EFFECTS OF PROPOFOL ANESTHESIA AND SEX ON CEREBRAL BLOOD FLOW

Pelin Aksit Ciris[1], Maolin Qiu[2], and R. Todd Constable[3]

[1]Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [2]Diagnostic Radiology, Yale University, School of Medicine, New Haven, CT, United States, [3]Diagnostic Radiology, Neurosurgery, and Biomedical Engineering, Yale University, School of Medicine, New Haven, CT, United States

Introduction: Cerebral Blood Flow (CBF) is closely related to brain activity. CBF amplitude and distribution changes with sex[1-8], and sex differences in arterial blood flow velocity have been observed even in early childhood[9]. CBF also changes with anesthetic agents, and sex specific sensitivities to several anesthetics have previously been observed[10-17]. Despite such evidence strongly suggesting the potential for sex specific changes in CBF with anesthesia, female subjects are frequently excluded from studies to avoid potential variations due to hormonal changes across the reproductive cycle[18]. This practice may not only severely limit our understanding of brain physiology and management of anesthesia, but also confound interpretation of perfusion or functional MRI studies performed under anesthesia. The current study presents absolute CBF across the whole brain before and during Propofol anesthesia, and highlights significant differential effects of sex and anesthesia.

Methods: Thirty two normal subjects participated in this IRB-approved study (13 females, ages: 21-31; 19 males, ages: 20-30). Experiments were performed at 3T (Tim Trio, Siemens, Erlangen, Germany) using a 32 channel head coil. CBF data was acquired while awake and during Propofol anesthesia (2mg/ml). Absolute CBF was noninvasively quantified using Q2TIPS PASL[19] over 20 transverse slices, and high-resolution 3D and 2D T1w images at same locations were used for registration across subjects. CBF parameters were 192x256mm FOV, 4x4x4mm, TE/TI1/ TR/sliceTR:20ms/1.4s/3s/52.3ms, 10cm adiabatic inversion 2cm inferior/superior, and bipolar gradient of 5cm/sec; PD acquisition with CBF parameters except TR/TI/TD=8s/6.05s/0. CBF was calculated from the difference between interleaved labeled and control image pairs averaged over multiple acquisitions. Quantification used sex specific blood T1 values of 1673ms (males) and 1728ms (females)[1], data was motion and drift corrected, smoothed with an 8mm Gaussian kernel, processed in each subjects' space, then registered to MNI space. Statistical significance of CBF changes was assessed via student's t-tests across Awake vs. Propofol conditions (paired) and across sexes (unpaired). Family Wise Error (FWE) correction was applied for multiple comparisons via Monte Carlo simulations (AlphaSim, AFNI) in gray matter (GM) masks of eight random volunteers. Mean CBF values were obtained within Brodmann Areas (BA) defined on the MNI brain.

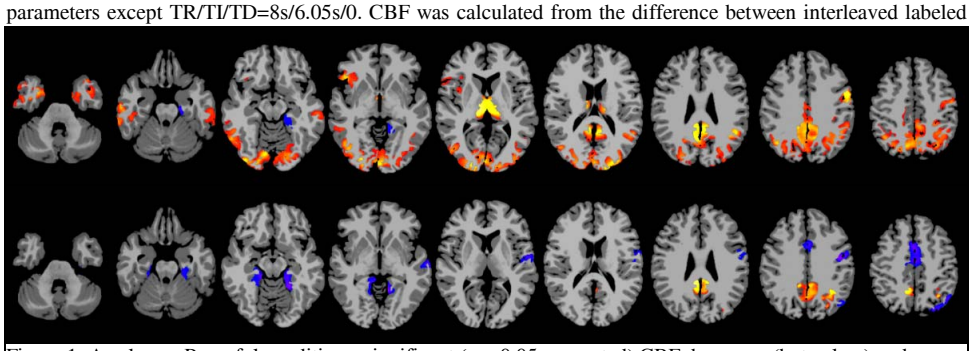

Figure 1: Awake vs. Propofol conditions, significant ($p < 0.05$, corrected) CBF decreases (hot colors) and increases (cool colors) shown for females (top), and males (bottom).

