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REVIEW

Normobaric Hyperoxia Therapy in Treating Stroke

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Abstract: Normobaric hyperoxia (NBO) is a standard oxygenation intervention for various conditions/diseases including stroke. The present review summarizes the current literature addressing the neuroprotective mechanisms of NBO in acute ischemic stroke (AIS), intracranial hemorrhage, and chronic cerebral ischemia, as well as its combination with other therapies to identify a more appropriate and effective NBO treatment method and to benefit more patients in clinical settings. The primary mechanism of action of NBO is the elevation of the interstitial partial pressure of oxygen in arterial blood (PaO_2) in brain tissue. NBO preconditioning yields moderate production of free radicals before AIS, which can increase antioxidant enzyme production, alter mitochondrial membrane lipids, increase tumor necrosis factor-alpha (TNF-α) converting enzyme levels, stimulate the hypoxia-inducible factor signaling pathway, upregulate glutamate transporters, Na^+–Ca^+ exchanger, and the metabotropic glutamate receptor after AIS, thus conferring neuroprotection to brain tissue. NBO postconditioning benefits AIS by protecting the penumbra and extending the recanalization time window, indicating that reperfusion is critical for the beneficial effects of NBO. Some previous clinical trials have obtained negative results because they enrolled non-reperfused cohorts. Given penumbra protection, NBO can enhance the efficacy of recanalization therapy, including thrombolysis and endovascular treatment. Clinical studies have indicated that NBO benefits only patients with reperfusion, which is consistent with animal-based research. NBO combined with medications, such as ethanol, minocycline, and edaravone, can more effectively treat AIS than NBO alone. Moreover, NBO demonstrates promise for the treatment of intracranial hemorrhage and chronic cerebral ischemia. NBO is a safe and effective therapy for stroke; however, eligible populations should be restricted to those with penumbra or ischemic and hypoxic brain tissues.

Keywords: normobaric hyperoxia, ischemic stroke, hemorrhagic stroke, penumbra

Introduction

Normobaric hyperoxia (NBO), supplied via cannula or facemask (eg, simple mask) at 1 atmosphere pressure (101.325 kPa), is a standard oxygenation intervention used for various conditions/diseases, particularly stroke.[1–3] Oxygen can easily diffuse across the blood-brain barrier (BBB) to rapidly increase oxygen concentration in brain tissue.[4] Although long-term oxygen supplementation is harmful to organs, short durations or intermittent use is safe, well tolerated, and effective in various populations.[5,6] In those diagnosed with acute ischemic stroke (AIS), the primary goal of NBO is to protect the penumbra from infarction. It is well-established that NBO can significantly increase the interstitial partial pressure of oxygen in arterial blood (PaO_2) close to the pre-ischemic level in the ischemic penumbra, but not in the core.[7,8] In theory, high oxygen concentration(s) contribute to oxidative stress-related injury; however, oxygen therapy does not appreciably increase oxygen radical generation and damage in cerebral ischemia.[9] Regarding clinical settings, a large body of retrospective research indicates that increasing the oxygenation index in patients diagnosed with AIS is

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associated with lower in-hospital mortality.[10] The advantages of NBO in treating AIS are clear. Based on the protective efficacy of NBO on the penumbra in AIS, NBO may not only mitigate hypoxic damage in perihematoma in intracranial hemorrhage (ICH), but also reduce chronic injury in ischemic hypoxic brain tissue in chronic cerebral ischemia (CCI).[11,12] Moreover, given the mechanisms of NBO in treating ischemic stroke, recanalization or reflow within a short period is critical to the protective process. As such, selecting the most appropriate methods and suitable population(s) is very important for effective NBO treatment of stroke. Accordingly, the present review summarizes the current literature addressing the neuroprotective mechanisms of preconditioning and postconditioning NBO in stroke (AIS, ICH, and CCI), as well as its combination with other therapies, to identify a more appropriate and effective NBO treatment method and to benefit more patients in clinical settings.

