A Pilot Study of Normobaric Oxygen Therapy in Acute Ischemic Stroke

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Background and Purpose—Therapies that transiently prevent ischemic neuronal death can potentially extend therapeutic time windows for stroke thrombolysis. We conducted a pilot study to investigate the effects of high-flow oxygen in acute ischemic stroke.

Methods—We randomized patients with acute stroke (<12 hours) and perfusion-diffusion "mismatch" on magnetic resonance imaging (MRI) to high-flow oxygen therapy via facemask for 8 hours (n=9) or room air (controls, n=7). Stroke scale scores and MRI scans were obtained at baseline, 4 hours, 24 hours, 1 week, and 3 months. Clinical deficits and MR abnormalities were compared between groups.

Results—Stroke scale scores were similar at baseline, tended to improve at 4 hours (during therapy) and 1 week, and significantly improved at 24 hours in hyperoxia-treated patients. There was no significant difference at 3 months. Mean (±SD) relative diffusion MRI lesion volumes were significantly reduced in hyperoxia-treated patients at 4 hours (87.8±22% versus 149.1±41%; $P=0.004$) but not subsequent time points. The percentage of MRI voxels improving from baseline "ischemic" to 4-hour "non-ischemic" values tended to be higher in hyperoxia-treated patients. Cerebral blood volume and blood flow within ischemic regions improved with hyperoxia. These "during-therapy" benefits occurred without arterial recanalization. By 24 hours, MRI showed reperfusion and asymptomatic petechial hemorrhages in 50% of hyperoxia-treated patients versus 17% of controls ($P=0.6$).

Conclusions—High-flow oxygen therapy is associated with a transient improvement of clinical deficits and MRI abnormalities in select patients with acute ischemic stroke. Further studies are warranted to investigate the safety and efficacy of hyperoxia as a stroke therapy. **(*Stroke*. 2005;36:797-802.)**

Key Words: magnetic resonance imaging ■ neuroprotection ■ oxygen ■ stroke

Identifying strategies to extend the thrombolysis time window is an important area of stroke research.[1] One approach is to arrest the transition of ischemia to infarction ("buy time") until reperfusion can be achieved. Hyperoxia might be a useful physiological therapy that slows down the process of infarction and has shown promise in studies of myocardial infarction.[2] Tissue hypoxia is a key factor contributing to cell death after stroke and oxygen easily diffuses across the blood–brain barrier. Moreover, oxygen has multiple beneficial biochemical, molecular, and hemodynamic effects.[3–5] Hyperbaric oxygen therapy (HBO) has been widely studied because it significantly raises brain tissue pO_2 ($ptiO_2$). Transient "during-therapy" clinical improvement was documented 40 years ago,[6] and HBO proved effective in animal studies.[7–9] However, the failure of 3 clinical stroke trials[10–12] has reduced the enthusiasm for using HBO in stroke.

In light of the difficulties with HBO, we have begun to investigate normobaric oxygen therapy (NBO), or the delivery of high-flow oxygen via a facemask. NBO has several advantages: it is simple to administer, noninvasive, inexpensive, widely available, and can be started promptly after stroke onset (for example, by paramedics). Whereas brain $ptiO_2$ elevation with NBO is minor as compared with HBO, the critical mitochondrial oxygen tension is extremely low,[13] and even small increases in $ptiO_2$ might suffice to overcome thresholds for neuronal death. Recent studies indicate that brain $ptiO_2$ increases linearly with rising concentrations of inspired oxygen,[14] and increases nearly 4-fold over baseline have been documented in brain trauma patients treated with NBO.[3] A recent in vivo electron paramagnetic resonance oximetry study has shown that NBO significantly increases $ptiO_2$ in "penumbral" brain tissue.[15] In rodents, NBO therapy during transient focal stroke attenuates diffusion-weighted MRI (DWI) abnormalities, stroke lesion volumes, and neurobehavioral outcomes[4,16,17] without increasing markers of oxidative stress.[16] Based on preclinical results, we conducted

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a pilot clinical study to examine the risks and benefits of NBO in stroke. We hypothesized that clinical and MRI parameters of ischemia would transiently improve during NBO.

