Review article

Normobaric hyperoxia therapy in acute ischemic stroke: A literature review

Qijian Wang [1], Xiao Zhang [1], Yijun Suo [1,***], Zhiying Chen, Moxin Wu, Xiaoqin Wen, Qin Lai, Xiaoping Yin [**], Bing Bao [*]

Department of Neurology, The Affiliated Hospital of Jiujiang University, Jiujiang, China

A B S T R A C T

Background: Ischemic stroke is one of the most severe cerebrovascular diseases that leads to disability and death and seriously endangers health and quality of life. Insufficient oxygen supply is a critical factor leading to ischemic brain injury. However, effective therapies for ischemic stroke are lacking. Oxygen therapy has been shown to increase oxygen supply to ischemic tissues and improve prognosis after cerebral ischemia/reperfusion. Normobaric hyperoxia (NBHO) has been shown to have neuroprotective effects during ischemic stroke and is considered an appropriate neuroprotective therapy for ischemic stroke. Evidence indicates that NBHO plays a neuroprotective role through different mechanisms in acute ischemic stroke. Recent studies have also reported that combinations with other drug therapies can enhance the efficacy of NBHO in ischemic stroke. Here, we aimed to provide a summary of the potential mechanisms underlying the use of NBHO in ischemic stroke and an overview of the benefits of NBHO in ischemic stroke.
Methods: We screened 83 articles on PubMed and other websites. A quick review was conducted, including clinical trials, animal trials, and reviews of studies in the field of NBHO treatment published before July 1, 2023. The results were described and synthesized, and the bias risk and evidence quality of all included studies were assessed.
Results: The results were divided into four categories: the mechanism of NBHO, animal and clinical trials of NBHO, the clinical application and prospects of NBHO, and adverse reactions of NBHO.
Conclusion: NBHO is a simple, non-invasive therapy that may be delivered early after stroke onset, with promising potential for the treatment of acute ischemic stroke. However, the optimal therapeutic regimen remains uncertain. Further studies are needed to confirm its efficacy and safety.

1. Introduction

With the aging population, stroke has become a universal health problem and the second leading cause of death worldwide.

---

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: brianjju@163.com (Y. Suo), xiaopingbuxiao@126.com (X. Yin), baobing840608@163.com (B. Bao).
[1] co-first authors.

Ischemic stroke is characterized by acute onset, rapid disease change, high disability and mortality, and poor prognosis. Acute ischemic stroke (AIS) results in heterogeneous changes in cerebral blood flow (CBF) and brain metabolism in the affected region [1]. As the brain is susceptible to hypoxia, insufficient brain oxygen plays a crucial role in the primary and secondary events leading to neuronal cell death and damage [2–4]. Therefore, improving cerebral oxygenation is a reasonable treatment strategy for AIS. Specifically, normobaric hyperoxia (NBHO) is considered to be a good approach due to its potential clinical advantages. NBHO refers to the process of continuously administering oxygen to patients via a mask or oxygen hood under normal atmospheric pressure. The commonly utilized oxygen concentration is 40–100 % [5,6]. Studies have recently demonstrated that NBHO treatment effectively reduces infarct volume and neurological deficits in rodents following AIS [7–10]. Moreover, studies have found that NBHO treatment is associated with clinical deficiencies and improved survival in patients with AIS [11,12]. In addition, short-term NBHO therapy was found to have a high neuroprotective effect when commenced early after stroke onset [13–15]. NBHO therapy may play a role by improving brain metabolism, increasing CBF, reducing oxidative stress, and protecting microvessels [13–15]. As NBHO is inexpensive and non-invasive, it has the potential to be widely available and is easy to administer to patients with acute stroke by medical staff under different conditions, such as administration by paramedics or at home. Overall, there are many advantages of NBHO that make it an excellent treatment candidate for AIS. This review provides a summary of the potential mechanisms underlying the use of NBHO in ischemic stroke and an overview of the benefits of NBHO in ischemic stroke.

