Detecting CBF Changes Distant From Cerebral Infarct (Diaschisis) Using CASL MRI

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INTRODUCTION: CBF is a correlate of brain metabolism and a biomarker of several brain pathologies [1]. PET methods have been widely used for detection of hypo-perfusion in stroke-affected areas of the brain. However, recent methodological advances have shown arterial spin labeling (ASL) to be a reliable technique for detection of decreases in CBF associated with disease [1]. While PET uses expensive radiological exogenous tracers, ASL relies on arterial blood water as an endogenous tracer making it safer and more economical. Also, stability of ASL measurements with time makes it ideal for tracking CBF changes due to recovery. The goal of this on-going study is two-fold: 1) to demonstrate the feasibility of continuous ASL (CASL) in detecting neuronally-mediated reduction in CBF due to diaschisis (*i.e.*, hypo-perfusion in areas distant from the focal infarct) by comparing CASL-based CBF with metabolic rates assessed with PET in subjects with sub-cortical infarcts. 2) to optimize CASL quantification of CBF in the presence of infarct by investigating the effect of transit time at multiple post labeling delays (PLD).

METHODS: *Subjects* Here we present data from a 54 y.o. right-handed male diagnosed with sub-acute left-thalamic infarct. Written consent was obtained as approved by the institutional IRB. **MRI** images were acquired in a 1.5T scanner (Philips Medical Systems) using a standard transmit-receive coil. For CASL, single shot SE-EPI: TR/TE=4s/36ms, θ=90º, FOV=220x198 mm^2, acq. matrix=64x58, 13 slices (8mm/1mm-gap) were acquired. To induce the adiabatic inversion of water spins, a block-shaped RF pulse, 1.8s long, 35 mG amplitude, and a *z*-gradient, 0.25 G/cm, was applied prior to acquisition of each labeled image [2]. To correct for off-resonance effects, an amplitude modulated (250 Hz sine) RF pulse of the same power and gradient was applied before the acquisition of each control [2]. Labeling plane was positioned 100mm beneath the center of the imaging volume. 30 control/label pairs were acquired for each PLD (100 to 1100 ms, step of 100 ms). A high resolution, 3D T1 (SPGR): TE/TR=3 ms/34 ms, θ =45°, 100 slices (1.5mm/1mm-gap), FOV=240x240mm^2, acq. matrix=256x256, was also acquired. All EPI images were motion corrected, co-registered to the SPGR image, and spatially normalized to MNI standard space using SPM99. Each control-label pair yielded a % change (Mcntrl-Mlabel/Mcntrl) and a CBF [mL/100g•min] image, using the formula derived by Alsop *et al.*[2]. For each acquisition slice the effective PLD was computed as PLD=[(acq. slice –1) • (64) + PLD] ms thus accounting for the inter-slice time acquisition. For each PLD, average % changes were computed for the conjunction of the acquisition slice and subject's posterior probability gray mask (P[GM]>.8) for left and right hemispheres separately. To minimize the effect of motion in comparison among PLDs, only voxels belonging to the same acquisition slice were analyzed. **PET** (ECAT HR+, Siemens/CTI) was acquired for 30min after 30min of intravenous administration of 10 mCi ^{18}FDG. Prior to PET, 10 min 68Ge/68Ge transmission scan was performed. PET images were reconstructed to a 128x128x63 matrix (1.7x1.7x2.4 mm). Brain ^{18}FDG activity was expressed as the standard uptake value, SUV =(activity * body weight)/injected dose. PET image was coregistered to the SPGR and spatially normalized to the MNI space for spatial comparison with CASL images**.**