Materials and Methods

This randomized, placebo-controlled study with blinded MRI analysis was approved by our hospital's Human Research Committee. The inclusion criteria were: (1) nonlacunar, anterior circulation ischemic stroke presenting <12 hours after witnessed symptom onset or <15 hours after last seen neurologically intact; (2) ineligible for intravenous/intra-arterial thrombolysis; (3) National Institutes of Health Stroke Scale (NIHSS) score ≥4; (4) pre-admission modified Rankin scale (mRS) score ≤1, and (5) mean transit time (MTT) lesion larger than DWI lesion (perfusion–diffusion "mismatch") with evidence for cortical hypoperfusion on MRI. To minimize time to treatment, "mismatch" was assessed during the initial MRI, using a visual estimate for >20% difference between DWI and MTT lesion size. The exclusion criteria were: (1) active chronic obstructive pulmonary disease; (2) >3 L/min oxygen required to maintain peripheral arterial oxygen saturation (SaO_2) >95% as per current stroke management guidelines;[18] (3) rapidly improving neurological deficits; (4) medically unstable; (5) pregnancy; (6) inability to obtain informed consent; and (7) contraindication for MRI. Eligible patients gave consent and were randomized by opening sealed envelopes containing treatment allocation to the NBO group (humidified oxygen via simple facemask at flow rates of 45 L/min) or the control group (room air or nasal oxygen 1 to 3 L/min if necessary to maintain SaO_2 >95%). NBO was stopped after 8 hours; however, nasal oxygen was continued if clinically warranted.

National Institutes of Health Stroke Scale (NIHSS), mRS, and Scandinavian Stroke Scale (SSS) scores were recorded after the admission MRI. NIHSS scores and MRI scans were repeated at 4 hours (range, 2.5 to 5.5 hours); 24 hours (range, 20 to 28 hours); 1 week (range, 5.5 to 8.5 days); and 3 months (range, 80 to 115 days). SSS and mRS scores were repeated at 3 months. The unblinded clinical investigator monitored patients during therapy. Imaging technique details are presented in the appendix.

Manual MRI analysis was performed by 2 neuroradiologists blinded to clinical presentation, treatment group, clinical course, and medications. Stroke volumes were calculated from DWI images except for 1-week and 3-month time points, when fluid-attenuated inversion recovery images were used. Lesions were outlined on each axial slice using a commercially available image analysis program (ALICE; Perceptive Informatics, Waltham, Mass) to yield total volumes. Reperfusion (defined as clear identification of a previously occluded artery on magnetic resonance angiography [MRA] or >50% decrease in MTT lesion volume in patients without arterial cutoff on initial MRA) was determined on 4-hour and 24-hour MRIs. Postischemic hemorrhage was ascertained on 24-hour gradient-echo MRIs.

Automated MRI analysis was performed to determine the fate of individual voxels on apparent diffusion coefficient (ADC) maps, as per their change in signal intensity above or below a threshold of 600×10^{-6} mm^2/s (≈45% of normal[19]) from baseline to the 4-hour and 24-hour time points. Voxels with signal intensity constantly above threshold were considered *"never-abnormal*;" remaining voxels were grouped as follows: (1) *no reversal*, signal intensity below threshold at all time points; (2) *temporary early reversal*, signal intensity below threshold at baseline, improving to an above-threshold value at 4 hours, but reverting at 24 hours; (3) *sustained early reversal*, signal intensity below threshold at baseline, improving to an above-threshold value at 4 hours and 24 hours; (4) *late reversal*, signal intensity below threshold at baseline and 4 hours, improving to an above-threshold value at 24 hours; and (5) *progression to ischemia*, signal intensity above threshold at baseline, worsening to a below-threshold value at 4 hours or 24 hours. We further analyzed voxels with "sustained early reversal" for "late secondary decline"[19] on the 1-week MRI.

For each patient, outlines of the baseline MTT lesion were transferred onto coregistered perfusion maps at each time point, and relative cerebral blood volume, relative cerebral blood flow, and relative cerebral MTT values were calculated within these regions after normalizing to a region of gray matter in the contralateral hemisphere.

The prespecified primary outcome was a comparison of DWI lesion growth at 4 hours between groups. Secondary outcomes were mean NIHSS scores and perfusion parameters at 4 hours, the percentage of ADC voxels undergoing reversal at 4 hours or 24 hours, brain hemorrhage at 24 hours, and 3-month stroke lesion volumes and NIHSS and mRS scores. We initially planned to enroll 40 patients in this pilot study to allow formal power calculations. The interim analysis showed positive results, which are presented herein.