Results and Discussion: Mean GM CBF decreased from 51.8±13.1to 45.7±13.1 mL/min/100 mL between the Awake and Propofol conditions in females, and remained stable in males (40.1±10.9 and 42.2±12.3 mL/min/100 mL, respectively). Figure 1 shows the spatial distribution and direction of significant CBF changes in response to Propofol, for each sex. Changes were not symmetric across hemispheres, and differed across sexes. In females (Figure 1, top), the most significant effect of Propofol was a large decrease in CBF in the thalamus; CBF also significantly decreased in the primary sensory, primary motor, sensory association areas; BA6, 24 and 40; primary visual and visual association areas; BA23, 31, 19, 39, 7; BA20, 21, 38; the right Insula, BA44, 45, and 47, and increased in the left BA19, Fusiform and Parahippocampus. In males (Figure 1, bottom), the dominant effects of Propofol were decreases in CBF in BA 23, 31, 39 and 7, and increases in BA21, Fusiform, and Parahippocampus; BA19, BA24, 32, and 6; left BA39 and 7, BA21 and 22; and left visual association, primary sensory, primary motor, and primary auditory areas. Figure 2 shows the spatial distribution of significant CBF differences between sexes, during both the Awake and Propofol conditions. Where significant differences were observed, CBF was always lower in males compared to females. While awake (Figure 2, top), CBF differences between sexes were significant in BA21, Putamen and Caudate. During Propofol (Figure 2, bottom), CBF differences between sexes were still significant in the Caudate, however, mostly on the left; and the distribution of significant CBF differences between sexes changed to include BA10, 11, 25, and 32; BA19 and 39; as well as in BA7, 31,23.

Propofol was associated with global vascular and metabolic depression in the human brain, with the most significant CBF decreases seen in the thalamus, precuneus and parietal areas across eight female volunteers using PET[20]. In our case, the most significant Propofol induced CBF decrease was also observed in the thalamus in females, in excellent agreement with this study. Furthermore, sevoflurane anesthesia was found to significantly decrease both baseline and task induced changes in CBF within inspected visual and auditory regions of interest[21]. Despite a different anesthetic and unknown sex of subjects, our observation of anesthesia induced CBF decreases in the same areas is also encouraging.

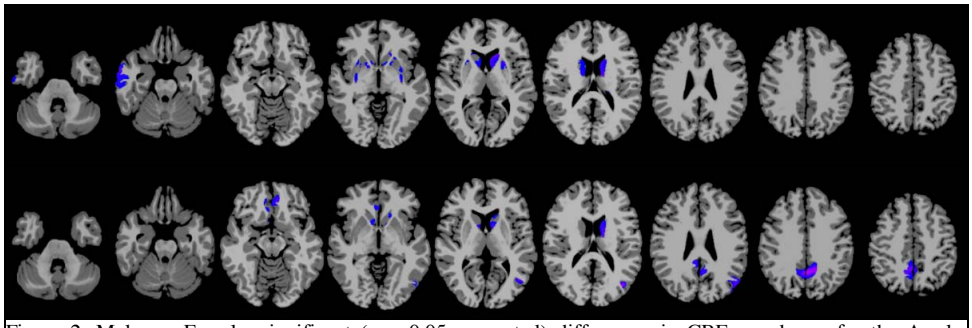

Figure 2: Male vs. Female, significant ($p < 0.05$, corrected) differences in CBF are shown for the Awake condition (top), and during Propofol anesthesia (bottom). Cool colors indicate lower CBF values in males.

Conclusion:

Little is known about sex and anesthetic effects on cerebrovascular physiology; however, our findings were in good agreement with the limited available literature. Propofol and sex both had significant effects on CBF, and such variations should be considered in the interpretation of perfusion or fMRI studies conducted under anesthesia. It is known that females tend to emerge faster from general anesthesia, but with poorer overall quality of recovery[22]. Sex differences in hormones, body composition, and cardiovascular/ventilator/hepatic function… suggest accompanying differences in pharmacokinetics and pharmacodynamics, such that dosages based only on weight and age may lead to inaccurate effective concentrations in target tissues. Improved understanding of the mechanisms underlying these differences, could lead to more specific models of cerebrovascular responses, improved assessment of anesthetic requirements and better management of anesthesia in all patients.

References: [1] Ciris MRM 2013; 24984 [2] Daniel PsychRes 1989;27 [3] Esposito JNuclMed 1996;37 [4] Bertsch BrainRes 2009;1267 [5] Kastrup JCBFM 1999;19 [6] Liu MRM 2012;68 [7] Parkes MRM 2004;51[8] Devous JCBFM 1986;6 [9] Tontisirin Pediatrics 2007;119 [10] Xue AnesthAnal. 1997;85 [11] Xue BrJ Anaesth.1998;80 [12] Parker BrJAnaesth. 1992;69 [13] Semple BrJAnaesth. 1994;72 [14] MacLeod JClinPharm 1979;19 [15] Palva MedBiol 1985;63 [16] Greenblatt Anesthe 1984;61[17] Loryan EurJClinharma 2012;68 [18] Mawhinney TranslStrokeRes. 2013; 4 [19] Luh MRM 1999;41 [20]Schlünzen ActaAnaest2012;56 [21] Qiu MRM 2008; 60 [23] Buchanan BrJAnaesth 2011;106.