# Subcortical versus cortical effects of anesthesia on blood oxygenation: in vivo evidence from UHF MRI

Luisa Ciobanu[1], Lynn Uhrig[2], Boucif Djemai[1], Denis Le Bihan[1], and Béchir Jarraya[2,3]

[1]*Neurospin, CEA, Gif sur Yvette, France,* [2]*Equipe Avenir INSERM Bettencourt Schueller, Neurospin, CEA, Gif sur Yvette, France,* [3]*Unité de Neurochirurgie Fonctionnelle, Henri-Mondor Hospital, Créteil, France*

**Target audience**: Neuroscience, neuroimaging, anesthesiology and medicine communities

**Purpose:** The non-invasive, *in vivo* monitoring of the effects of anesthetic agents on brain blood oxygenation remains highly challenging. Even when the systemic hemodynamics is kept stable, anesthetic agents can locally affect the cerebral hemodynamics and metabolism. A recent study showed that UHF MRI is capable of revealing differences in blood brain oxygenation level induced by isoflurane, medetomidine and ketamine/xylazine[1] in a rat model. Such differences were visible to a much lower extent at lower magnetic fields (7T). In this report, we extend the study to include anesthetic agents commonly used in clinical practice (propofol, midazolam and sevoflurane) and to compare their effects on the blood oxygenation in subcortical and cortical regions.

**Methods:** 300 g Sprague-Dawley male rats (n = 15) were obtained from Janvier (Saint Isle, France). During general anesthesia, animals were mechanically ventilated (Bioseb, Vitrolles, France) and received a mixture of air/oxygen ($FiO_2$ = 0.33). All available physiological parameters (blood pressure, respiration rate, expired $CO_2$, temperature) were monitored and kept constant throughout the experiment to ensure normocapnic and normoxic conditions. Initially, the animals were anesthetized and maintained under isoflurane (1.2 MAC) during which time a series of gradient echo images was acquired. Next the animals were administered propofol (7mg/kg bolus followed by 45mg/kg/h, i.v.), midazolam (2mg/kg bolus followed by 0.25mg/kg/min i.v.) or sevoflurane (2.4 MAC) and the isoflurane was discontinued. A new set of gradient echo images was acquired 30 minutes after isoflurane was turned off. The UHF MR experiments were performed on a horizontal bore, 17.2T BioSpec (Bruker BioSpin, Etlingen, Germany) imaging system using a transmit/receive 3 cm diameter surface coil. The acquisition parameters were: 2D gradient echo, in-plane resolution 80 µm, FOV = 25.6 mm×25.6 mm (matrix size 320×320), flip angle α = 45°, TR/TE = 350/8 ms, thk = 0.2 mm, Nslice = 16, NEX = 14. The 2D MR images were analyzed in Matlab 1.2 (MathWorks, Natick, Massachusetts). Using a rat brain stereotaxic atlas[2] four regions of interest (ROIs) located in the cortex, hippocampus, striatum and thalamus were selected (Fig.1). For each ROI the average signal intensity was extracted and the number of pixels with intensities smaller than 75% of this average counted[1]. All the anesthetics were compared with isoflurane by computing the ratio of hypointense pixels (detected vessels) counted under the two conditions ($R_v$). In the analysis 6 animals from a previous study were included, for which the second anesthetics, following isoflurane, were medetomidine (0.3 mg/kg, i.v.) and ketamine/xylazine (100/10 mg/kg, i.p.).

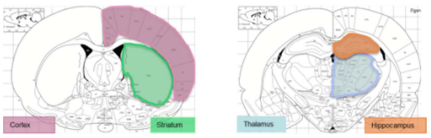


**Fig.** 1 Selected ROIs for data analysis

**Results:** Sevoflurane resulted in a lower contrast between tissue and venous blood vessels in all analyzed ROIs when compared to propofol, midazolam, medetomidine and ketamine/xylazine (Fig. 2). Moreover, based on how the different anesthetics affected the four different subcortical and cortical regions (Fig.3) they could be divided in three groups: group 1 (propofol and midazolam) - higher contrast in cortical than in subcortical regions, group 2 (sevoflurane and medetomidine -similar contrast in subcortical and cortical regions and group 3 (ketamine/xylazine)- higher contrast in subcortical than in cortical regions.