2. Methods

We screened 83 articles on PubMed and other websites. The website includes PubMed, Web of Science-SCI, CRS Core paper library and Elsevier Science Direct, with the key words of normobaric hyperoxia and acute ischemic stroke. After removing most of the literatures through titles and abstracts, some of them are of low quality, only abstracts are relevant, there is no valid information, and there is no peer-reviewed literature. A quick review was conducted, including clinical trials, animal trials, and reviews of studies in the field of NBHO treatment published before July 1, 2023. The results were described and synthesized, and the bias risk and evidence quality of all included studies were assessed (Fig. 1).
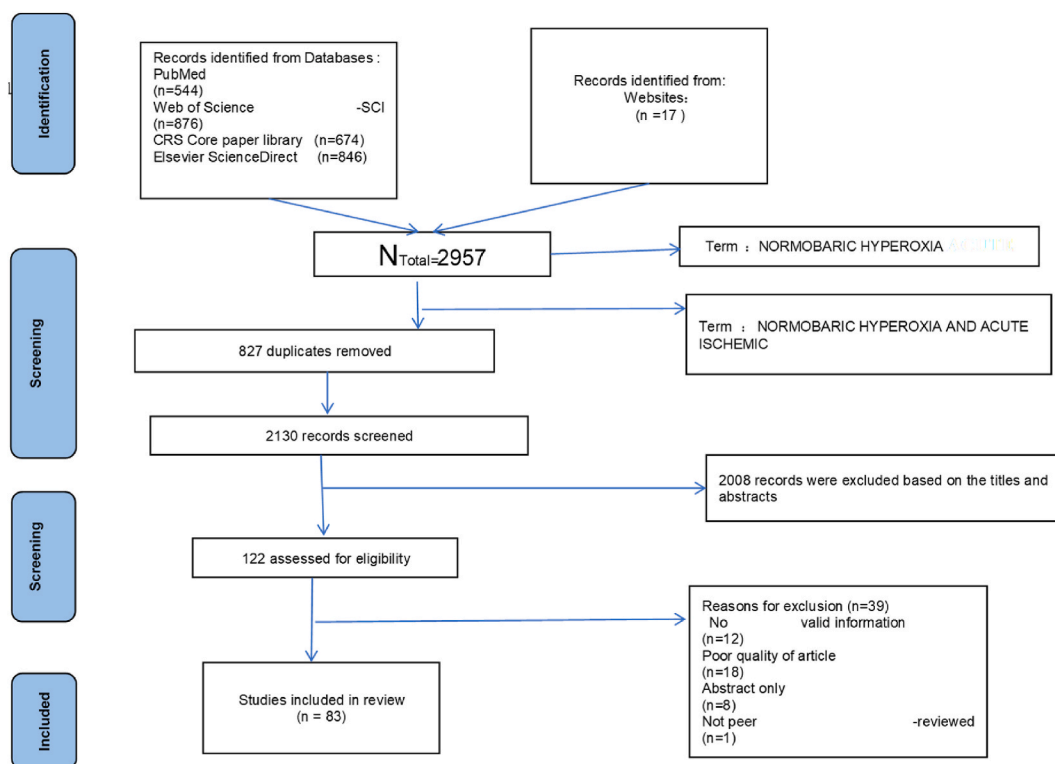

Fig. 1. The retrieval flowchart.

3. Results

3.1. Mechanisms underlying NBHO

3.1.1. Increasing the oxygen content of brain tissue and improving CBF

Liu et al. showed that NBHO treatment could maintain the oxygenation state of the ischemic penumbra close to the pre-ischemic level after ischemic stroke. NBHO significantly increased the partial pressure of oxygen in the penumbra, but not in the core area, and improved the oxygenation state of the penumbra, resulting in decreased reactive oxygen species (ROS) production, matrix metalloprotein-9 (MMP-9) expression, and caspase-8 production in the penumbra, considerably reducing the infarct volume and improving neurological function in a rat model of transient focal cerebral ischemia [16]. Shin et al. found that NBHO can increase the availability of oxygen to tissue and improve CBF during focal cerebral ischemia. NBHO can immediately increase the concentration of oxygenated hemoglobin in the ischemic core and improve the CBF of the ipsilateral cerebral cortex [17,18].