Patient Data

Characteristic	Hyperoxia (n=9)	Controls (n=7)
Age, y (mean, range)	67 (37–88)	70 (49–97)
Female	5 (56%)	4 (57%)
Stroke etiology		
Cardioembolic	6	5
ICA atherosclerosis/thrombosis	3	0
ICA dissection	0	1
Cryptogenic embolism	0	1
Intravenous heparin on day 1	5 (56%)	5 (71%)
Stroke Scale Scores (median, range)		
Admission NIHSS	14 (4–22)	11 (8–21)
4-h NIHSS	12 (2–15)	13 (10–26)
24-h NIHSS	6 (4–16)	15 (11–26)
1-wk NIHSS	6 (0–22)	14 (7–23)
3-mo NIHSS	3 (0–19)	13 (1–19)
Admission Scandinavian Stroke Scale	27 (6–55)	32 (2–39)
3-mo Scandinavian Stroke Scale	47 (16–60)	32 (30–56)
3-mo mRS (mean±SD)	3.2±2.2	4.1±1.6
MRI Characteristics (median, range)		
Time intervals		
Onset to MRI-1, h	7.4 (1.6–13.4)	6.8 (3.5–8.9)
MRI-1 to MRI-2, h	4 (2.6–4.7)	4.5 (3.5–5.7)
MRI-1 to MRI-3, h*	24.4 (21.3–26.5)	25 (22.5–27.7)
MRI-1 to MRI-4, d*	6.6 (3.7–8.2)	6.2 (4.0–9.9)
MRI-1 to MRI-5, d*	99 (54–106)	116 (107–152)
Postischemic hemorrhage on MRI-2	1 (asymptomatic)	1 (fatal)
Postischemic hemorrhage on MRI-3*	4 (50%)	1 (17%)
Reperfusion		
MRI-1 to MRI-2	0 (0%)	1 (14%)
MRI-2 to MRI-3*	4 (50%)	0 (0%)

*Excluding 1 patient per group with postischemic hemorrhage.

MRI-1 indicates first MRI; MRI-2, second MRI, MRI-3, third MRI; MRI-4, fourth MRI; MRI-5, fifth MRI.

Statistical Analysis

SPSS for Windows v11.0 (SPSS) was used for the "intention to treat" statistical analysis. All values are reported as median (range) or mean±SD. For intergroup comparisons, we applied the Student *t* test, Mann–Whitney *U* test, or Fisher exact test; for intragroup comparisons, we applied the paired *t* test or Wilcoxon rank-sum test as appropriate. $P<0.05$ was considered significant.

