Implementation and evaluation of an MRI protocol for assessment of cerebrovascular reserve in the rhesus monkey – characterizing the aging brain

A. Coimbra[1], M. A. Holahan[1], Y. Tymofyeyev[2], R. Hargreaves[1], J. J. Cook[1], D. S. Williams[1]

[1]Imaging Research, Merck Research Laboratories, West Point, PA, United States, [2]Biometrics Research, Merck Research Laboratories, West Point, PA, United States

Introduction:

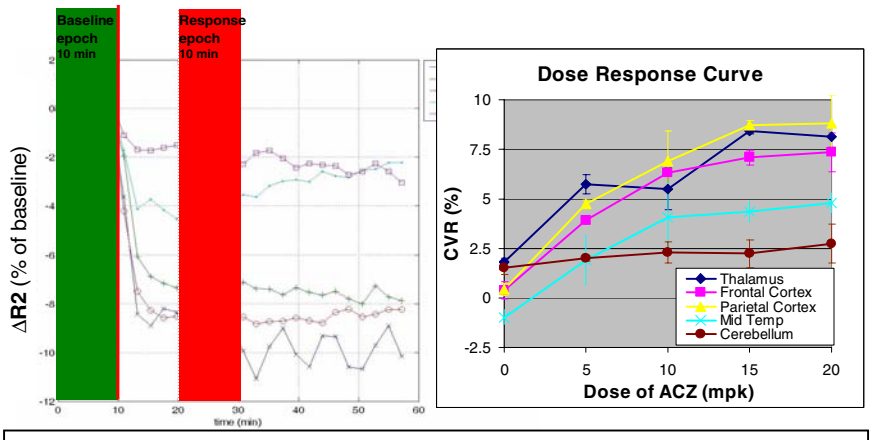
Cerebrovascular autoregulation ensures adequate blood perfusion to match demands for oxygen and nutrients. Autoregulatory capacity can be quantified by measuring cerebral blood flow (CBF) or volume (CBV) change following administration of acetazolamide, a carbonic anhydrase inhibitor with cerebral vasodilating properties. Cerebrovascular reserve (CVR) is defined as the maximal capacity under a vasodilatory challenge. In the clinic, CVR is used in the evaluation of vascular impairment associated with cerebrovascular diseases and is commonly employed in pre- and postoperative evaluation of patients with occlusive diseases, arteriovenous malformation, and chronic idiopathic hydrocephalus [1]. It has also been suggested that it may be useful in characterization of normal aging and dementia [2,3]. The present work used MRI to measure CVR in rhesus brains, in order to evaluate its responsiveness and test-retest repeatability in readiness for possible use in clinical trials .

Methods:

A Siemens / Trio 3T scanner equipped with an eight channel head array coil was used and two sequences acquired: 1) an MPRAGE sequence (TR/TE/NA/FA 1.47s/4.38ms/4/12°, 128x128x64 mm^3 FOV, 256x256x80 matrix) was used to obtain an anatomical image used for the purposes of ROI definitions; and 2) a multi-echo gradient-echo (ME-GE) sequence, (TR/NA/FA 0.37s/6/20°, TE=3.57,7.8, 11.8, 15.8, 20.1 ms, 2D, 15x 3mm Tx slices, 3.75mm slice spacing, 151x151 mm2 FOV, 64x64 matrix), was used to assess changes in blood flow through measurement of R2*. All animal handling procedures were approved by the Institutional Animal Care and Use Committee. Two young adult rhesus were scanned repeatedly on different days for assessment of both optimal ACZ dose and repeatability of CVR. For every scanning session animals were sedated (Ketamine), intubated, mechanically ventilated and anesthesia was maintained with 1.5% isofluorane; end-tidal CO_2 was monitored and maintained at around 35 mmHg (prior to ACZ dose) by manipulation of the respirator. Assessment of optimal ACZ dose was evaluated with i.v. bolus injection of either saline solution (N=3 for each monkey) or acetazolamide (ACZ, a carbonic anhydrase inhibitor) at 5 (N=2), 10 (N=2), 15 (N=4) and 20 mpk (N=4), 10 minutes into the ME-GE acquisition. R2* was evaluated by pixel-by-pixel fitting of the multi gradient echo image signal intensity to a mono-exponential. CVR was assessed by the following formula: $CVR = (100\%) * (AUC_{baseline} - AUC_{response})/AUC_{baseline}$, where $AUC_{baseline}$ is the area under the R2* time curve before ACZ injection and $AUC_{response}$ is the AUC 10 to 20 minutes after injection of ACZ, as schematically indicated in the figure. Acquired image data was transferred to a Linux Station for processing. Processing and analyses tools were developed in-house using MATLAB (MathWorks Inc., http://www.mathworks.com/), with calls to external functions from the SPM2 package (University College London, http://www.fil.ion.ucl.ac.uk/spm/). In short, a set of region of interests (ROI) was predefined in a T1 weighted image of each monkey; every scanned image was co-registered to the same prior image so that the prior ROIs could be propagated to the co-registered images and used for estimation of R2* curves and CVR on equivalent ROIs at each trial. Dose response curves were obtained and repeatability of CVR measurements was assessed by statistical modeling and analyses of its variance components. reliability is reported in terms of coefficient of variation (CV). Power analysis was used to estimate population size needed to power a test of group mean difference (e.g., demented subjects compared to controls).

Results:

Clear dose response profiles were observed in both monkeys that reached plateau at 15 mpk dose (figure). Cortical CVR at plateau ranged from 2 to 7%. Cerebellum, pons and hippocampus remained essentially unresponsive. Striatum and Thalamus showed mean CVRs at plateau of 4.4 and 5.6%, respectively. CVs for cortical regions averaged 10-30% in most cases in both animals. Estimates of population size needed to detect group mean differences of ~50% in CVR (given currently estimated variances) are approximately 10 per group.



Left: Sample normalized R2* curves and epochs used to estimate CVR. Right: Dose related response profile for different ROIs in one monkey. Note plateau starting at 15 mok dose.

Conclusions:

Based on the present results, the optimum ACZ dose producing maximal vasodilation (response) in the rhesus is 15 mpk. Test retest repeatability is reasonable and population size numbers estimated for powering group comparisons relatively small. The present results suggest that measurements of CVR are reliable and could be used in the future to characterize CVR in aging in focused studies in animal and human subjects.

[1]Boles-Ponto et al. 2004; [2]Petrella et al. 1998; [3]Pavics et al. 1999