3.1.2. Improving mitochondrial function

Mitochondrial dysfunction is one of the main causes of secondary brain injury, leading to oxidative stress and energy deficiency, which results in brain cell apoptosis and necrosis [19]. NBHO can effectively increase the oxygen tension in brain tissue, which can increase the oxygen concentration around the mitochondria, facilitate aerobic oxidation to extract raw materials, enhance the activity of oxidoreductase in mitochondria, and increase aerobic metabolism [20]. After transient ischemic stroke, zinc plays a crucial role in the pathway of mast cell death through the accumulation of zinc in mitochondria. Furthermore, NBHO treatment can reduce the accumulation of cytosolic free zinc in the penumbra of rats with ischemic stroke and inhibit mitochondrial zinc overload. NBHO may prevent ischemic stroke by regulating the level of mitochondrial zinc [21].

3.1.3. Reducing damage to the blood-brain barrier

Ischemia/reperfusion-induced blood-brain barrier (BBB) injury is the leading cause of bleeding transformation after vascular recanalization [22,23]. However, some biomarkers are closely related to BBB damage, such as occlusive hormone and MMP-9. MMP-9-mediated occlusive degradation may be an essential mechanism of BBB damage in the early stage of transient focal cerebral ischemia. NBHO treatment can reduce the increase of MMP-9 and the degradation of occlusive hormone in ischemic BBB microvessels, thus significantly reducing early BBB destruction. In addition, it has been reported that ischemia/reperfusion-induced BBB injury leads to the increase of blood occlusive hormone in ischemic rats and patients with AIS after intravenous injection of tissue plasminogen activator (tPA). NBHO can downregulate blood occlusive hormone levels during ischemia/reperfusion in rats and humans and significantly improve neurological function [13,24]. Liang et al. found that early NBHO treatment can slow down the destruction of the BBB after ischemic stroke. NBHO may also protect the BBB by inhibiting the expression of *AQP4* and *NHE1* and reducing the degradation of a scaffold protein (TJP) [25,26]. NBHO can also reduce the damage caused by ischemic stroke by increasing the activity of antioxidant enzymes to change the permeability of the BBB [27].

3.1.4. Reducing oxidative stress

When the oxygen content in brain cells is too high or too low, it may trigger the production of ROS and lead to oxidative damage [28,29]. Increasing oxygen levels through standard oxygen therapy, particularly excessive oxygenation, may lead to oxidative stress and free radical damage. However, NBHO does not increase oxidative stress in treating ischemic stroke [10]. Instead, it may reduce the production of ROS [7]. Short-term NBHO treatment does not promote additional oxidative stress in acute ischemic animal models and may reduce oxidative stress or reactive nitrogen species according to the experimental conditions. If the variables that control oxygen delivery are managed to achieve the best clinical results, patients can benefit from early NBHO [30]. Tang et al. showed that NBHO treatment with 95 % oxygen during ischemia can reduce ROS production in the ischemic brain by inhibiting NADPH oxidase [31]. The combination of NBHO and transplantation of encapsulated choroid epithelial cells is more effective in treating ischemic brain injury than NBHO or encapsulated choroid plexus epithelial cells alone. Combined use of the two treatments has a protective effect on cerebral ischemia/reperfusion injury induced by oxidative stress in rats by increasing the activities of superoxide dismutase and catalase [27]. Recently, a study showed the neuroprotective effects of NBHO treatment by reducing oxidative stress and maintaining the level of connexin-43 in astrocytes, which could be used for the clinical treatment of ischemic stroke [32].

3.1.5. Inhibiting apoptosis

The combination of NBHO and minocycline can inhibit the expression of caspase-9, which mainly plays a mediating role in apoptosis after cerebral ischemia [33]. In addition, combination therapy may also interfere with the apoptosis-inducing factor (AIF)-mediated apoptosis pathway and play a neuroprotective role. You et al. showed that NBHO may reduce apoptosis around a hematoma by inhibiting the expression of hypoxia-inducible factor (HIF) 1α and vascular endothelial growth factor (VEGF), which confirmed the neuroprotective effect of NBHO [34]. In addition, other studies have shown that NBHO combined with ethanol can reduce apoptosis in transient ischemic stroke. Moreover, combination therapy was found to significantly increase the expression of anti-apoptotic factors (Bcl-2 and Bcl-xL) and considerably reduce the expression of pro-apoptotic proteins (BAX, caspase-3, and AIF), and play a neuroprotective role [35].