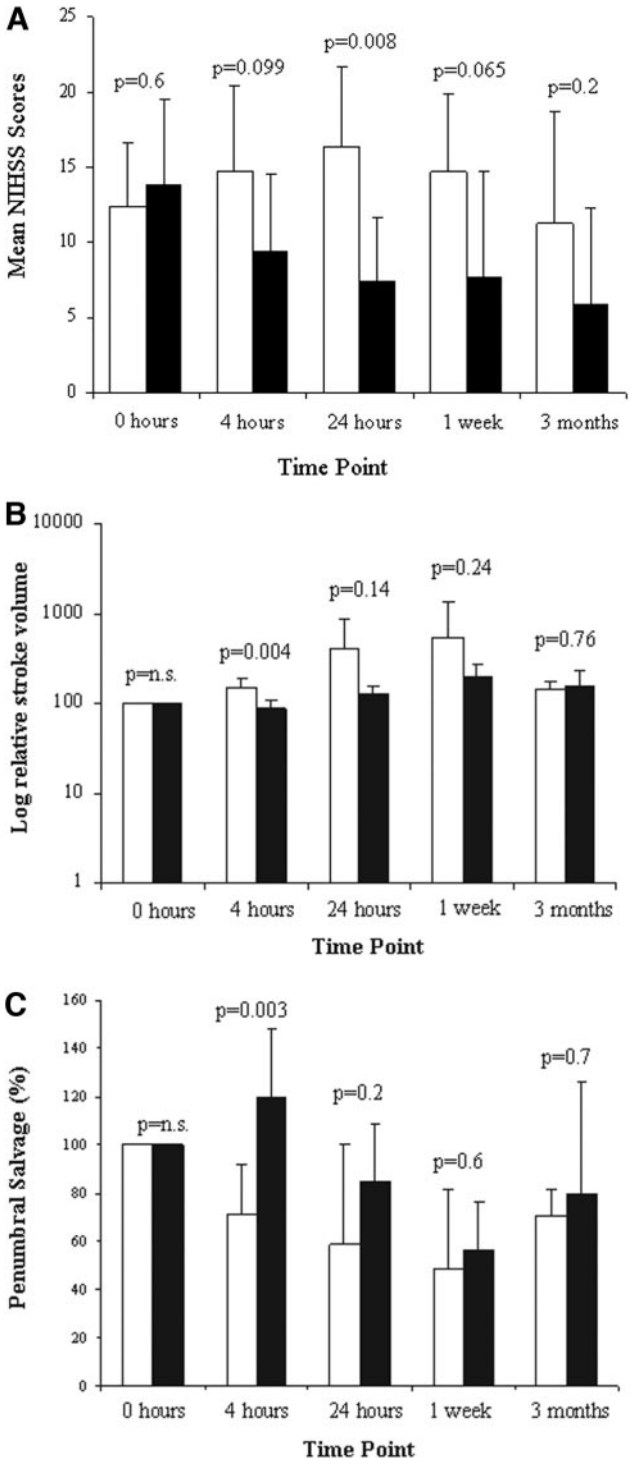

Figure 1. A, NIHSS scores. B, Percent change in relative stroke lesion volumes. C, Penumbral salvage or the ratio of acutely hypoperfused tissue salvaged from infarction [(baseline MTT volume) − (infarct volume at later time point)] to the acute tissue at risk for infarction [(baseline MTT volume) − (DWI volume at baseline)].[21] Controls, white bars; NBO, black bars; mean±SD.

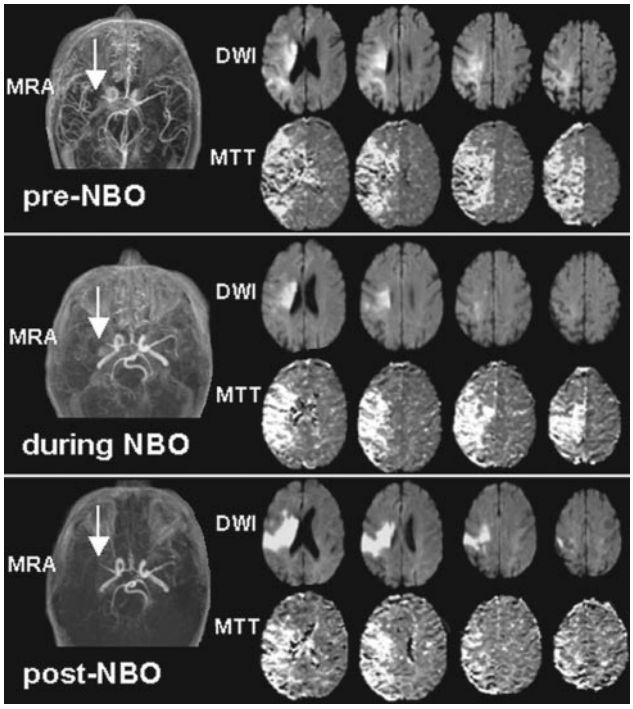

Figure 2. Serial MRI findings in a patient with cardio-embolic right MCA stroke treated with NBO for 8 hours. Top, Baseline (pre-NBO) MRI, 13.1 hours after symptom onset, shows a large DWI lesion, a larger MTT lesion, and MCA occlusion (arrow) on head MRA. Middle, A second MRI after 3.75 hours (during NBO) shows 36% reduction in the DWI lesion, stable MTT deficit, and persistent MCA occlusion. Bottom, A third MRI after 24 hours (post-NBO) shows reappearance of DWI abnormality in some areas of previous reversal; MTT image shows partial reperfusion (39% MTT volume reduction, mainly in the ACA territory); MRA shows partial MCA recanalization.

