Using 3D GRASE-ASL to measure Hypercapnic changes in Cerebral Blood Flow and Arterial Arrival Time

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Introduction:
Arterial Spin Labeling (ASL) has proved to be an important technique to obtain perfusion-weighted MR images and is an ideal technique for clinical studies involving cerebrovascular disease. Two recent developments have improved ASL for quantitative experiments. First, implementation of a single-shot volumetric (3D) acquisition has improved SNR and the amount of brain coverage (3D GRASE-ASL [1]). Second, the collection of multiple inversion time data has improved our ability to estimate perfusion levels. The purpose of the present study was to assess the sensitivity of 3D GRASE-ASL. It was hypothesized that GRASE-ASL would be a sensitive method to measure the regional effects that mild hypercapnia has on blood flow, i.e. causing an increase in Cerebral Blood Flow (CBF) and reducing the Arterial Arrival Time (AAT). To test this hypothesis, a group of healthy control participants were scanned under two conditions: 1) baseline, and 2) during administration of remifentanil (Remi), a drug that is known to increase arterial CO_2 and induce a hypercapnic response.

Methods:
The appropriate ethics review board approved this study involving ten healthy control participants (one woman, nine men, mean age: 31 ± 6 years). A 6min 30sec pulsed multiple inversion time GRASE-ASL [1] protocol and 1min calibration acquisition were performed twice using a 3 T Siemens Trio MRI system, one scan at baseline and another after stabilized physiology during to a target-controlled intravenous infusion of remifentanil (dose: 1.0 ng/mL). Participants wore a tight-fitting mask and a gas analysis system was used for real-time display. Pulse rate, end tidal O_2 and end tidal CO_2 were recorded throughout, along with blood pressure readings before each scan. Perfusion-weighted GRASE ASL images were collected using the following parameters: 12 channel head coil, TR/TE/τ/TI = 3100 / 39.9 / 2000 / [500:250:2500] ms (where τ is the tag duration); 64 x 64 x 24 matrix; resolution: 3.125 x 3.125 x 5 mm^3. CBF and AAT fitting were performed for each voxel using least squares fitting and the standard model of Buxton [2] for the 9 TI measurements. For each subject, the z-statistic was used to threshold voxels whose CBF and AAT estimates were found to be significant ($Z > 2.3$, $P < 0.01$). Voxel-wise group statistics for absolute CBF and AAT values were performed using non-parametric permutation testing (5000 permutations), an appropriate test for these non-Gaussian data. Voxels were reported significant after correcting for multiple comparisons ($P < 0.01$).

Results:
GRASE-ASL images showed a clear difference between the two conditions for each subject (Fig. 1), owing to the hypercapnia. $P_{ET}CO_2$ increased significantly from 42 ± 2.9 to 51 ± 3.2 mmHg from Baseline to Remi, respectively ($P < 0.0001$), while blood pressure and heart rate remained unchanged ($P>0.1$). CBF increased globally from 55.0 ± 14.5 to 70.3 ± 21.3 mL/ 100 g tissue / min from baseline to Remi, respectively. The average Cerebrovascular Response (CVR) was calculated as 4.9 ± 1.07 % CBF / mm Hg, which is consistent with a mild hypercapnia condition [3]. As a control test, no significant difference was found when comparing hemispheres during either condition (CBF L vs R Baseline, Remi, $P < 0.11$, $P < 0.48$). Across the group, AAT was significantly reduced in the Remi condition in 14 of 24 slices ($P < 0.05$). Furthermore, several regions were found to be significantly different in both CBF and AAT maps across subjects at a voxel level, as shown in Figure 2 and 3, respectively, and overlaid on a standard brain.

Discussion:
In this study we demonstrated that it is possible to use GRASE-ASL to detect changes in CBF and AAT in the whole brain with 3D coverage, at an individual as well as group level, associated with pharmacologically-induced hypercapnia. Consistent with previous studies [3,4], an increase in CBF was found globally and uniformly across the brain. A large proportion of reduced AAT voxels (Figure 3) were found in Middle (MCA) and Anterior Cerebral Artery vascular regions (ACA), and attempts to differentiate arterial from tissue contributions is an active area of research in our laboratory. To our knowledge this is the first demonstration that ASL can be used to detect changes in CBF and AAT at a voxel-wise level as a consequence of pharmacological manipulation.

References:
1. Gunther M, Magn Reson Med, 2005, 54(2):491.
2. Buxton RB, Magn Reson Med, 1998, 40:383.
3. Noth U, JMRI, 2006, 24:1229.
4. St Lawrence KS, JMRI, 2002, 15(6):628.

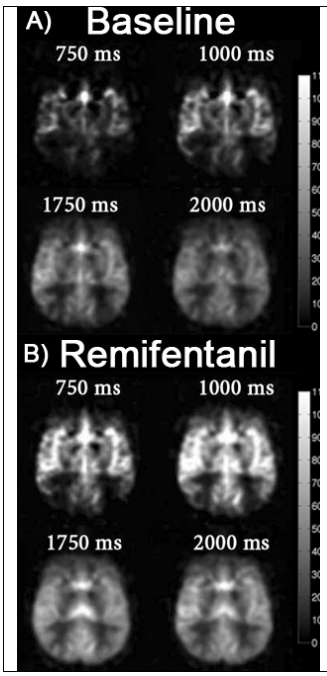

Figure 1: Representative difference images from one subject at 4 selected time points in the kinetic curve (i.e. TI: 750, 1000, 1750, 2000 ms) at A) Baseline and B) after Remi. Difference images in A) and B) are at the same windowing level.

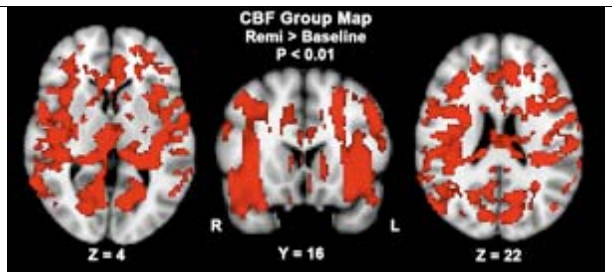

Figure 2: Voxels where CBF Remi > Baseline ($P < 0.01$, corrected) across 10 participants.

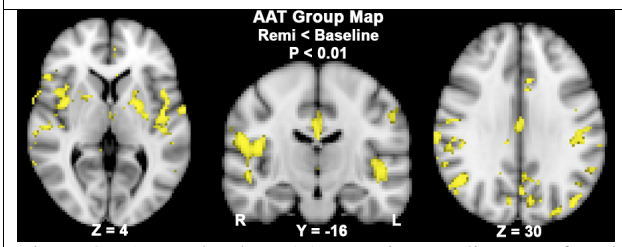

Figure 3: B) Voxels where AAT Remi < Baseline were found bilaterally in frontal and parietal lobes ($P < 0.01$, corrected, note: different views c.f. Fig2).