RESULTS: 1) Fig.1 shows SPGR, PET and CASL-flow (PLD=1000ms) images at the slice of infarct. In the frontal lobe: CASL-CBF was 17.9 % lower on the side of infarct (left) ($p<.0001$) while PET SUV was 9.6%. In occipital lobe: CASL-CBF decrease on the side of infarct was ~7% but did not reach significance; PET SUV difference was 1.8%. The local CASL-CBF at the infarct was 17 mL/100g•min, 71% lower than its mirror ROI in the right hemisphere. **2)** Transit time changes due to vascular damage are a confound in CASL-based quantification of CBF. Separating the effect of transit time is important in studying diaschisis where the goal is to correlate hypoperfusion with hypometabolism and not distal vascular damage. To show that there was no marked difference in vascular transit time in the side of infarct as compared to the unaffected side, we performed a three-parameter least-squared fit to estimate transit time and flow for each acquisition slice in the left and right hemisphere separately. Results of the fit are shown in Fig.2 with δa denoting vascular transit time at a given slice. Fig 3 shows CASL % signal from left slices *vs* time. For the sake of clarity, we show data only from odd slices in the affected side (slice 5 containing most of the infarct). Solid lines represent best fits. As expected, there is a slice/PLD dependent arterial transit time after which the signal decreases independent of PLD and slice position. The fit to the data from the right hemisphere yielded similar δa and 15% higher flow values.

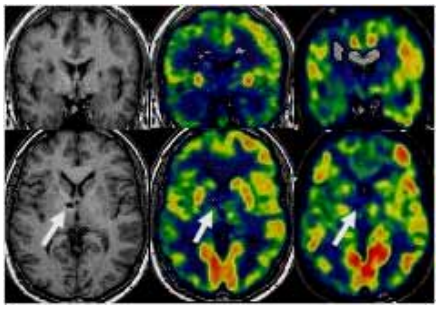

Fig.1 SPGR (left), PET (middle), and CASL (right) images. The arrow indicates site of infarct. (Note that intensity values for PET and CASL correspond to different units)

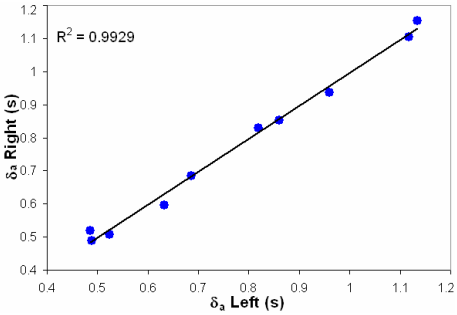

Fig.2 : Vascular transit times (δa) for left (x-axis) *vs.* right (y-axis) sides of each acquisition slice obtained from the best fit to the flow model.

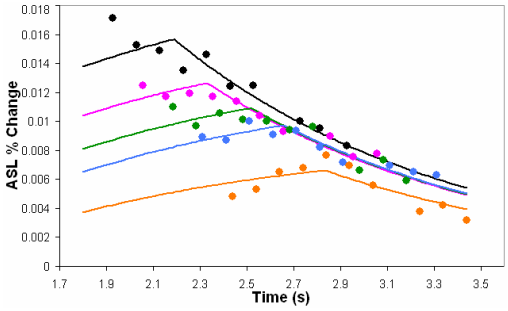

Fig.3 : Left hemisphere CASL % signal *vs.* time. Data for a given slice were acquired at multiple PLDs. Slice acquisition was in ascending order, (slice 3 (black), slice 11 (orange)). Solid lines correspond to best fits.

DISCUSSION: We have presented preliminary results showing feasibility of CASL MRI for detection of changes in CBF due to diaschisis. CASL CBF correlated well with regional metabolic activity as assessed with FDG PET. Results from multiple PLD measurements suggest that, in the absence of vascular damage, arrival times are not markedly different in the side of infarct as compared to the contra-lateral side. This result is important in cases when within-subject analysis is necessary. Although these preliminary results support the hypothesis that the detected CBF depression is directly related to diaschisis, (*i.e.*, neuronally mediated hypometabolism rather than distal vascular damage), clearly data from more subjects are needed for any conclusions to be drawn. More importantly, these results cannot differentiate between the vascular and microvascular contributions in the ASL signal because in adopting the one-compartment model, for PLD>δa, the total ASL signal is independent of tissue transit time [4]. Discrepancies between PET and CASL were noticed and a map of the CASL/PET ratio (figure not shown) indicated areas of focal decoupling between CBF and metabolism which needs to be better understood. Furthermore, in multiple PLD CASL experiments, a potential source of error is the signal variation due to PLD-dependent magnetization transfer effects. For this study, this error is minimized through within-subject right-left comparison.

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