The Time Course of Normobaric Hyperoxia on Acute Ischemic Stroke

Preconditioning with Normobaric Hyperoxia on Acute Ischemic Stroke

Ischemic tolerance is an important mechanism for protecting the brain tissue from severe ischemia. NBO preconditioning can also relieve ischemic injury in the brain tissue. Extensive research by Bigdeli et al demonstrated that pre-ischemic intermittent NBO—rather than prolonged exposure to hyperoxia—can simulate the moderate production of oxygen-free and hydroxyl radicals.[13] Repeated sublethal injuries increases antioxidant enzyme production (superoxide dismutase, catalase, glutathione peroxidase, peroxidase, and glutathione reductase), which play a pivotal role in brain ischemic tolerance.[13–15] Moreover, during both ischemia and reperfusion (I/R), a large amount of free radicals is produced in the brain, leading to incremental changes in mitochondrial membrane lipids. The elevation of mitochondrial membrane lipids causes mitochondrial decay, failure of the electron transmission chain, and inhibition of energy production, ultimately leading to cell death.[16] NBO preconditioning induces changes in the brain lipidome, including cholesterol ester, triglyceride, lysophosphatidylcholine, phosphatidylethanolamine, phosphatidylcholine, ceramide, cerebroside, cholesterol and sphingomyelin, all of which prevent free radical-induced injury.[17]

Preconditioning with NBO upregulates glutamate transporters (EAAT1, EAAT2 and EAAT3) in the rat brain.[18,19] Glutamate transporters in neurons and glia remove glutamate from the extracellular space, preventing the concentration of extracellular glutamate from increasing to neurotoxic levels.[20,21] Inhibition of the glial glutamate transporter EAAT2 aggravates brain edema after transient focal cerebral ischemia in rats.[19] Glutamate is highly expressed in the core and penumbra of cerebral infarction, where it over-activates ionotropic glutamate receptors (NMDA and AMPA) causing an influx of calcium (Ca^{2+}) and sodium (Na^{+}) ions. This process facilitates protease activation, lipase activation, free-radical increase, altered transcription, protein kinase C activation, hydrolysis of protein phosphatase inhibitor, and cell swelling, ultimately leading to subsequent cell death.[22] Therefore, the elevation of glutamate transporters induced by NBO preconditioning can prevent brain tissue from glutamate-induced injury. Simultaneously, NBO preconditioning can also upregulate the Na^{+}–Ca^{+} exchanger (NCX family, NCX1, NCX2 and NCX3), which can reduce the extent of brain infarct volume after brain ischemia.[23,24] NBO preconditioning has another effect on upregulating both metabotropic glutamate receptor (mGluR) I and II.[25] mGluR I and II are associated with oxidative stress in the brain.[26] Increased mGluR I and II lead to an increment in glutathione levels that exert neuroprotection on the ischemic brain after intermittent NBO treatment.[25] Furthermore, NBO preconditioning increases tumor necrosis factor-alpha (TNF-α) converting enzyme (TACE) expression, consistent with a protective role for TNF-α release.[18,19] TACE expression contributes to a rise in TNF-α, which participates in the development of ischemic tolerance after excitotoxic stimuli.[27,28] As mentioned, NBO-induced upregulation of glutamate transporters may, in part, be mediated by the TACE/TNF-α pathway.[18,29] NBO preconditioning also stimulates the hypoxia-inducible factor (HIF) signaling pathway, causing increased expression of vascular endothelial growth factor (VEGF) and erythropoietin.[30] The HIF signaling pathway regulates neurogenesis and angiogenesis through increased VEGF and erythropoietin, leading to neural stem cell proliferation and migration of neural progenitors.[31,32]

The interval between the initiation of preconditioning NBO therapy and the onset of ischemic stroke significantly affects the neuroprotective effects conferred by NBO. Specifically, ischemia occurring 15 days after the completion of intermittent NBO preconditioning is associated with higher Neurological Deficit Score, larger infarct volumes, and

