Age-Dependent Regional Cerebral Blood Volume (rCBV) in Gray Matter and White Matter of the Canine Brain

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Purpose

The integrity of the cerebrovasculature is essential in maintaining cognitive function during aging (Kalaria, 1996). Cerebrovascular abnormalities are commonly found in approximately 60-90% of patients with Alzheimer's disease (AD). Various forms of cerebrovascular dysfunction, such as regional reductions in blood supply and disruptions in the blood-brain barrier (BBB) may be important factors in the development of AD. Beyond 60 years of age, decreased cerebrovascular perfusion correlates significantly with cognitive impairment, cortical atrophy, periventricular white matter hyperintensities, and ventricular enlargement (Meyer at al., 2000). Chronic hypoperfusion may lead to loss of metabolic and nutritional support for neurons. A number of clinical studies also suggest that chronic cerebral hypoperfusion is a significant risk factor in pathological aging (e.g. Alzheimer's disease; De La Torre, 1997, 2000, 2002), because decreased blood volume may increase post-translational modification of the amyloid precursor protein into toxic beta-amyloid fragments throughout the brain (Bennet, 2000; Lin et al., 1999). The neuropathological hallmarks of aging in the dog are similar to those reported in humans. Amyloid deposition, cortical atrophy, and ventricular volume all increase with advancing age and correlate with impaired cognitive and behavioral performance. In the present study, we investigated the rCBVs for gray and white matter brain regions in young and very old beagle dogs. The rCBV was quantified from the contrast first-pass peak perfusion study to investigate the age-related changes between white matter and gray matter.

Methods

MRI studies were performed on 59 beagle dogs ranging from 3 months to 15 years of age. Dogs were separated into infant (< 6 months), young (6 months - 3 years), middle-aged (4-8 years), old (9-11 years), and senior (12 years and up) age groups. The study was performed on a GE-LX 1.5T mobile MRI scanner using the quadrature knee coil. After the localizer scan, a 3D SPGR sequence was applied to obtain the anatomic images from the whole brain. Three slices, from the frontal cortex, thalamus, hippocampus and cerebellum, were then acquired for the dynamic susceptibility contrast perfusion study using a spin-echo EPI pulse sequence. The parameters were TR= 2s, TE= 60ms, slice thickness= 8mm, matrix size= 128x128, FOV=20 cm (minimal allowed FOV for this pulse sequence). Ninety scans were prescribed to acquire images over a 3-min period. After 10 baseline images were acquired, a bolus injection of the contrast agent Gd-DTPA-BMA, (Omniscan®, 0.15 mmol/kg) was administered. The signal intensity-time curve was measured from the gray matter, white matter, and one voxel from the carotid artery as the arterial input function. An adaptive clustering algorithm was applied to automatically segment the gray matter and white matter. The vessel was determined from the pixel showing the earliest signal reduction after contrast injection. The baseline intensity was calculated by averaging the intensities from 6^{th} to 10^{th} frames, then the signal time course was converted to the $\Delta R2^*$ curves. The rising and the ending time frames were determined from the first pass peak to calculate the peak width. Due to the spatial resolution, the selected vessel-voxel might cover tissues outside the vessel, which rendered it unusable. Only 27 subjects (9 male and 18 female) with first-pass peak width in the vessel $\Delta R2^*$ curve smaller or equal to those measured from gray matter and white matter curves were analyzed. The $\Delta R2^*$ curve was fitted to a Gamma Variant function and the area under the first-pass peak was calculated. The area measured from gray or white matter was then normalized to the value measured from the vessel to obtain the final rCBV for age-dependent correlation analysis.

Results

Correlations between age and rCBV values in gray and white matter regions of the dog brain are shown in figure 1. Age significantly correlated with decreased rCBV values in both gray [$t(26) = -3.36$, $p = .003$] and white [$t(26) = -3.01$, $p = .006$] matter. A multivariate ANOVA of the effects of age on rCBV indicated a significant main effect of age for both gray [$F(4,22) = 3.82$, $p = .017$] and white matter [$F(4,22) = 4.10$, $p = .012$]. The effects of age on total rCBV values for each brain region however, differed between the groups. In gray matter regions, the total rCBV was significantly lower in senior dogs compared to infant ($p = .014$) and young ($p = .041$) dogs (figure 2). In white matter regions, total rCBV values were significantly lower in senior ($p = .010$) and old dogs ($p = .039$) compared to infant dogs (figure 3). No other group comparisons reached statistical significance ($p > .05$).

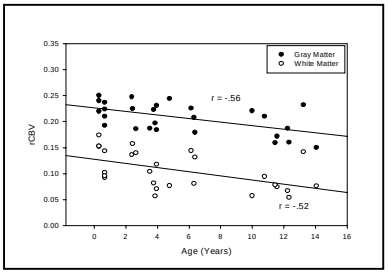

Figure 1.

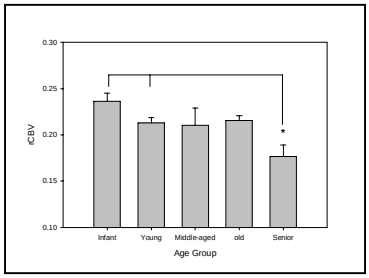

Figure 2.

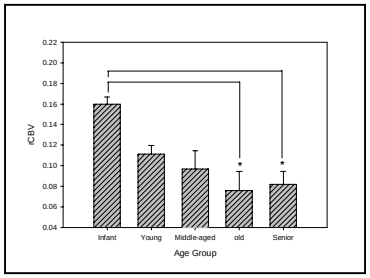

Figure 3.

Discussion

In the present study, contrast enhanced MR imaging indicated that total rCBV decreases in the brain of aging dogs. These changes however, differed between gray and white matter measures. In gray matter, age-related decreases in rCBV were greatest in the senior dogs compared to the youngest dogs. By contrast, rCBV values were lower in the white compared to gray matter in all animals and both old and senior dogs had significantly lower rCBV values in white matter regions of the brain relative to infant dogs. These findings suggest that age-related changes in white matter rCBV may precede similar changes in gray matter rCBV and may suggest a link between rCBV and amyloid deposition in the dog. Hypoperfusion, which is known to increase cleavage of amyloid precursors, and the age at which decreased white matter rCBVs were observed in the present study, correspond to the age of onset of amyloid deposition in the beagle dog brain (i.e. old dogs as early as 8 years of age).

Acknowledgements:

This research is supported by a grant from the NIH (No. AG17066-02S1).