Time dependent treatment outcomes of NBO in experimental ischemic stroke

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Target audience: Researchers in stroke, neuroprotection, oxygen therapy, animal models.

Purpose: Previous studies have shown normobaric hyperoxia (NBO) to be effective in extending treatment time window in animal model of transient cerebral ischemia. However, both positive and negative effects of NBO treatment have been reported[1-3]. As such, it is highly likely that the efficacy of NBO treatment in the early phase of ischemic insult is critically dependent on the treatment duration. To test this hypothesis, we evaluated the effects of varying treatment duration for NBO administration (25 and 150 min) on the 60-min MCAO model of stroke, longitudinally and noninvasively using quantitative MRI.

Methods: 19 Male rats (250-300g) were subjected to 60-min MCAO (Groups I-III). Using a randomized and double-blinded experimental design, animal groups received following treatments: group I with normal air (n=6), group II with 25 min of NBO treatment (starting from 30-55 min post MCAO, n=5) and group III with 150 min of NBO treatment (starting from 30-180 min post MCAO, n=8).

Quantitative CBF, ADC and T2 maps were acquired at 7T and analyzed as described elsewhere[4]. Initial lesion volume was defined by ADC lesion at 30 minutes. Edema corrected final lesion volumes were derived from 48hr T2 maps and percent lesion growth was calculated for all animals. One-way ANOVA with Tukey's post hoc test was used for comparisons across groups. A P-value of 0.01 was taken to be statistically significant. Data shown in figure and texts are group averaged mean ± SEM.

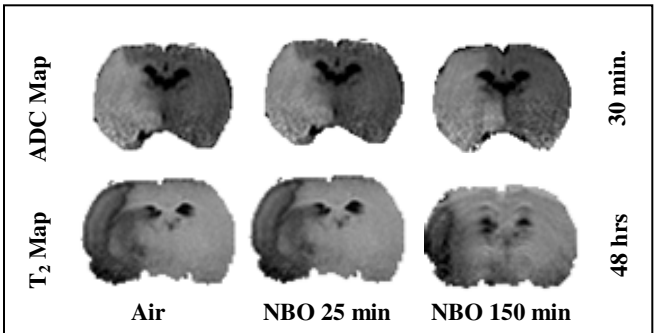

Fig.1 ADC and T2 maps for animals from groups I- III (inverted LUT)

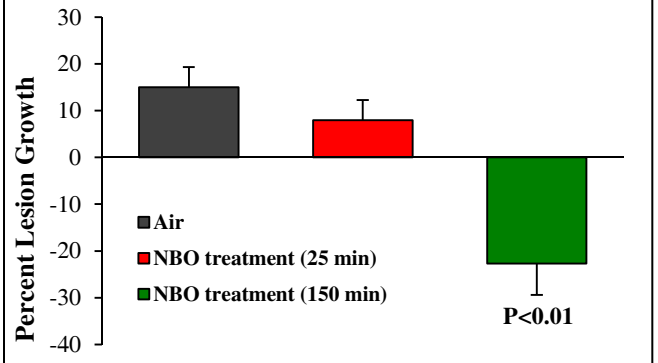

Fig 2. Percent growth in lesion volume across groups I-III

Results: All animal groups showed similar initial perfusion deficit (data not shown) and similar ADC defined lesion volumes (group I: 168±14 mm^3, group II: 181±32 mm^3, group III: 178±13 mm^3) before treatment **(Fig. 1)**, indicating the reproducibility of MCAO surgery. In the air group, lesion volume at 48hr increased 15±4% compared to 30 min after stroke (final volume= 188±32 mm^3). In the 25-min NBO group, lesion volume at 48hr increased 8±4% compared to 30 min after stroke (final volume= 200±18 mm^3). In contrast, in the 150-min NBO group, lesion volume at 48hr decreased 23±7% compared to 30 min after stroke (P<0.01, final volume= 146±11 mm^3) (**Fig. 2**).

Discussion: We found that early pre-reperfusion NBO treatment (25 min) showed a trend of improvement compared to air treated group but failed to reach any significance (most likely due to shorter treatment duration). By contrast, early administration of NBO with longer treatment duration (150 min) reduced lesion volume by 22.7 %. A few NBO studies have shown that early pre reperfusion NBO affords neuroprotection[1,3] whereas delayed post insult treatment with NBO may lead to increased ischemia induced brain damage[2]. Michalski et. al. have shown that early NBO administration (60 min treatment) reduces functional impairment and decreases BBB permeability in acute experimental stroke[3]. Haelewyn et. al. have shown that moderately delayed NBO administration (1 hour post MCAO) reduced excitotoxin-induced calcium influx and neuronal degeneration but favored ischemia-induced brain damage and neuronal death[2]. These findings indicate that the treatment outcomes of NBO are critically dependent on the treatment window and treatment duration.

Conclusion: We found 150-min NBO treatment in the 60-min MCAO stroke model to be neuroprotective. The 25-min NBO treatment showed a trend of improvement but did not reached statistical significance. NBO treatment has the potential to expand the treatment time window as well as salvage tissue. Future studies will investigate additional treatment duration, lower oxygen concentration (i.e., 70% O2), combination therapy, as well as possible molecular mechanisms of neuroprotection such as probing tissue oxygenation, oxygen free radial damage and inflammatory responses associated with NBO treatment.

References: [1] Qi Z, Med. Gas Res. 2013;3(1):2. [2] Haelewyn B, Med. Gas Res. 2011;1(1):2.[3] Michalski D, Exp. Transl. Stroke Med. 2011;3(1):5. [4] Shen Q, J. Cereb. Blood Flow Metab. 2004;24(3):280–90.