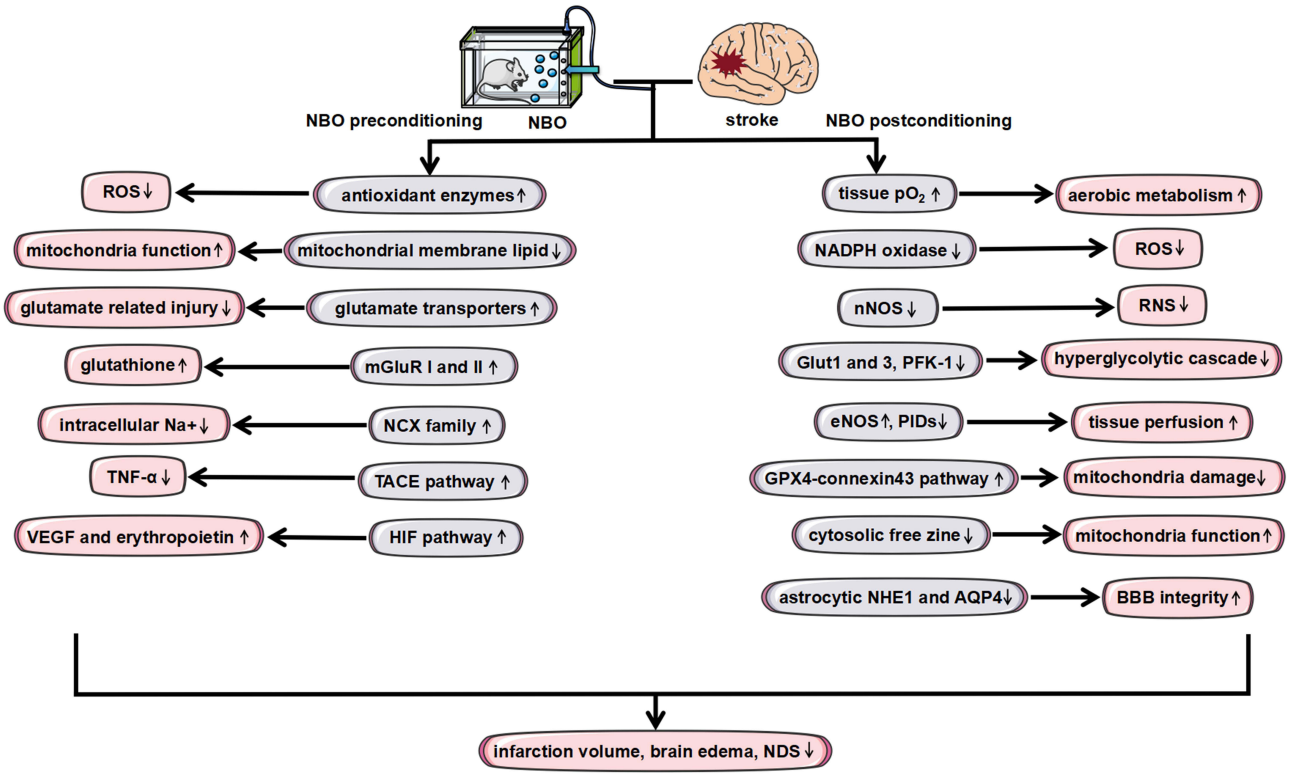

Figure 1 Mechanisms of normobaric hyperoxia (NBO) therapy in acute ischemic stroke (AIS). NBO preconditioning increases antioxidant enzyme production, alters mitochondrial membrane lipids, increases tumor necrosis factor-alpha (TNF-α) converting enzyme levels, stimulates the hypoxia-inducible factor signaling pathway, and upregulate glutamate transporters, Na^+–Ca^+ exchanger, and metabotropic glutamate receptor after AIS. NBO postconditioning can reduce infarction volume, improve metabolism, increase tissue perfusion, reduce free-radical generation, ameliorate hyperglycolytic cascades, maintain mitochondrial function, and preserve blood-brain barrier integrity. Both NBO preconditioning and postconditioning reduce infarction volume, ameliorate brain edema, and improve neurological deficits.

increased cerebral edema compared with ischemia occurring merely 2 days post-treatment.[33] These findings suggest that, while NBO preconditioning induces effective neuroprotection, its benefits are transient, potentially due to a gradual decline in the antioxidant response and ischemic tolerance induced by preconditioning therapy. In summary, the primary mechanistic goals of NBO preconditioning in the treatment of AIS are to decrease oxidative stress-related injury, reduce glutamate-induced damage, and stimulate neurogenesis and angiogenesis after an ischemic attack (Figure 1). NBO therapy may represent a promising approach for both primary and secondary prevention of ischemic stroke. However, clinical trials remain scarce despite a substantial body of animal-based research supporting the effectiveness of pre-ischemic NBO treatment.

Effect of Normobaric Hyperoxia Postconditioning on Acute Ischemic Stroke

NBO is routinely performed after stroke in clinical settings. Therefore, animal studies investigating the effects of post-ischemic NBO are considered to be more relevant for guiding clinical treatment. It is widely recognized that NBO yields significant efficacy in reducing infarct volume, especially in ischemic models with reperfusion.[34–37] In other words, the primary neuroprotection conferred by NBO is to extend the reperfusion window and offer lasting tissue protection in temporary ischemia.[38] Kim et al indicated that NBO widened the reperfusion time window in rats by up to 2 h without increasing superoxide radical generation. However, the benefit of NBO is not sustained in permanent ischemia.[39,40] Thus, NBO may be the most appropriate adjunct therapy to extend the time window for recanalization treatment (thrombolysis and endovascular treatment [EVT]), rather than routine medical treatment.[39]