3.1.6. Other mechanisms

In addition to the above mechanisms, NBHO may also inhibit the depolarization around the infarction, reduce inflammation,

reduce intracranial pressure, and enhance neuronal metabolism to play a role [17,33,36–38].

Moreover, we draw Table 1 and Fig. 2 to summarize the mechanism of NBHO.

3.2. Combined NBHO treatment

3.2.1. Clinical experiments

The application of NBHO in AIS has a positive effect, particularly in combination with other drugs increase its efficacy. Intravenous thrombolysis with tPA is an effective treatment for patients with stroke [18]. Studies have confirmed that NBHO can improve oxygenation of hypoxic brain tissue after stroke, delay ischemic stroke progress, and improve stroke prognosis through various direct and indirect mechanisms [17,39,40]. Moreover, NBHO therapy may improve the prognosis of patients with AIS [41], and evidence indicates that NBHO combined with intravenous thrombolysis is safe and feasible [24]. NBHO has the potential to serve as an efficacious adjuvant therapy for tPA thrombolysis in ischemic stroke in the clinic [24,25]. Compared with tPA alone, NBHO combined with tPA can significantly improve neurological function and reduce brain edema, cerebral hemorrhage severity, and mortality after delayed tPA treatment [25]. The combined use of NBHO and tPA can reduce the infarct volume more than tPA alone; however, further prospective studies are required to establish the safety and efficacy of treatment in patients with AIS [42]. Li et al. claim that previous studies have not demonstrated that the neuroprotective effect of NBHO may be due to prolonged ischemia time and lack of successful ischemia/reperfusion. Recent reports found that compared with endovascular therapy alone, NBHO combined with endovascular therapy is a safe and feasible treatment, which can significantly reduce the infarct volume of patients with AIS, increase short-term neurobehavioral scores, and improve the 90-day neurological prognosis [43]. NBHO is a well-studied non-pharmacologic approach to decelerate core expansion and preserve penumbra, leading to neuroprotective effects. The combination of neuroprotection and mechanical thrombectomy provides new treatment directions for patients with AIS [44].

3.2.2. Animal experiments

3.2.2.1. Combination treatment of NBHO and cilostazol.
The combination of NBHO and cilostazol has been shown to prevent acute brain injury in mice with focal cerebral ischemia and subacute brain injury and inhibit apoptotic cell death. The mechanism may be that the improvement of regional CBF after reperfusion is related to the activity of endothelial nitric oxide synthase. Cilostazol increases cAMP to inhibit superoxide dismutase, leading to a neuroprotective effect against increased levels of metallothionein 1 and 2 mediated by cerebral ischemia [45–47].

3.2.2.2. Combination treatment of NBHO and minocycline.
The combination of NBHO and minocycline has more substantial neuroprotective and vascular protective effects than monotherapy and can effectively reduce brain injury in transient focal cerebral ischemia [33]. Combination therapy significantly inhibits MMP-2/9 induction, occlusive degradation, caspase-3 and -9 activation, and AIF induction in ischemic brain tissue. Its protective effect is achieved by inhibiting MMP-2/9-mediated occlusive degradation and weakening the caspase-dependent apoptosis pathway.

3.2.2.3. Combination treatment of NBHO and edaravone.
In a comparison of NBHO combined with edaravone treatment and edaravone monotherapy [48], edaravone can scavenge various free radicals (particularly hydroxyl radicals), during induces, inhibit lipid peroxidation products and oxidative DNA damage, and has anti-inflammatory effects [49]. Through different mechanisms, the combination of NBHO and edaravone can prevent neuronal injury after focal cerebral ischemia/reperfusion in mice.

3.2.2.4. Combination treatment of NBHO and N-acetylcysteine.
Although the protective effect of *N*-acetylcysteine after cerebral ischemia is limited, the combined treatment of *N*-acetylcysteine and NBHO can effectively prevent BBB damage and significantly improve the prognosis of brain injury, which may be related to better neurovascular protection and the inhibition of HIF1α and VEGF induction, tight junction protein degradation, PARP-1 activation, and free radical scavenging [50].

Table 1
Mechanisms underlying NBHO.

