Effects of Scopolamine on Cerebral Blood Volume: A Pharmacological Model to Validate Contrast Enhanced MRI in Assessing Cerebral Blood Volume in a Canine Model of Aging

D. Tapp[1], J. Araujo[2], Y. Chu[1], E. Head[3], N. W. Milgram[2], O. Nalcioglu[1], M-Y. Su[1]

[1]Tu & Yuen Center for Functional Onco-imaging, University of California, Irvine, California, United States, [2]Pharmacology, University of Toronto, Toronto, Ontario, Canada, [3]Institute for Brain Aging and Dementia, University of California, Irvine, California, United States

Purpose

Impaired cholinergic function may play a critical role in dementia related to Alzheimer's disease [1] possibly by modulating blood flow and vessel dilation. Administration of the cholinergic antagonist, scopolamine, reduces cerebrovascular blood flow in healthy controls comparable to Alzheimer's disease (AD) and mild cognitive impairment (MCI)[2]. Dynamic susceptibility contrast MRI (DSC-MRI) combines high resolution magnetic resonance imaging (MRI) and paramagnetic intravascular susceptibility contrast agents to yield cerebral blood volume (CBV) without the need for ionizing radiation. Decreased CBV was recently observed in AD and MCI patients [3] and transgenic Alzheimer's models [4] using DSC-MRI. In the present study, DSC-MRI was used to examine the relationship between age and cholinergic function on CBV in young and old beagle dogs.

Methods

Twenty-four beagle dogs (aged 2-15 years) were used in the study. Subjects received a baseline and treatment DSC-MRI scan in which scopolamine was administered post-anesthetic for imaging. 90 images per subject were acquired using a GE-LX 1.5T mobile MRI and a SE-EPI pulse sequence (TR/TE = 2s/60ms; slice thickness = 8mm; 128 x 128 matrix; 20 cm FOV). After 10 baseline images, a 0.15 mmol/kg bolus of Gd-DTPA-BMA, (Omniscan®) was injected followed by a 10 cc saline flush. Post-contrast images were sampled for 80 scans. After baseline scans, subjects received a 30μg/kg dose of scopolamine and a second DSC-MRI approximately 60 minutes after scopolamine administration. A subset of animals (n=7) received a third scan 24 hours following the second scan. For these animals, scopolamine was administered 60 minutes before anesthetic induction for MRI scanning to compare differences in pre and post anesthesia scopolamine effects on CBV. The signal intensity-time curve was measured from GM, WM, (figure 1) and one voxel from the carotid artery as the arterial input function. Automatic segmentation of GM and WM was performed with an adaptive clustering algorithm. The baseline signal was calculated by averaging MRI signal-intensities from the 6^{th} to 10^{th} frame and signal intensity-time curves were converted to ΔR2 curves for GM, WM, and the vessel voxel (figure 2). ΔR2 curves were modeled to the Gamma Variate function using the Nelder-Mead simplex algorithm as shown in figure 3 for GM (A) and WM (B). The area under each modeled curve was calculated for GM, WM, and the vessel voxel. Areas measured from GM or WM were further normalized to the value measured from the vessel to obtain the final CBV for each subject.

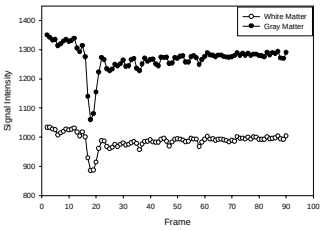

Figure 1. Example of the typical signal intensity time curve derived for each dog from GM and WM.

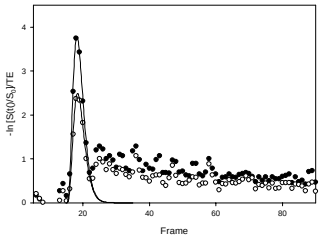

Figure 2. Relative signal change for GM (filled circles) and WM (open circles) brain compartments for 90 scans in the dog brain. Solid lines indicate fitted gamma variate curves.