Results

We randomized 9 patients to the NBO group and 7 to the control group. Hypoventilation did not develop in any patient. None reported discomfort from the facemask. Mean blood glucose, mean arterial BP at baseline, 4 hours, and 24 hours, and anticoagulant and antiplatelet use were not significantly different between groups. Arterial blood gases were drawn for clinical reasons in 3 patients: the PaO_2 (mm Hg) was 368 and 420 in 2 NBO patients and was 99 in 1 control patient. The Table shows patient characteristics. Soon after the admission MRI, 1 control patient had a massive brain hemorrhage and died;[20] 1 NBO patient had an asymptomatic brain hemorrhage temporally associated with a supratherapeutic partial thromboplastin time from intravenous heparin treatment. Individual patient data are available online (Appendix; see http://stroke.ahajournals.org).

Median NIHSS, SSS, and mRS scores are presented in the Table, and intergroup comparisons of mean NIHSS scores are shown in Figure 1A. In the NBO group, clinical improvement was noted as early as 15 to 20 minutes after starting the 8-hour hyperoxia therapy. As compared with baseline, mean NIHSS scores were significantly lower at 4 hours ($P=0.016$), 24 hours ($P=0.03$), and 3 months ($P=0.03$).

All patients had ICA and/or proximal MCA occlusion with substantial perfusion deficits (MTT lesion volume >90 mL in 13 of 16 patients). Mean MTT (NBO, 125.9±65 mL versus control, 130.5±81 mL; $P=0.9$) and DWI (NBO, 29.3±22 mL; control, 27.1±39 mL; $P=0.89$) lesion volumes were comparable at baseline. At 4 hours, reperfusion was evident in 1 control patient; however, mean MTT lesion volumes were not significantly different between groups ($P=0.4$). At

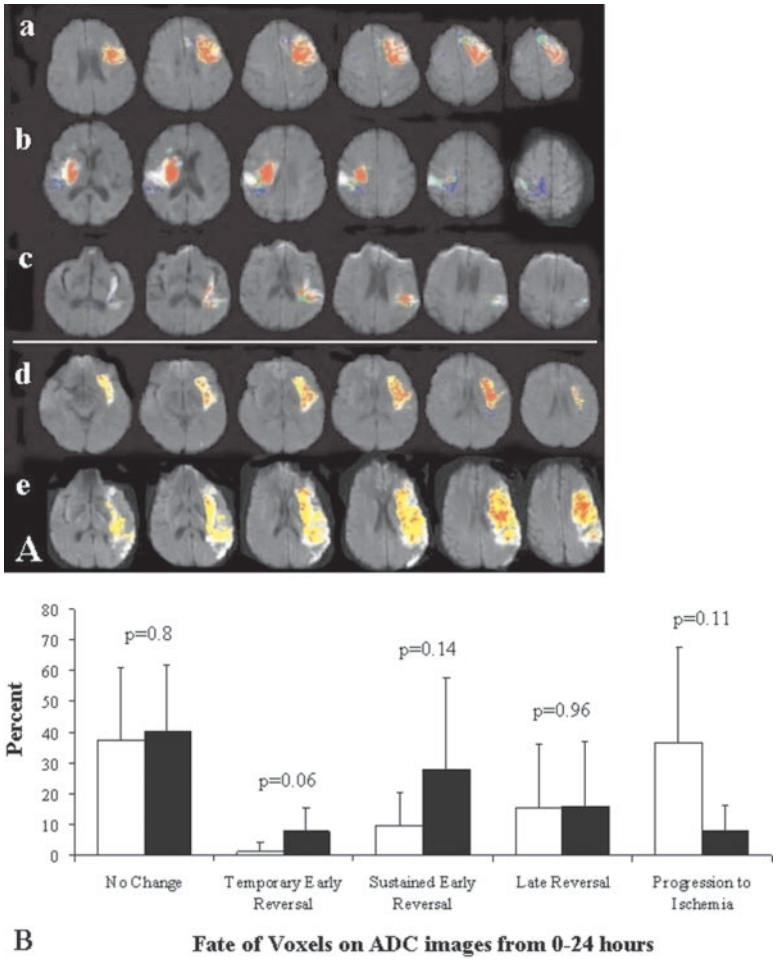

Figure 3. A, 24-hour DWI image with color-coded overlays showing fate of individual ADC voxels from 0 to 24 hours in 3 NBO (a to c) and 2 control (d, e) patients. Patient b is the same as in Figure 2. Voxels undergoing *temporary early ADC reversal* (green) and *sustained early ADC reversal* (blue) are present mainly in the lesion periphery and clearly evident in all NBO patients. The few voxels undergoing *late ADC reversal* (cyan) do not have a distinct distribution pattern. Voxels showing *no change* (red) predominate in the center of the DWI lesions in both groups, and voxels showing *progressive ischemia* (yellow) are most evident in the control patients. B, Bar graph showing the fate of individual voxels (mean±SD) on ADC maps from 0 to 24 hours. Controls, white bars; NBO, black bars.