Mode of action	Possible molecular mechanisms
Increase the oxygen content of brain tissue and improve cerebral blood flow	Reactive oxygen species (ROS), matrix metalloprotein-9, caspase-8 decreased [16]
Improve the function of the mitochondria	Enhance activity of oxidoreductase in mitochondria [20] and regulate mitochondrial zinc [21]
Reduce the damage to the blood–brain barrier (BBB)	Reduce the increase of matrix metalloproteinase-9 and the degradation of occlusive hormone in ischemic BBB microvessels [13,24], possibly by inhibiting the expression of *AQP4* and *NHE1* and reducing the degradation of stent protein (TJP) [25,26]
Reduce oxidative stress	Reduce ROS production, inhibit NADPH oxidase [31], increase the activities of superoxide dismutase [27] and catalase, and maintain the level of astrocyte connexin [32]
Inhibit apoptosis	After cerebral ischemia, the expression of caspase-9 interferes with the apoptosis inducing factor (AIF)-mediated apoptosis pathway [33], inhibits expression of hypoxia inducible factor-1α and vascular endothelial growth factor, increases expression of apoptosis factors (Bcl2 and Bclxl) [34], and significantly decreases expression of pro-apoptotic proteins (Bax, caspase-3 and AIF) [35]

Fig. 2. Mechanism of NBHO. NBHO, normobaric hyperoxia.

3.2.2.5. Combination treatment of NBHO and melatonin. The synergistic effect of NBHO and melatonin on CBF in the ischemic core and penumbra is better than that of either alone, and is related to the reduction of IgG extravasation, DNA fragmentation, infarction volume, brain swelling, and nervous system score; the decrease of pro-apoptotic protein Bax activity; and the increase of NOS, anti-apoptotic Bcl-xL, and survival kinase Akt activity. Studies have shown that NBHO, combined with free-radical scavenging drugs, can enhance their efficacy [51].

3.2.2.6. Combination treatment of NBHO and ethanol. Using NBHO or ethanol alone, infarct volume decreased slightly to 38 % and 37 %, respectively, while it decreased significantly by 51 % when using NBHO and ethanol together. Compared with the reduction of 24 % and 23 % of NBHO or ethanol therapy, the combination of NBHO and ethanol also significantly reduced neurological impairment by 48 %. Compared with ethanol monotherapy, the cell mortality of NBHO and ethanol combination therapy decreased by 49 % and 31 %, respectively [35]. Similarly, compared with the minimal or no protein expression changes induced by NBHO or ethanol alone, combined therapy significantly increased the expression of anti-apoptotic factors (Bcl-2 and Bcl-xL) and significantly decreased the expression of pro-apoptotic proteins (BAX, caspase-3, and AIF), and inhibited apoptosis. In addition, the combined treatment of NBHO and ethanol enhanced the neuroprotective effect of each treatment, and its mechanism is related to the reduction of oxidative stress [52].

3.2.2.7. Combination treatment of NBHO and methylene blue. Rodriguez et al. showed that compared with methylene blue (MB) or NBHO alone, MB + NBHO combined therapy further reduced infarct volume and functional defects. These improvements were visible for up to 28 days, which may be explained by the enhanced cell energy supply and the improved oxidative stress [53]. MB + NBHO combined therapy may also restore vital function by improving chronic oxygenation, inflammation, apoptosis, autophagy, and mitotic phagocytosis.

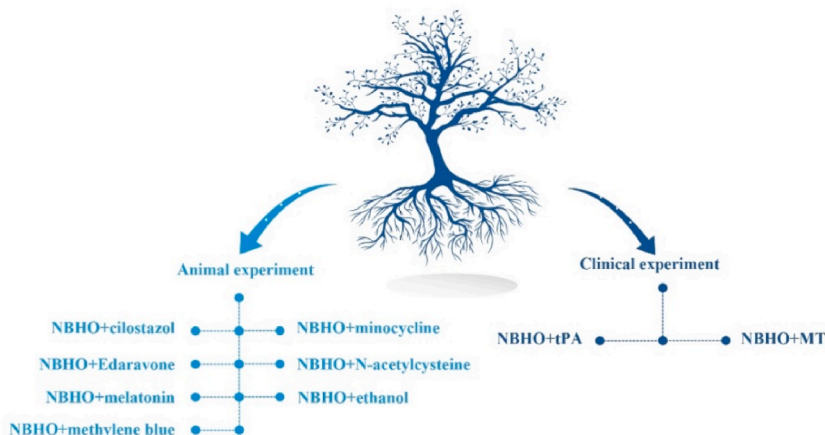Moreover, we draw Fig. 3 to summarize the combined NBHO treatment and Table 2 shows it in animal experiments.