Using magnetic resonance imaging (MRI), Singhal et al demonstrated that NBO can enhance aerobic metabolism, preserve neuronal integrity and reduce MRI abnormalities in the ischemic brain.[41–44] Given the efficacy in increasing interstitial PaO_2 in the penumbra, other studies have shown that NBO significantly reduces ADP/ATP ratio, reactive

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oxygen species (ROS) levels, and tissue acidosis after AIS, indicating restoration of impaired energy metabolism.[45,46] Moreover, the expression of glucose transporters 1 and 3 (Glut1 and 3) and the glycolytic rate-limiting enzyme phosphofructokinase-1 (PFK-1), which results in hyperglycolytic cascade, are attenuated by NBO via AMPK signaling.[45]

In addition to elevating interstitial PaO_2 in the penumbra, NBO can also augment or preserve tissue perfusion.[8,36,41,42,44,47,48] The mechanism of improved ischemic tissue perfusion by NBO may be attributed to enhanced nitric oxide (NO) production by endothelial NO synthase (eNOS) through O_2 substrate availability, suppression of peri-infarct depolarization, and vasoconstrictive effects on circulation in the penumbra.[47,48]

NADPH oxidase is known to produce ROS after cerebral I/R.[49] The NADPH catalytic subunit gp91phox (or Nox2) is critically implicated in AIS and knockout of Nox2 results in significant reduction of NADPH oxidase activity during ischemia.[50,51] It has been demonstrated that NBO can attenuate Nox2-containing NADPH oxidase, which is an important mechanism underlying NBO-afforded brain protection.[51–55] Through inhibiting NADPH oxidase, NBO treatment can relieve oxidative stress-related injury, suppress matrix metalloproteinase-9 (MMP-9) induction and inhibit the degradation of occludin, attenuating of disruption of the BBB and the development of edema in the brain.[8,51,53,56–58] Under ischemic conditions, several proposed mechanisms are associated with the activation of Nox2, such as phosphatidylinositol 3-kinase (PI3K)/Akt pathways, inflammatory cytokines and metabotropic glutamate receptors.[59–61] NBO treatment reduces reperfusion injury through activation of the PI3K/Akt pathway.[62] In addition to oxygen radicals, other free radicals, such as reactive nitrogen species—formed by the reaction of NO with superoxide under ischemic conditions—is also alleviated by NBO via suppressing neuronal NO synthase.[63] By retarding free-radical generation, NBO can relieve ischemic damage, micro-circulation failure, and tissue inflammation.

NBO also has a beneficial effect on mitochondria. NBO alleviates ischemia-induced cytochrome c (CytC) release from mitochondria through stimulating the GPX4-connexin[43] pathway in astrocytes.[64] As such, NBO can reduce mitochondrial damage by maintaining redox homeostasis in astrocytes, rather than increasing oxidative stress.[64] Furthermore, NBO can also reduce cytosolic free zinc accumulation in the penumbra and suppress zinc overload in mitochondria after ischemic stroke, which improve mitochondrial membrane potential and, ultimately, protect neurons in the penumbra.[65] Mitochondrial integrity maintains cell survival. Therefore, NBO attenuates autophagy, which is over-activated by I/R.[66] Meanwhile, NBO decreases caspase-8 cleavage in the penumbra during I/R.[8]

The membrane proteins Na^+/H^+ exchanger 1 (NHE1) and aquaporin 4 (AQP4) play a pivotal role in the development of brain edema after ischemia.[67] NHE1 is associated with H^+ extrusion in exchange for Na^+ in astrocytes, which maintain BBB function.[68] Excessive NHE1 activation during ischemia is crucial for Na^+ overload, resulting in Ca^{2+} entry via reversal of the Na^+/Ca^{2+} exchanger (NCX).[69] The increased cytosolic Ca^{2+} triggers a neurotoxic cascade.[68,69] Similarly, AQP4, which is mainly expressed in perivascular astrocyte end-feet, is also associated with BBB function.[70] Increased AQP4 level(s) can destroy BBB integrity, leading to water entering brain tissues, resulting in brain edema.[71] NBO is capable of retarding exacerbation of brain edema through suppressing the expression of NHE1 and AQP4.[72]

Similar to NBO preconditioning, the timing and method of NBO post-conditioning also affect neuroprotection. Compared with NBO initiated during ischemia, NBO delivered during reperfusion is unlikely to have a protective impact and may even exacerbate neuronal injury and death in brain tissue, despite reducing excitotoxic calcium influx and subsequent degeneration.[8,73] Liu et al reported that intermittent NBO (oxygen oscillation) during ischemia yielded more neuroprotection than continuous or short NBO.[62] Therefore, intermittent NBO starting during ischemia is critical to maximize its benefit for patients diagnosed with AIS. The mechanisms of NBO postconditioning are described in Figure 1.