24 hours, 4 NBO-treated patients but no additional control patients showed reperfusion on MRI, and mean MTT lesion volumes were significantly lower than baseline in the NBO group (87.8±48 mL versus 125.9±65 mL; $P=0.04$).

Asymptomatic petechial hemorrhages were evident on 24-hour MRI scans in 4 NBO patients and in 1 control patient ($P=0.6$), were located in the deep MCA territory, and were associated with arterial recanalization (3 patients) and previous microbleeds (1 patient).

At 4 hours (during therapy), relative DWI lesion volumes decreased in 6 NBO-treated patients, with >20% reduction in 3 patients. DWI reversal was most evident in the lesion periphery (Figure 2) and was not associated with regions of tissue reperfusion. Among controls, only 1 patient had a smaller DWI volume at 4 hours, and the reduction was minor (5%). Mean relative DWI volumes were significantly smaller in the NBO group as compared with controls at 4 hours (87.8±22% versus 149.1±41%; $P=0.004$), but not significantly different at 24 hours, 1 week, and 3 months (Figure 1B). *Penumbral salvage*[21] was significantly higher in the NBO group at 4 hours (Figure 1C).

Voxels showing temporary and sustained ADC reversal were located mainly in gray matter and white matter regions in the lesion periphery (Figure 3A). The NBO group tended to have a higher average percentage of voxels undergoing "temporary early reversal" (Figure 3B). Although the percentage of "sustained early reversal" voxels was 3-fold higher in the NBO group than controls, the difference was not statistically significant. Temporary or sustained ADC reversal in voxels totaling a volume >1.5 mL was observed in 6 NBO and 1 control patient ($P=0.1$). There was no significant difference in the percentage of voxels with "late secondary decline."

Mean relative cerebral blood volume and mean relative cerebral blood volume increased significantly from baseline to 4 hours and 24 hours in the NBO group, but not in the control group; mean relative cerebral MTT showed no significant change over time in either group (Figure 4).

Discussion

In this study, high-flow oxygen therapy started within 12 hours after onset of ischemic stroke transiently improved clinical function and MRI parameters of ischemia. Treatment benefit was most evident at 4 hours (during therapy) when there was no evidence for arterial recanalization—a factor associated with DWI improvement.[22] However, some benefit persisted at 24 hours and at 1 week, perhaps related to subsequent reperfusion and/or direct effects of oxygen therapy. These positive results, despite small patient numbers, are different from earlier and larger clinical studies, probably because MTT>DWI "mismatch" was used as an inclusion criterion. This imaging pattern is believed to indicate the

