Negative cerebral blood flow and BOLD responses to somatosensory stimulation in spontaneously hypertensive rats

R. F. Leoni[1,2], D. B. de Araujo[2], and A. C. Silva[1]

[1]Cerebral Microcirculation Unit, National Institute of Neurological Diseases and Stroke - NINDS/NIH, Bethesda, Maryland, United States, [2]Department of Physics and Mathematics, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil

INTRODUCTION

Some functional magnetic resonance imaging studies conducted both in animals as well as in humans have reported negative BOLD responses associated with a stimulus [1-6]. The negative response has been explained either by a decrease in local neuronal activity (i.e., neuronal surround inhibition) [2, 5] or by a decreased cerebrovascular reserve (i.e., vascular steal effect) [6]. Since arterial hypertension causes vascular remodeling and results in impairment of cerebrovascular autoregulation [7], it may cause the appearance of negative response in functional experiments. In the present study, we measured the cerebral blood flow (CBF) and blood oxygenation level dependent (BOLD) responses following somatosensory stimulation in spontaneously hypertensive rats (SHR) and normotensive controls, to investigate if cerebrovascular impairment related to hypertension leads to negative CBF and BOLD responses.

MATERIALS AND METHODS

Thirty SHR (266 ± 35 g) and twenty-five age-matched normotensive controls (n = 5 Sprague Dawley – SD, n = 20 Wistar Kyoto – WKY, 247 ± 29 g) were anesthetized under alpha-chloralose, orally intubated and mechanically ventilated. Functional images were obtained at 7T MRI (Bruker-Biospin, Billerica, MA) with the following parameters: TR/TE=250/15ms, FOV=25.6x25.6cm2, matrix=64x64, slice thickness=2mm, and labeling time=217.60ms. For ASL, a small home-built figure-8 shaped labeling coil was positioned under the neck of the animal. For somatosensory stimulation, needle electrodes were inserted in both forepaws (3Hz, 2-mA pulses). The paradigm consisted of 8 epochs of 120 images (40 off/40 on/ 40 off). Arterial blood gases were sampled before and after the scan through a PE-50 catheter inserted into the right femoral artery. Significant differences across the data were tested with a Student's t-test or ANOVA.

Table 1: *Average CBF and BOLD response amplitudes for normotensive (SD and WKY) and hypertensive (SHR) rats.*

	Normotensive rats		*Hypertensive rats*	
	CBF (%)	**BOLD (%)**	**CBF (%)**	**BOLD (%)**
Positive Response	84 ± 45	2.8 ± 1.0	80 ± 32	2.8 ± 0.9
Incidence	25/25 (100%)		30/30 (100%)	
Negative Response	-68 ± 16	-1.2 ± 0.4*	-46 ± 14*	-1.1 ± 0.5*
Incidence	3/25 (12%)		20/30 (67%)	

*P < 0.05 versus positive response

RESULTS AND DISCUSSION

All physiologic parameters were kept within normal values throughout the experiments: $PaCO_2$ = 34 ± 4 mmHg, PaO_2 = 109 ± 18 mmHg, pH = 7.44 ± 0.04 mmHg (mean ± std.dev). Mean arterial blood pressure was higher for SHR (159 ± 15 mmHg) than for normotensive rats (122 ± 15 mmHg, p < 0.05). Among the SHR, 20/30 rats presented negative CBF and BOLD responses after forepaw stimulation in regions surrounding the somatosensory cortex (Table 1), whereas only 3/25 normotensive rats showed negative signals. The spatial extent of the negative response in the SHR was comparable to that of the positive response, but limited to only a few pixels in the 3/25 normotensive rats. Fig. 1a,c,e show representative functional data from an SHR, while Fig. 1b,d,f show data for a normotensive rat. In all cases, the surround negative responses had smaller amplitudes than the positive responses in S1 (Table 1; Fig.1c-f). Because the negative responses were largely associated with the presence of hypertension, their likely cause is due to a vascular stealing effect [6] related to impaired vascular reactivity and unlikely to be related to neuronal inhibition [3].

CONCLUSIONS

The results suggested that the negative CBF and BOLD responses in areas surrounding the somatosensory cortex may be related to an impaired vascular reactivity caused by hypertension. Studies are currently underway to investigate the effects of altering blood pressure on the negative fMRI response.

REFERENCES: [1] Bressler D et al., *PLoS One* 2007, 2(5):e410. [2] Shmuel A et al, *Nat Neurosci* 2006 9(4):569-77. [3] Kamba M et al., *J Magn Reson Imaging* 2007, 26:1506-23. [4] Smith A et al., *Hum Brain Mapp* 2004, 21:213-220. [5] Devor A et al., *J Neurosci* 2007, 27(16)4452-59. [6] Harel et al., *JCBFM* 2002, 22:908-917. [7] Iadecola C and Davisson R, *Cell Metab* 2008, 7:476-484.

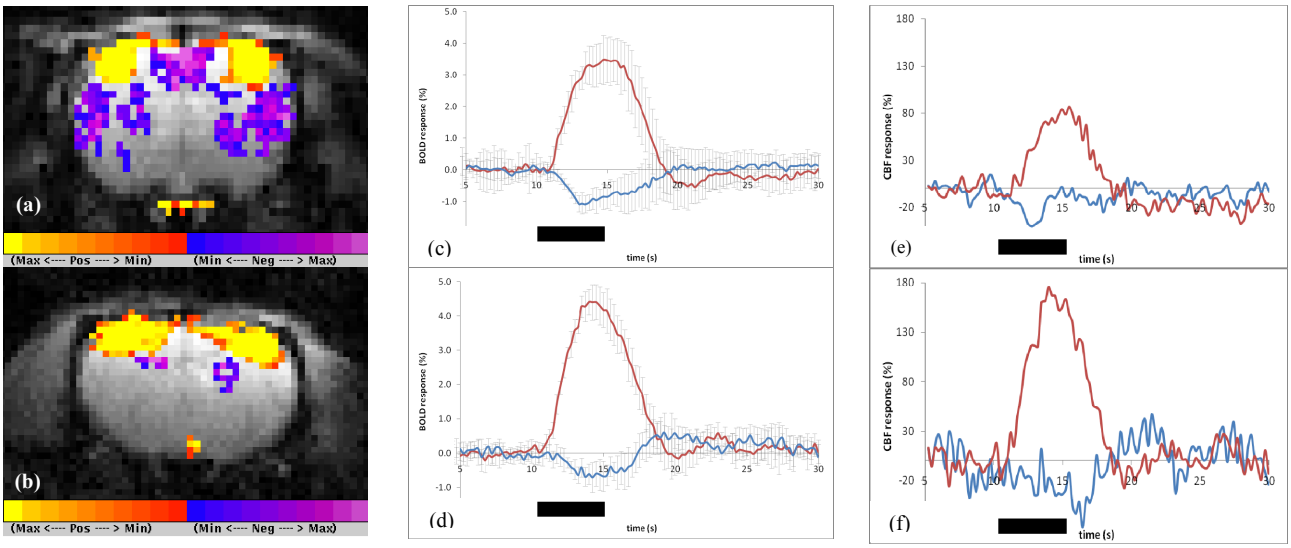

Figure 1: (a) Representative functional maps from a SHR and (b) a WKY rat. Corresponding time courses for positive (red curve) and negative (blue curve) BOLD (c – SHR, d – WKY) and CBF (e – SHR, f – WKY) responses. Horizontal bar indicates stimulation period (5s).