The efficacy of NBO in cerebral ischemia has been tested in multiple clinical trials; however, the results have been disappointing (Table 1).[6,42,43,58,74–85] We and other teams have analyzed the existing literature, and the secondary analysis revealed limited evidence supporting NBO for the treatment of stroke.[86,87] Studies investigating the effect of NBO on AIS imaging tests have reached beneficial conclusions; however, those investigating the effect of NBO on the clinical neurological and functional scores of patients without recanalization therapies have reached negative—or even harmful—conclusions. In addition, studies enrolling patients undergoing recanalization therapies, including thrombolysis and EVT, especially those diagnosed with anterior circulation AIS, have demonstrated the beneficial effects of NBO. Confirmation of the null hypothesis has been due to most enrolled patients not achieving reperfusion during NBO. As

Table 1 The Efficacy of NBO in Clinical Studies

Study	Design	Sample Size	Populations	NBO Protocol	Outcomes	Efficacy
Rønning, 1999[75]	RCT	292/258	Stroke onset<24 hours	100%O_2, 3L/min, 24 hours	SSS; BI; Mortality	Harmful
Singhal, 2005[42]	RCT	9/7	AIS onset<12 hours	100%O_2, 45L/min, 8 hours	NIHSS; SSS; mRS; MRI test	Beneficial
Chiu, 2006[76]	Pilot study	17/29	Middle cerebral artery infarction onset<48 hours	40%O_2	Mortality	No improved
Singhal, 2007[43]	Pilot study	4/2	AIS onset<12 hours	100%O_2, 45L/min, 8 hours	MRI test; lactate	Beneficial
Padma, 2010[77]	RCT	20/18	AIS onset<12 hours	100%O_2, 10L/min, 12 hours	NIHSS; mRS; BI; MRI test	No improved
González, 2010[78]	RCT	8/6	AIS onset<12 hours	100%O_2, 45L/min, 8 hours	MRI test	Beneficial
Roffe, 2011[79]	RCT	148/141	Stroke onset<24 hours	100%O_2, 2L/min or 3L/min, 72 hours	NIHSS; GCS	No improved
Wu, 2012[80]	RCT	10/6	AIS onset<12 hours	100%O_2, 45L/min, 8 hours	MRI test	Beneficial
Ali, 2014[81]	RCT	148/141	Stroke onset<24 hours	100%O_2, 2L/min or 3L/min, 72 hours	mRS; BI; Motality	No improved
Mazdeh, 2015[82]	RCT	26/25	Stroke onset<12 hours	50%O_2, 12 hours	mRS; BI; Mortality	Beneficial
Roffe, 2017[6]	RCT	2668/2668	Stroke onset<24 hours	100%O_2, 2L/min or 3L/min, 72 hours	mRS; BI; Mortality	No improved
Shi, 2017[58]	RCT	9/9	AIS with thrombolysis	100%O_2, 10L/min, 4 hours	NIHSS	Beneficial
Li, 2021[83]	Retrospective study	125/102	AIS with thrombolysis	100%O_2, 10L/min, 4 hours	NIHSS; mRS; MRI test	Beneficial
Cheng, 2021[84]	RCT	88/87	Anterior circulation AIS with vessel recanalization	50%O_2, 15L/min, 6 hours	NIHSS; mRS; MRI test	Beneficial
Cheng, 2022[85]	RCT	44/43	Posterior circulation AIS with vessel recanalization	50%O_2, 15L/min, 6 hours	NIHSS; mRS; MRI test	No improved
Li, 2022[74]	RCT	43/43	Anterior circulation AIS with vessel recanalization	100%O_2, 10L/min, 4 hours	NIHSS; mRS; MRI test	Beneficial
Li, 2025[88]	RCT	140/142	Anterior circulation AIS with vessel recanalization	100%O_2, 10L/min, 4 hours	NIHSS; mRS; MRI test	Beneficial