**Discussion:** The differences observed between the vessel-tissue contrast under different anesthesia conditions were certainly induced by changes in blood oxygen level (i.e. a decrease in oxygenation leads to an increase in contrast in T2* weighted images) produced by an altered metabolic load or altered cerebral blood flow (CBF). The variations observed between the anesthetics used and across different brain regions are in agreement with the mechanism of action of these agents. Specifically, sevoflurane ($R_v$ ~ 1 in Fig. 3) increases mean CBF in the same way as isoflurane does[3]; midazolam and propofol (similar $R_v$ distribution across brain regions) reduce CBF similarly [4]; ketamine (very different $R_v$s between cortical and subcortical regions) acts on cerebral metabolic rate for glucose utilization[5] in a regional manner and xylazine is known to lower CBF. While no data was found on medetomidine several studies reported that dexmedetomidine decreases CBF[6], consistent with the higher vessel-tissue contrast observed.

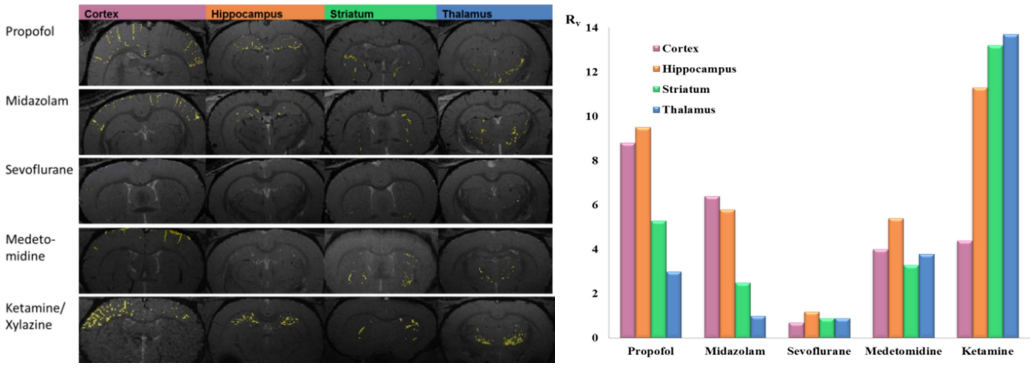


**Fig. 2** (Left) Rat brain images (coronal sections) acquired *in vivo*, at 17.2T under general anesthesia using different anesthetic agents. The yellow regions show pixels below the 75% intensity threshold corresponding to blood vessels. (Right) Median ratio ($R_v$) between the hyponintense pixels counted under the five different anesthetics and isoflurane.

**Conclusion:** Due to the extreme sensitivity to brain blood oxygenation level changes induced by anesthetic agents, UHF MR studies have the potential to screen future anesthesia drugs for their action on cerebral blood oxygentaion. More generally, UHF may also play a role during preclinical screening of new pharmacological agents for their effect on brain oxygenation on a local basis. However, further investigations are necessary to fully understand the relationship between the anesthetic agent used and the vessel-tissue contrast observed.

**References:** 1. Ciobanu L. et al. Effects of anesthetic agents on brain blood oxygenation level revealed with ultra-high field MRI. PLoS ONE 2012; 7(3): e32645. 2. Paxinos, Academic Press, 1998. 3. Lenz C. et al. Coupling of local cerebral blood flow to local cerebral glucose utilization during isoflurane and sevoflurane anesthesia. Anesthesiology 1998; 91(3): 889-90. 4. Ogawa Y. et al. The different effects of midazolam and propofol sedation on dynamic cerebral autoregulation. Anesth Analg, 2010; 111(5):1279-84. 5. Lei H. et al. The effects of ketamine–xylazine anesthesia on cerebral blood flow and oxygenation observed using nuclear magnetic resonance perfusion imaging and electron paramagnetic resonance oximetry. Brain Res. 2001; 913: 174–179. 6. Rozet I. Anesthesia for functional neurosurgery: the role of dexmedetomidine. Current Opinion in Anesthesiology 2008; 21(5), 237-43.