Effect of Normobaric Hyperoxia (NBO) on Progression of Ischemic Stroke

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TARGET AUDIENCE Researchers in stroke, oxygen therapy and neuroprotection.

INTRODUCTION Tissue hypoxia plays a critical role in primary and secondary cascades leading to cell death in cerebral ischemia[1]. Normobaric hyperoxia (NBO) has been shown to increase oxygen tension and reduce infarct size in several experimental stroke models[2,3]. NBO treatment in ischemic stroke doubles oxy-hemoglobin concentration in ischemic core within 60 minutes[4]. Laser speckle flowmetry and multispectral imaging studies have shown that NBO improves cerebral blood flow in cortex and reduces occurrence of peri-infarct depolarizations[4]. NBO treatment stabilizes the blood brain barrier and inhibits inflammatory processes secondary to cerebral ischemia[5]. On the other hand, some studies found that NBO is detrimental in stroke and leads to damage due to free radial production [6]. In this paper, we used quantitative MRI to longitudinally evaluate the effects of NBO on ischemic stroke and to test the hypothesis that NBO treatment is neuroprotective in a transient middle cerebral artery occlusion (MCAO) model in rats.

METHODS Male rats (250-300g) were subjected to 90-min MCAO[7]. Using a randomized, double-blinded experimental design, one group (n=6) received normobaric hyperoxia (100% O_2) from 30-80 minutes post MCAO, and the control group (n=6) received air throughout the experiment. Quantitative CBF (cerebral blood flow), ADC (apparent diffusion coefficient) and T2 were acquired at 7T and analyzed as described elsewhere[7]. Initial lesion volume was defined by ADC lesion at 30 minutes. Final infarct volumes were derived by day-2 T2 maps[7]. Edema correction was applied [8]. Paired t-test was used for comparison between initial lesion and final infarct within NBO- and air-treated groups and unpaired t-test was used for comparison between NBO- and air-treated groups. A P-value of 0.05 was taken to be statistically significant. Data showed in figures and texts are mean ± SEM.

RESULTS In the control group, ADC-defined lesion volume grew during MCAO and reversed after reperfusion during the first 3 hours (**Figure 1**). By comparison, in the NBO group, lesion decreased slightly during MCAO and decreased further after reperfusion. The ADC lesion volume of the NBO group was smaller than control group at all time points measured except at 30 minutes. The group-averaged initial ADC-defined lesion volume at 30 minutes and final T2-defined infarct volume at 2 days after stroke were evaluated (**Figure 2**). In the control group, the initial lesion volume grew larger at day 2 (18.5±9.6%, P=0.04). By contrast, in the NBO group, the initial lesion volume became smaller at day 2 (-8.2±5%, P=0.03). The NBO-treated infarct volume was significantly smaller than air-treated infarct volume at day 2 by 27.4% (P<0.01) (**Figure 3**).

DISCUSSION The major finding is that NBO treatment decreased infarct size compared to control at day 2. NBO treatment stopped, and in many cases decreased, ADC lesion growth at the acute phase, thereby delaying the progression of ischemic penumbra to ischemic core. With reperfusion, substantially more tissue was salvaged compared to controls. We concluded that NBO treatment as administered herein was neuroprotective. Future studies will investigate NBO treatment at different MCAO durations and different NBO treatment durations in both acute and chronic phase. fMRI and behavioral outcome measurements can also be included.. The implication of these findings is that NBO can be used to "buy" time and expand the treatment time window in stroke patients. MRI offers a unique and sensitive means to longitudinally monitor NBO treatment effect. NBO is cost effective and can be readily administered by emergency responders onsite. NBO can also be used in combination with other treatments.

REFERENCES [1] Zauner, A. et al. Neurosurgery 51, 289–302 (2002). [2] Fujiwara, N. et al. BMC neuroscience 10, 79 (2009). [3] Kim, H. Y. et al. Ann. of neurology 57, 571–5 (2005). [4] Shin, H. K. et al. Brain 130, 1631–42 (2007). [5] Michalski, D. et al. Exp. & translational stroke med. 3, 5 (2011). [6] Singhal, A.B. Int. Journal of Stroke 191–200 (2006). [7] Shen, Q. et al. JCFM 31, 2076–85 (2011). [8] Tatlisumak, T. et al. Stroke 29, 850–858 (1998). *Supports: NIH R01-NS45879, CTSA 8UL1TR000149.

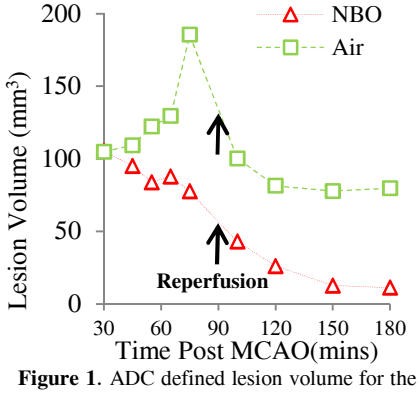

Figure 1. ADC defined lesion volume for the NBO- and air-treated group in first 3 hours after MCAO

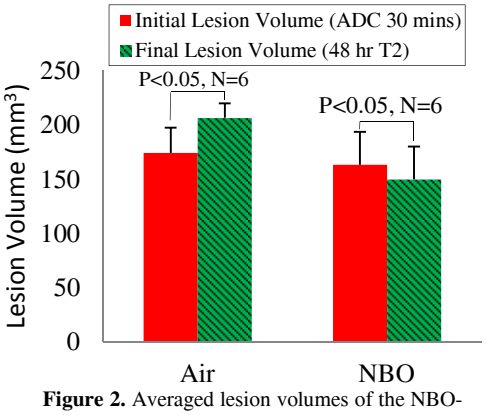

Figure 2. Averaged lesion volumes of the NBO- and air-treated group at 30 minutes and 48 hours.

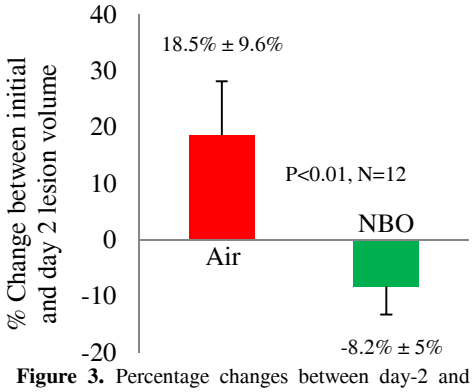

Figure 3. Percentage changes between day-2 and initial lesion volumes of NBO- and air-treated group.