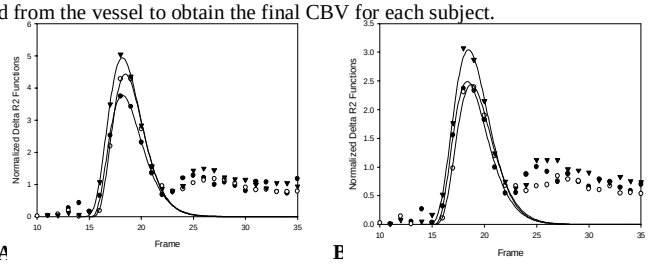

Figure 3. Normalized GM (A) and WM (B) ΔR2 fitting curves at baseline (filled circles), post-anesthetic scopolamine (open circles), and pre-anesthetic scopolamine (filled triangle) conditions. Solid lines indicate normalized gamma variate fitting curves.

Results

GM-CBV was higher than WM-CBV [$F(1,16) = 172.97$, $p = .001$] and did not differ between baseline and post-anesthetic scopolamine (figure 4). Figure 5 shows GM and WM-CBVs for animals that received three DSC-MRI scans. GM-CBV was higher than WM-CBV ($p = .018$) in all three conditions. GM-CBV was higher when scopolamine was administered before anesthesia (SCP-PreA) compared to baseline ($p = .043$). For these animals CBV was higher at baseline in GM (U = 0.00, $p = .034$) and WM (U = 0.00, $p = .034$) compartments and marginally higher in GM in the SCP-PreA condition (U = 1.00, $p = .077$) in young compared to old dogs (figure 6).

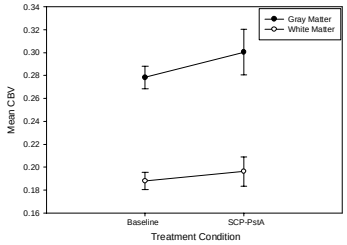

Figure 4. CBV values for GM and WM compartments during baseline and post-anesthetic scopolamine challenge conditions.

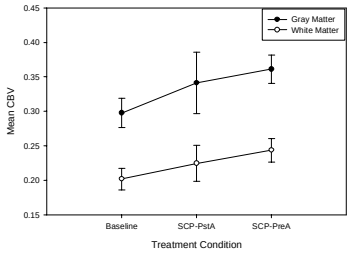

Figure 5. CBVs for GM and WM compartments at three treatment time points. CBV values were higher for GM at all three time points. Scopolamine administered before anesthesia induction produced higher CBVs compared to other conditions.

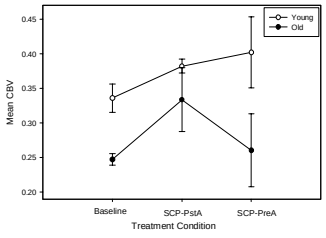

Figure 6. CBVs for GM in old and young dogs at baseline, post- and pre-anesthetic scopolamine administration.

Discussion

In this study, GM-CBV was consistently higher than WM-CBV. When scopolamine was administered pre-anesthesia, GM-CBV was higher compared to baseline, which suggests that induction of anesthesia before drug administration may alter drug pharmacokinetics or pharmacodynamics. Further, the absence of scopolamine effects on CBV in old dogs may reflect an age-dependent decrease in cholinergic function or tone. Reduced CBV, cholinergic tone, or cholinergic function in aged dogs parallels human aging and may account for cognitive and behavioral impairments observed in aging dogs.

References

[1] Perry. Br Med Bull. 1986, 42:63-69. [2] Pearlson et al. Arch Gen Psychiatry. 1992, 49(5):402-408. [3] Harris et al. Am J Neuroradiol. 1998, 19(9):1727-1732. [4] Wu et al. Neurosci Lett. 2004, 365(3):223-227.

Acknowledgements. This research is supported by a grant from the NIH (AG17066-02S1).