Differential spatio-temporal cerebral blood volume response to normobaric oxygen therapy in an experimental rat stroke model

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Introduction: Recent experimental and human stroke studies indicate that normobaric oxygen therapy (NBO) may be a potent neuroprotectant [1-3]. In a pilot human study [1, 4], neurological deficit scores, diffusion-weighted MRI (DWI) abnormalities, and brain lactate levels improved during NBO. Since NBO does not significantly increase brain tissue oxygen levels, the mechanism of these surprisingly potent effects remains unclear. The results of rodent and human studies using perfusion-weighted MRI (PWI) [1, 3] and laser speckle flowmetry [5] suggest that NBO alters cerebral hemodynamics, which in turn may afford neuroprotection. We therefore investigated NBO-induced changes on cerebral blood volume (ΔCBV) in different brain regions over time using MRI after stroke in rats using a superparamagnetic intravascular contrast agent with long blood half-life (monocrystalline iron oxide nanocolloid, MION).

Methods: Unilateral stroke was induced in adult male wistar rats (n=10; 290 to 335 g; Charles River Laboratories, MA) by filament occlusion of the right middle cerebral artery (MCAO). Three rats with imaging artifacts (n=2) or unsuccessful MCAO (n=1) were excluded from analysis. Arterial blood gases were monitored throughout the experiment. Immediately after stroke induction, animals were positioned in an MRI scanner using an MRI-compatible rat stereotaxic headset with ear- and tooth-bars and mechanically ventilated under anesthesia. MRI were performed on a horizontal bore 9.4-T Bruker Biospec Imager (Bruker Biospin, Billerica, MA), equipped with a home-built rat head surface RF transmit and receiver coil with a diameter of approximately 30 mm. DWI and arterial spin labeling PW (ASL-PWI) were obtained at baseline to delineate 'core' and 'salvageable' tissue. DWI was acquired with field of view (FOV) of 25×25 mm2, 64×64 imaging matrix, nine contiguous slices (1mm per slice) and TR/TE=1000/38 ms with diffusion gradients applied in 6 non-collinear directions with b-value=997 s/mm2. ASL measurement was made using the two-coil continuous arterial spin-labeling method with three contiguous 1 mm slices (TR/TE=3700/13). Conventional gradient echo (GRE) were acquired with the same slices used by the DWI (TR/TE=300/5 ms). High iron doses (MION, 40 mg/kg) and short TE were used to increase sensitivity to functional CBV changes and reduce contamination from large vessel signals and susceptibility artifacts [6]. After administration of MION, inspired gas was alternated between room air and 100% oxygen (NBO), with each period of gas exposure lasting 10 minutes. GRE and DWI were repeated during each 10-min period of room air and NBO exposure. Prior to analysis, all GRE images were motion corrected using a software package (AFNI). DWI, ASL and GRE maps were co-registered to one another using a semiautomated co-registration program (MNIAutoReg [7]). Each rat brain was segmented into the following 4 regions of interest (ROIs): (a) 'Core', the acute DWI lesion, (b) 'Salvageable', the acute ASL-PWI lesion minus the 'Core' area, (c) CoreCNL, contralateral mirror equivalent of the Core, (d) SalvageableCNL, contralateral mirror equivalent of the Salvageable ROI (see Fig 1). ΔCBV in response to NBO followed by room-air were calculated [8]. The differences in ΔCBV between NBO (O2 ON) and room air were measured (see Fig 1) and compared across the 4 regions (ANOVA followed by post-hoc SNK test) at timepoints ~1h and ~3 h post-MCAO.

Results: All rats showed DWI lesions within larger ASL-PWI lesions in the right MCA territory (see Fig 1). Arterial pH, and PCO2 were stable. Arterial PO_2 was significantly higher during NBO than during room-air at 1 h (305±103 vs. 88±8 mm Hg, P=0.02) and at 3 h (315±106 vs. 91±14 mm Hg, P=0.03). CBV measurements were obtained at *early* (76±6 min post-MCAO) and *follow-up* (160±8 min) time points. At the early time point, ΔCBV with room air followed by NBO in the Salvageable ROI (+0.5±5.4%) was significantly different (P<0.01) from other regions (Core, -9.9±6.9%; CoreCNL, -9.3±6.1%; SalvageableCNL, -8.3±5.6%). One rat died between the early and follow-up time points. At 3 hours there was no significant difference between the 4 ROIs (Core, -1.2±2.4%; Salvageable, +0.3±4.4%; CoreCNL, -4.8±6.2%; SalvageableCNL, -4.3±7.1%), suggesting that NBO's hemodynamic effects diminish over time.

Discussion: CBV responses to NBO are both spatially and temporally heterogeneous. The mechanisms of peri-infarct tissue salvage as a result of NBO therapy may be due to reductions in CBV in normal regions with preservation and even slight elevation in the penumbra. Hemodynamic changes, e.g. "steal phenomena", may be a key neuroprotective mechanism of NBO. However, our results suggest that these changes are relatively short lived. Future studies which also measure changes in CBF in response to NBO may help further elucidate the mechanisms of this promising new therapy.

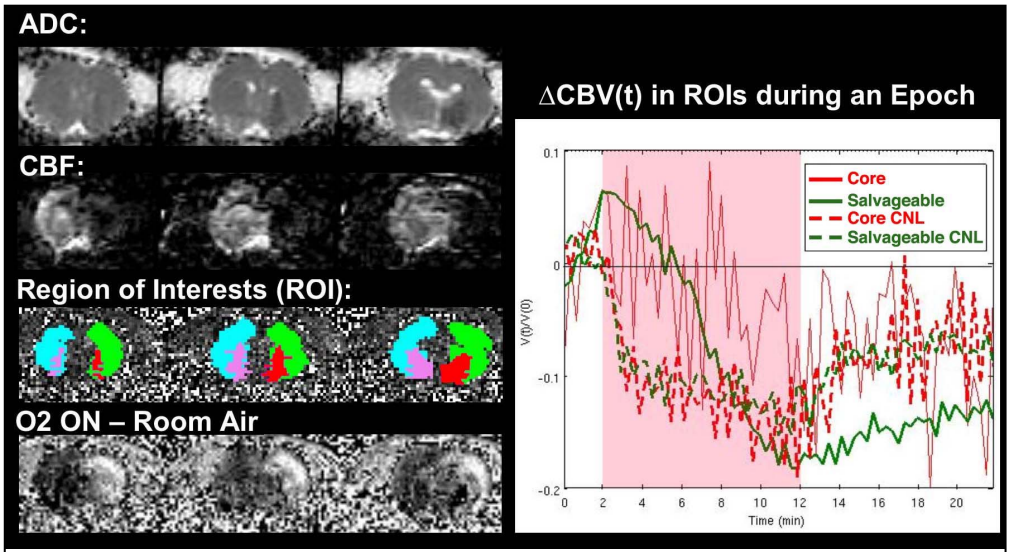

Fig 1: Example of ROI delineation of Core (Red), Salvageable (Green), CoreCNL (pink) and SalvageableCNL (cyan) in a rat. Also shown are the changes over time for the first 20 min epoch for the 4 ROIs. Note that the Core is very noisy, while CNL ROIs follow similar time courses.

References:

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