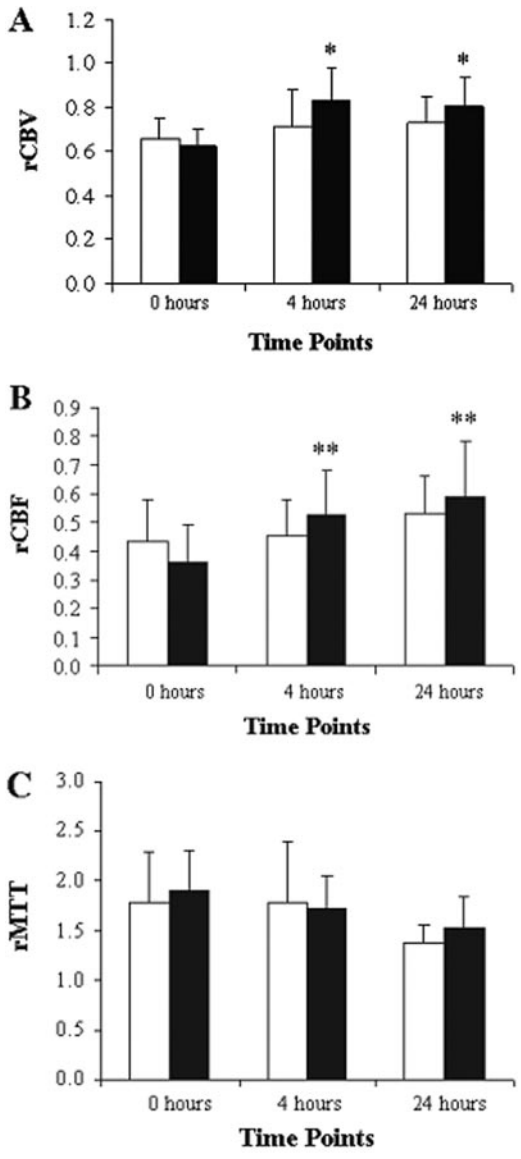

Figure 4. Relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), and relative MTT (rMTT; normalized values, mean±SD) from brain regions showing visible rMTT prolongation at baseline. These parameters were not significantly different between groups at any time point; however, in the NBO group, rCBV and rCBF increased significantly (*$P<0.01$; **$P<0.05$) over baseline values. Controls, white bars; NBO, black bars.

presence of penumbral tissue, or the target tissue for neuroprotection. An increasing number of stroke therapeutic trials using this selection criterion are reporting success.[23] Whereas further studies are mandated to investigate NBO's therapeutic time window, optimum duration, and effects in different stroke subtypes, the results of the present study indicate that by delaying ischemic necrosis, NBO might have utility as a stroke therapy, particularly as an adjunctive therapy that widens the time window for reperfusion and other neuroprotective therapies, and that multiparametric MRI can effectively quantify neuroprotection.

Clearly, larger studies are needed to validate these preliminary results. Nevertheless, this is among the first studies (similar to the citicholine trial[24]) demonstrating similar neuroprotection in humans as previously obtained in animals.[4,16,17] The concordance between changes in clinical and MRI measurements, and their temporal correlation with NBO exposure (Figure 1A), provides substantial evidence that NBO is beneficial if administered for short durations after acute hemispheric stroke. Although the degree and durability of clinical improvement was greater than anticipated, similar good outcomes were observed in the "sham control' group (treated with 100% oxygen at normal atmospheric pressures) of a recent HBO clinical trial.[12,25] Clinical and radiological improvement occurred relatively late (the median time from symptom onset to second MRI was 12 hours), suggesting that in patients with mismatch, NBO can ameliorate ischemic necrosis beyond the present thrombolytic time window.

Hyperoxia induces vasoconstriction in normal brain tissue. However, in this study, hyperoxia increased relative cerebral blood volume and relative cerebral blood volume within areas of initial MTT abnormality, consistent with results of our rodent experiments.[4] Previous clinical studies have documented paradoxical vasodilatation in the ischemic brain after oxygen exposure.[26] Overall, these data suggest a novel neuroprotective mechanism for hyperoxia: shunting of blood from nonischemic to ischemic brain tissues.

Hyperoxia therapy can decrease respiratory drive in patients with chronic lung disease, decrease cardiac output, and increase systemic vascular resistance.[27] Decades of research have emphasized the harmful tissue effects of oxygen free radical injury.[28] Our preclinical studies indicate that hyperoxia's benefit in reducing infarct volume outweighs the risk of enhanced free radical injury.[16] Similarly, in this study, we found no evidence for clinical or radiological worsening with NBO. Four NBO-treated patients had asymptomatic petechial postischemic hemorrhage, raising the possibility that oxygen worsened reperfusion injury. However, such hemorrhages have been correlated with successful recanalization (as in 3 of 4 patients in this study), reduced infarct size, and better clinical outcomes.[29]

At present, stroke patients receive variable amounts of oxygen in the ambulance and current guidelines do not support the routine use of in-hospital oxygen.[18] An observational study found worse 1-year survival in patients with mild-to-moderate stroke who received oxygen.[30] However, in that study, a substantial proportion of "treated" patients did not receive oxygen, low doses (3 L/min) of oxygen were administered for as long as 24 hours, the time to therapy was relatively late, and 12.7% had primary brain hemorrhage. In light of our preclinical and clinical experiences, we believe that further studies are promptly needed to investigate the utility of high-flow oxygen in acute ischemic stroke (both in the prehospital setting and as an adjunctive therapy with tPA), and to determine the optimum duration of therapy. NBO may ultimately prove to be a simple, widely accessible, and potentially cost-effective therapeutic strategy that improves stroke outcomes around the world.

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