Abbreviations: RCT, randomized controlled trial; AIS, acute ischemic stroke; SSS, Scandinavian stroke score; BI, Barthel index; NIHSS, National Institute of Health Stroke Scale; mRS, modified rankin scale.

discussed, the primary mechanistic goal of NBO is to "freeze the penumbra"; therefore, without blood retention, NBO cannot inhibit infarction expansion. Imaging tests assess perfusion and metabolism, revealing the effects of NBO on the brain tissue during the acute phase of AIS. Without reperfusion after the acute phase, the penumbra progresses to an infarction, thus eliminating the neuroprotective effects of NBO. When reperfusion occurs through recanalization therapies, the penumbra protected by NBO changes to normal brain tissue, thereby enhancing the neuroprotective effect of NBO. Therefore, reperfusion therapy alone may enhance the efficacy of NBO in cerebral ischemia.

Combining Normobaric Hyperoxia with Other Adjuvant Therapies in Acute Ischemic Stroke

Adjuvant Use of Normobaric Hyperoxia in Intravenous Thrombolysis

Considering the neuroprotective role of NBO in the ischemic penumbra and BBB, it is considered to be an ideal adjunct therapy to improve the efficacy and safety of tissue-type plasminogen activators (tPA). The most important effect of NBO on ischemia is the expansion of the therapeutic time window for successful reperfusion during tPA treatment, especially under delayed tPA administration. Animal studies have demonstrated that early NBO treatment could slow the evolution of ischemic BBB damage, decrease MMP-9 production, and reduce the loss of tight junction proteins (TJPs), leading to significant neurological improvement and reduced infarction volume, brain edema, cerebral hemorrhage and mortality after delayed tPA treatment.[54,89–91] Imaging studies have revealed that 60 min NBO treatment before thrombolysis could reduce infarct size and decrease the frequency of gross parenchymal hemorrhage by reducing early BBB permeability and improving microvascular integrity after tPA-induced reperfusion.[92] In clinical settings, a retrospective study found that NBO combined with intravenous thrombolysis could reduce infarct volume and improve long-term outcomes.[83]

However, a prospective or randomized controlled trial is lacking. The OPEN-3 clinical trial is an ongoing multicenter, randomized, controlled Phase III study in China that aims to evaluate the safety and efficacy of NBO in patients undergoing intravenous thrombolysis (NCT05965687). We anticipate that these results will further consolidate evidence supporting the effect of NBO on ischemic stroke.

However, other studies have reported conflicting results. Fujiwara et al did not find a beneficial effect of NBO on augmenting the efficacy of tPA thrombolysis and noted no induced cerebral hemorrhage or edema after NBO.[93] David et al indicated that combining NBO and tPA exacerbated ischemic brain damage and swelling compared with NBO or tPA alone, because NBO facilitated the catalytic and thrombolytic efficiency of tPA; the synergistic effect of combined NBO and tPA may worsen brain injury.[94] Notably, NBO combined with tPA performed after reperfusion could induce oxidative stress-related injury, particularly in cases with severe infarction, which may lead to brain edema and hemorrhagic transformation. Therefore, NBO should be initiated during the ischemic phase regardless of tPA administration.

Adjuvant Use of Normobaric Hyperoxia in Endovascular Treatment

Because the penumbra can potentially be rescued if blood flow is restored in a timely manner, NBO may serve as an early intervention to preserve the penumbra and "buy time" for combination therapies to achieve better outcomes.[38,95] As mentioned, whether early or late use of NBO, if cessation of blood supply is relieved, NBO can reduce the final infarction volume. Therefore, patients with AIS receiving rapid blood flow restoration through EVT appear to be more suitable for NBO treatment in clinical settings. Recent randomized controlled trials revealed that NBO therapy (100% O_2 via a face mask, 10 L/min) for 4 h in patients who underwent EVT, can significantly reduce the infarction volume within 24–48 h and result in lower modified Rankin Scale (mRS) scores at 90 days. In addition, the safety of NBO is also satisfactory, as the incidences of ICH, death, and other adverse events were similar to those without NBO.[74,88] Serum assessments find that NBO can maintain BBB integrity and reduce brain injury in patients with AIS undergoing EVT.[96] Further dose-escalation study demonstrated that NBO therapy for 4 and 6 hours appeared to be more effective.[97] Another earlier randomized controlled trial reached a similar conclusion using a different NBO protocol (50% O_2 via a face mask, 15 L/min) started after vessel recanalization and continued for 6 h. The trial revealed that NBO could improve the degree of 90-day disability, decrease 90-day mortality, and profoundly reduce 24 h infarction volume, without increasing adverse events.[84] Although these trials obtained a favorable conclusion, it is noteworthy that they only enrolled patients with anterior circulation stroke, excluding those with posterior circulation stroke. Only 1 randomized trial currently focuses on NBO after EVT for posterior circulation stroke; however, despite using the same NBO treatment paradigm, it only found a trend, rather than a significant effect of NBO in this cohort.[85] The reason for the different effectiveness of NBO on anterior and posterior circulation stroke after EVT remains unknown. We considered that this may be because the brainstem has a smaller penumbra than the hemisphere or basal ganglia due to the smaller infarction volume in posterior circulation stroke. The small penumbra limits salvage of the ischemic brain tissue and further suppresses the efficacy of NBO. Therefore, we believe that NBO is an appropriate treatment strategy for patients undergoing EVT, especially those with anterior circulation stroke.

