# Discordant Responses to Cocaine in CBF and CBV: Implications for phMRI CMRO2 assessment

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**Introduction.**

Advanced techniques in fMRI methods enable BOLD contrast to be used in conjunction with CBF to calculate relative changes in $CMRO_2$ induced by task-driven activity through a hypercapnia calibration approach. Simultaneous measurement of cocaine-induced changes in CBF and $CMRO_2$ has been proposed by our group as a means to de-convolve the neural component from non-neural components in the complex phMRI signals [1]. This practice, however, makes the assumption that mapping changes in neural activity that are stimulated by pharmacological agents is as straightforward as mapping changes in neural activity that arise from cognitive or sensory stimuli. Two potential confounding effects of pharmacological agents may impact this assumption. First, The CBF-CBV relationships during the initial transient state and later steady state following a pharmacological challenge may be different. Second, it is questionable whether hypercapnia can be used as a calibration for the pharmacological fMRI model-based $CMRO_2$ calculations [2]. In order to fully examine the limits of the fMRI $CMRO_2$ method applied to psychopharmacological studies, simultaneous and direct measurements of CBF and CBV were made in the same laboratory animals following cocaine and hypercapnia challenges. The relationships between CBF and CBV changes during and after the initial several minutes' response to cocaine were investigated, and a comparison of the Grubb formula parameter α [3] measured following cocaine or $CO_2$ inhalation was made. Two questions were addressed: first, is the relationship between changes in CBF and CBV during the initial period (0 – 3 min) consistent with that of after steady state has been reached? Second, do cocaine stimulation and hypercapnia challenge share a same CBF and CBV coupling relationship?

*Animal Preparation:* Under urethane anesthesia (1.2g/kg), thirteen rats were artificially ventilated with room air at a tidal volume of 3.2 ml and respiration frequency of 55 Hz to maintain normal physiological status. Body temperature was maintained at 37 °C with a water circulated heat pad. The right femoral vein was cannulated (PE-50) for drug and contrast delivery. *Drug challenges:* two does of cocaine (1.0 mg/kg) challenges were employed with a 90-min interval allowing for drug washout. *Hypercapnia challenge:* 5% $CO_2$ was employed. *CBF experiments:* CBF measurements were performed on a Bruker Biospec 4.7T/40cm scanner with a 20-G/cm field gradient. Continuous arterial spin-labeling techniques were used. Paired images with a single-shot, gradient-echo EPI were acquired alternately: one with arterial spin labeling and the other without, using a custom-built actively decoupled surface coil (2.3-cm ID) for brain imaging and a neck coil for perfusion labeling. The MR parameters were: FOV=3.0 cm, slice thickness=1.5 mm, image matrix=64 x 64, giving an in-plane image resolution of 470 x 470 µm, TR=2 sec, and TE=18.7 ms. Continuous arterial spin labeling used a 1.7 sec square RF pulse to the labeling coil in the presence of 1.0 G/cm gradient along the flow direction. *CBV experiments:* MION (10 mg/kg) was introduced into the same imaging setting with TR=4sec for the same temporal resolution of CBF acquisition. Sequential CBF and CBV measurements were performed on five rats in response to hypercapnia and cocaine challenges. Repeated CBF or CBV measurements were performed on another four rats under two doses of cocaine challenges. Four rats were employed for sequential CBF-CBV measurements under hypercapnia conditions only. *Data analysis:* After CBV time courses were calculated based on pre- and post-MION baseline signal intensities, two non-linear model fitting analysis were performed based on CBF and CBV time courses. A differential exponential (Diff-Exp) model or a Beta model was used for fitting the negative or positive signals during the initial transient period or the prolong responses, respectively, following cocaine administration [4]. Cross-correlation analysis was performed to calculate $CO_2$ induced CBF and CBV changes. The percentage changes of CBF and CBV signals were calculated using AFNI. Significant CBF and CBV perturbations ($p<0.05$ after Bonferroni correction) from four coronal slices (interaural 11.2 - 6.7 mm, far from susceptibility artifacts contamination) were chosen for characterizing CBF-CBV responses to cocaine infusion during the initial transient period (0-3 min) and steady state (4-20 min).

**Results.**

While CBF showed a monophasic increase after cocaine infusion, CBV demonstrated a biphasic response with an initial decrease in CBV followed by prolonged CBV increase (Fig. 1, Fig. 2). A clear CBF-CBV discordant response to cocaine administration was illustrated in Fig. 2 during the initial transient period with a 3-4 min window. CBF-CBV recoupled during the steady state after cocaine administration (Fig. 2), however, with a significant lower α value in cortical and subcortical regions which are mainly involved in putative drug addition circuitry (Fig. 3).

