The relationship between changes in CBF and CBV is dynamically varying throughout stimulus duration but complex following stimulus offset

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SYNOPSIS

Quantification of the relationship between changes in CBF and CBV during functional activation is necessary to calculate changes in $CMRo_2$ from multi-modal MRI measurements. We investigated the relationship between dynamic changes in CBF and CBV by combing the modified fMRI method for CBF with contrast agent for CBV during forepaw stimulation with different stimulus duration. There is a dynamically varying relationship between changes in CBF and CBV throughout stimulus duration and the relationship becomes complex following stimulus offset. This is the first evaluation of the dynamic CBF-CBV relationship using only MRI methods.

INTRODUCTION

The relationship between changes in CBF and CBV is important for calculating changes in $CMRo_2$ from fMRI experiments [1]. Although recent human fMRI studies [3,4] have calculated changes in $CMRo_2$ using measured changes in BOLD and CBF during visual and motor stimulations, these predictions were generated using an assumed relationship between changes in CBF and CBV derived from prior PET hypercapnia study in primates under steady state conditions (i.e. $CBV=CBF^{\alpha}$, α=0.38 [2]). While prior studies [5,6] have examined the dynamic relationship between changes in CBF and CBV, the studies were limited by use of either non-quantitative methods or the CBF and CBV data had different spatial resolutions. Recently, we developed a modified fMRI method to measure CBF and BOLD responses with a temporal resolution 0.5 second [7]. In this study, this method was used in conjunction with superparamagnetic contrast agent to measure changes in CBV. Towards the goal of calculating transient changes in $CMRo_2$, we investigated the relationship between changes in CBF and CBV during forepaw stimulations in the rat with variable stimulus durations.

MATERIALS and METHODS

Animal preparation: Male Sprague-Dawley rats (n=4) were anesthetized and paralyzed with α-chloralose anesthesia (initial 80 mg/kg, supplement 20 mg/kg/1/2hr, i.p.) and *D*-tubocurarine chloride (0.5 mg/kg/½hr, i.p), respectively. An arterial line was used to monitor physiology (blood pH, pO_2, pCO_2) throughout the experiment. A block design forepaw stimulation (2 mA; 3 Hz) protocol was performed with different stimulus durations (from 4 to 32 s). *MRI measurements*: All fMRI experiments were performed on a modified 7T Bruker horizontal-bore spectrometer with gradient-echo EPI (TR/TE = 500/20 ms): slice thickness = 2 mm: FOV 2×2 cm^2. High temporal ΔCBF/CBF data were obtained with different flip-angles of BOLD signals using the convolution method [7]. After ΔCBF/CBF data were collected, ΔCBV/CBV measurements were performed using the iron oxide contrast agent, AMI-227 (Advanced Magnetics Inc; 2 mg/kg/0.9 cc bolus), which remains in the intravascular space for > 6 hours [8]. ΔCBV/CBV was calculated as described by Kennan et al [8].

RESULTS and DISCUSSION

The relationship between ΔCBF/CBF and ΔCBV/CBV are shown in figures during application of 4 (black), 8 (red), 16 (green) or 32 (blue) second forepaw stimulation. Figs. 1, 2, and 3 represent the relationship between ΔCBF/CBF and ΔCBV/CBV for three periods following stimulation onset: transition to a peak after stimulus onset; period from peak to stimulus offset; transition to baseline after stimulus offset. The dotted lines in each figure represent the value of α ranging from 0.05 to 0.4. During transition to a peak after stimulus onset (Fig. 1) the value of α ranged from 0.05 to 0.15. During period from peak to stimulus offset (Fig. 2) the value of α ranged from 0.10 to 0.25. During transition to baseline after stimulus offset (Fig. 3) the value of α ranged from 0.10 to 0.35. Since the power exponent, α, ranged from 0.10 to 0.25 under steady state (Fig. 2), caution is needed when calibrating by Grubb's power exponent. Interestingly, power exponents during the transition to a peak after stimulus onset were almost the same range (from 0.05 to 0.15). In contrast, the values during the transition to baseline after stimulus offset were dependent on stimulus duration. With 4 second stimulation, the power exponents in transitions to the peak were nearly the same as the ones during transition to baseline; but with longer stimulus duration, the ones in transitions to the peak were smaller than the ones in transition to baseline. This result indicates that the power exponent for steady state, even when directly measured during neuronal activation, cannot be used to calculate $CMRo_2$ for the transition state.

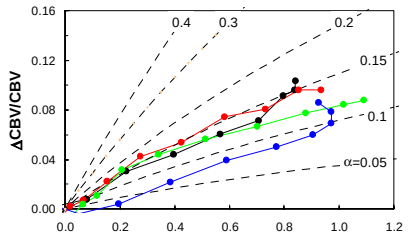

Figure 1

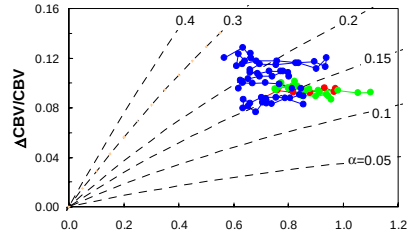

Figure 2

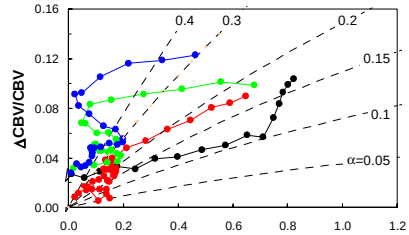

Figure 3

CONCLUSION

This is the first study to investigate the high temporal relationship between ΔCBF/CBF and ΔCBV/CBV during transition periods using only MRI methods. The modified fMRI method with contrast agent allows the prediction of $CMRo_2$ changes at high temporal resolution without the need for further perturbations (i.e. CO_2 challenge) or assumption (i.e. power exponent).

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