Nevertheless, opposing viewpoints exist. The primary mechanism of action of NBO treatment for AIS involves elevated PaO_2. In other words, a high PaO_2 appears to confer beneficial neuroprotective effects against AIS. However, a prospective observational study found that patients with admission $PaO_2 > 120$ mmHg experienced worse functional outcomes and higher mortality at 90 days after EVT compared to those with admission $PaO_2 \leq 120$ mmHg.[98] It should be noted that the oxygen therapy in this study was in the form of mechanical ventilation, which is completely different from NBO. Additionally, this was an observational study that included all consecutively admitted patients, rather than a randomized grouping and intervention. These 2 points could have biased the results toward the null hypothesis.

Combining Normobaric Hyperoxia with Medication

Several studies have investigated whether other adjuvant therapies can enhance the efficacy of NBO in AIS. Ethanol therapy is a candidate for combination therapy.[99] Cai et al found that combined NBO and ethanol therapy modulated pyruvate dehydrogenase, demonstrated by upregulated pyruvate dehydrogenase complex (PDH) and downregulated pyruvate dehydrogenase kinase (PDK).[100] The combined therapy also decreased lactic acidosis, Glut1, Glut3, PFK-1

and lactate dehydrogenase (LDH), indicating hyperglycolysis was suppressed.[101] In addition, the combination therapy inhibits PKC-Akt-NOX pathway and reduces cerebral monocarboxylate transporters.[102,103] All of the aforementioned mechanisms stabilize anaerobic metabolism, decrease oxidative damage and retard cell apoptosis, thus improving neurological deficit and reducing infarct volume.[91,100–106]

Minocycline is another treatment that combines NBO and ischemic stroke. Jin et al found that, compared with NBO or minocycline alone, combination treatment significantly reduced infarction volume and hemispheric swelling by reducing the levels of MMP-2, MMP-9, caspase-9 and caspase-3.[107] Other adjuvant drugs, such as N-acetylcysteine, edaravone, cilostazol, melatonin, and methylene blue, have been shown to reduce infarction volume, protect BBB integrity, and improve neurological deficits; however, the supportive evidence is weak.[108–112]

Normobaric Hyperoxia Used in the Treatment of Intracranial Hemorrhage

Theoretically, ICH-induced mechanical compression of the surrounding brain tissue is a major injury that can decrease aerobic metabolism and perfusion in the perihematoma, causing edema and even enlarging the hematoma. Similar to the ischemic penumbra, low perfusion and abnormal metabolism in the perihematoma exposes brain tissue to an ischemic hypoxic condition. Therefore, rescue of the perihematoma is key for treating ICH for which NBO may be a promising therapeutic candidate.[113] Zhou et al demonstrated that initiating NBO 30 min after inducing ICH significantly reduced hemorrhage volume, mitigated the development of post-hemorrhagic edema, and preserved BBB integrity, whereas NBO initiated at 60 min or 120 min yielded no beneficial effects.[114,115] NBO appears to attenuate the post-hemorrhagic breakdown of occludin, inhibit the activation of MMP-9 and suppress the upregulation of HIF-1α, collectively contributing to the reduction of hemorrhage volume and stabilization of the BBB. Similar to the ischemic puncture, perihematomal tissue exhibits a critical therapeutic window. Delayed NBO therapy may be effective or even detrimental because progressive injury to the perihematomal region and NBO-induced increases in intracellular oxygen levels in damaged cells can enhance ROS production, thereby exerting deleterious effects. Furthermore, given that MMPs and HIF-1α are involved in acute pathophysiological responses and extracellular matrix remodeling, as well as angiogenesis and neurogenesis during the delayed phase of brain injury, delayed inhibition of these pathways may evoke deleterious effects.[114,116,117] In addition, NBO also suppresses VEGF expression, which may inhibit cellular apoptosis potentially through the VEGF/PI3K/Akt/FoxO1 pathway.[118,119] NBO can effectively decrease the level of C3 which is able to rescuing microglia-mediated synaptic pruning after ICH.[120] There is no published clinical trial; however, a single-center, randomized controlled Phase II trial from our team registered a clinical trial (Clinicaltrials.gov, NCT04144868) that revealed the beneficial effect of NBO on ICH in clinical settings. Our findings indicate that early and intermittent administration of NBO in patients with ICH significantly improves 90-day prognosis, likely due to a reduction in perihematoma edema induced by NBO therapy. A small sample size, however, renders the study underpowered and restricts its clinical scope. As such, a well-designed, multicenter, randomized, controlled phase III trial is warranted to draw more convincing conclusions. NBO appears to be a promising approach to treating ICH, and more studies should be conducted to verify this conclusion.