Fig. 1

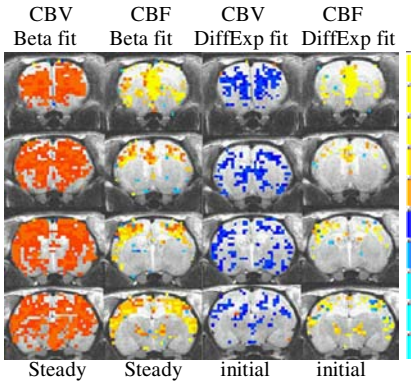
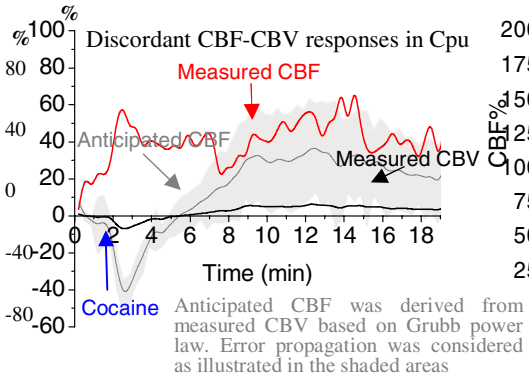
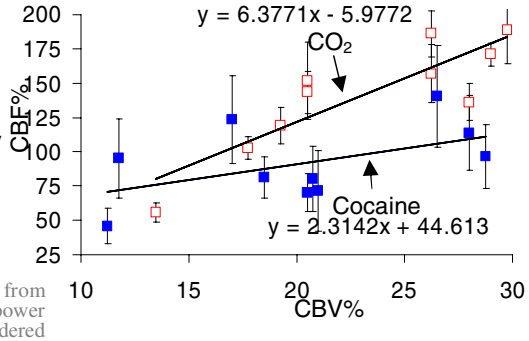



Fig. 2




Anticipated CBF was derived from measured CBV based on Grubb power law. Error propagation was considered as illustrated in the shaded areas

Fig. 3




**Discussion.**

Consistent findings of discordant responses to acute cocaine administration in CBF and CBV were reported in whisker barrel cortex using optical imaging and laser-Doppler flowmetry techniques [5]. Different groups reported initial decrease in CBV following cocaine infusion using MION contrast enhanced CBV imaging [6,7]. Putative mechanisms accounting for this transient discordant CBF-CBV response might be due to cocaine's complex effects not only on cerebral vascular but also peripheral vascular system. Cocaine induced peripheral blood pressure increases can induce cerebral precapillary sphincter constriction to maintain homeostatic blood flow in the brain, while postcapillary sphincter dilatation to prevent damaging the capillary bed from pressure increases [5]. The former effect would result in an increase in CBF due to reduced downstream resistance, but the later effect might produce a decrease in CBV mediated by a decrease in the capacity of the capillary bed. Such CBF-CBV decoupling could possibly occur before cerebral autoregulation establishment. The above hypothesis is supported by the results of the present study of a narrow 2-4 min time window before autoregulation could be established. The region specific distribution of this transient CBV decrease in dopaminergic pathways (Fig. 1) is unlikely due solely to interactions of cocaine with the cerebral vasculature, but probably involves a more complex interactive mechanism between parenchyma and blood vessels. The initial uncoupled and later distinct CBF-CBV relationship following cocaine challenge confounds phMRI $CMRO_2$ method on evaluation its cerebral oxygen metabolism. Simultaneously direct CBF and CBV measurements in the same experimental animal are warranted for understanding the complex hemodynamic responses induced by neuropharmacological agents. This study advances our understanding of the advantages and limitations of the fMRI $CMRO_2$ technique applied to pharmacological studies and illustrates the complex effects that cocaine has on both neural substrates and the cerebral vasculature.

References. [1] Schmidt *et al*., Psycopharmacology 2005 in press. [2] Chen, *et al.* MRM 2001;45:349-355. [3] Grubb *et al*., Stoke 1974;5:630-639. [4] Luo et al., MRM 2003;49:264-270. [5] Devonshire *et al*., Neuroimage 2004;22:1744-1753. [6]Marota, *et al*. Neuroimage 2000;11:13-23. [7] Schwarz et al., 2004;Neuroimage 23:296-304.