BOLD MRI were discrepant in two cases only. In a patient with impaired CO_2-reactivity in TCD and a normal result in BOLD MRI discrepancy may indicate sufficient blood supply via leptomeningeal collaterals.

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