Normobaric Hyperoxia Used in the Treatment of Chronic Cerebral Ischemia

CCI is a pathological condition induced by a persistent reduction in cerebral perfusion, leading to ischemia and hypoxia in brain tissue. CCI can cause various brain dysfunctions such as dizziness, cognitive impairment, and stroke.[121,122] Cerebrovascular atherosclerotic stenosis is the most common pathogenesis of CCI, with hypoperfusion being a pivotal mechanism accounting for these neurological deficits.[122,123] In theory, low cerebral blood flow in patients with CCI exposes the brain tissue to an ischemic-hypoxic condition, which is similar to that in the ischemic penumbra in brain infarction.[121] Therefore, given the satisfactory effectiveness of NBO on the penumbra in AIS, NBO may also yield beneficial effects on the ischemic-hypoxic brain tissue. Based on previous animal and clinical studies focusing on NBO in AIS, we hypothesize that NBO may also be a novel approach to the treatment of CCI.[12] To verify this, we evaluated the improvement of brain dysfunction in patients with CCI treated with NBO. Electroencephalography revealed that NBO rapidly ameliorated CCI-mediated brain wave anomalies, including

reduced abnormal high-power oscillations and slow paroxysmal activity associated with CCI, which may improve vascular cognitive impairment.[124]

Aside from cerebral arterial stenosis-mediated CCI, a form of CCI associated with cerebral venous stenosis has recently been proposed.[125–127] Venous outflow disturbance raises the pressure in arterio-venous anastomoses, thereby affecting arterial blood flow and volume.[128,129] Consequently, cerebral venous outflow disturbance may result in global brain hypoperfusion and elevated aerobic metabolism, a pattern similar to that observed in arterial stenosis-related CCI.[126] NBO therapy can elevate cerebral tissue pO2 and may ameliorate cerebral venous outflow disturbance-related deficits, especially headache and electroencephalogram brain dysfunction.[130] Current animal and clinical investigations of NBO for CCI are fewer than those for AIS; however, CCI populations are larger. Although we found preliminary beneficial effects of NBO, more studies are warranted to unravel mechanisms and determine effectiveness. CCI etiologies can be classified as large artery atherosclerotic stenosis, small arterial stenosis or occlusion, cardiogenic hypoperfusion, cerebral venous outflow disturbance, and other causes. Future NBO trials should stratify cohorts according to these subtypes.[121]

Conclusions

Although existing research remains at a relatively superficial level, we summarize the therapeutic mechanisms of NBO into 2 points. First, NBO elevates pO2 in the penumbra of AIS, as well as in perihemotoma of ICH and hypoxic-ischemic tissue of CCI, which reduces ischemia volume, improves metabolism, protects BBB integrity, and maintains mitochondrial function, thus expanding the therapeutic time window. Second, NBO increases the production of antioxidant enzymes and reduces free-radical generation, leading to alleviated oxygen stress-related injury in stroke. Reperfusion is critical for the beneficial effects of NBO in AIS. Therefore, only patients undergoing recanalization can benefit from NBO. Because aerobic metabolism plays a pivotal role in the NBO treatment of stroke, future research should emphasize the role of the mitochondria, particularly their involvement in mitophagy and fission/fusion dynamics. Given the heterogeneity observed in both animal and clinical studies, additional research is imperative to consolidate evidence supporting the effectiveness of NBO in treating stroke.

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Disclosure

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