Fig. 3. Combination treatments with NBHO. NBHO, normobaric hyperoxia.

Table 2
Combined NBHO treatment.

Clinical experiments		Animal experiments	
Combined treatment	Advantages	Combined treatment	Mechanism
NBHO + tissue plasminogen activator (tPA)	Significantly improves neurological function; reduces cerebral edema, cerebral hemorrhage severity and mortality after delayed tPA treatment [25]; and reduces infarct volume [42].	NBHO + cilostazol	May be related to increased endothelial nitric oxide synthase activity [45–47]
		NBHO + minocycline	Inhibition of MMP2/9-mediated obstructive degradation and reduction of caspase-dependent apoptotic pathway [33]
		NBHO + edaravone	Inhibition of lipid peroxidation products and oxidative DNA damage [48,49]
		NBHO + ethanol	Inhibition of HIF1α and VEGF induction, tight junction protein degradation, PARP-1 activation, and free radical scavenging [50]
		NBHO + methylene blue	Decreases activity of pro-apoptotic protein Bax and increases activity of nitric oxide synthase, anti-apoptotic Bclxl, and survival kinase Akt [51]
		NBHO + N-acetylcysteine	Significantly increases expression of anti-apoptotic factors (Bcl2 and Bclxl), significantly decreases expression of pro-apoptotic protein (Bax, caspase-3, and AIF), and inhibits apoptosis [52]
		NBHO + melatonin	Enhances cellular energy supply and improves oxidative stress [53]

4. Discussion

NBHO has long been considered an appropriate neuroprotective therapy for ischemic stroke. Different mechanisms of NBHO neuroprotective effects on nerves and vessels have been confirmed in AIS [7,10,13,16–38]. The combination of NBHO and other drugs has been shown to enhance the efficacy of NBHO alone, with excellent prospects for application in AIS [33,35,43–53].

Some negative effects of oxygen therapy should be noted; for example, therapy may limit activities such as getting out of bed and walking and increases the risk of lung and urinary tract infections associated with long-term oxygen therapy administered during bedrest. A high concentration of oxygen can cause vasoconstriction and lead to insufficient cerebral perfusion, which poses a threat to the brain [6,54]. Alva et al. discussed the cellular activities and pathways affected by hyperoxia and the strategies that have been developed to ameliorate injury and illustrated that acute hyperoxia injury impairs various cellular functions, manifesting ultimately as physiological deficits. Chronic hyperoxia, particularly in the neonate, can disrupt development, leading to permanent deficiencies [55]. Oxygen toxicity may also aggravate lung injury and cause pulmonary fibrosis, pulmonary hypertension, ischemia, and other pathophysiological changes, which may be fatal in severe cases [56]. In addition, organs such as the eyes, heart, and digestive tract are sensitive to high concentrations of oxygen, and different concentrations and prolonged NBHO may cause lens degeneration, angina, nausea, and vomiting [57,58]. In addition, AIS patients are commonly prescribed steroids and opioids, and further clinical research is needed to determine whether the use of NBHO interferes with the normal use of these medications and whether it exaggerates opioid-induced respiratory depression. Therefore, it is essential to choose an effective and safe oxygen therapy. NBHO has apparent benefits in clinical and basic research, and it has many potential applications in AIS. The benefits of NBHO may be related to the pressure of oxygen therapy, length of treatment, concentration of oxygen, mode of oxygen delivery, timing of treatment, combination/reperfusion with drugs, and other factors.

The standard oxygen therapies include hyperbaric oxygen (HBO) and NBHO. HBO is when a high concentration of oxygen is delivered in an environment where the ambient pressure is greater than the atmospheric pressure [59,60]. HBO is usually utilized for correcting hypoxia in conditions such as carbon monoxide poisoning or wound healing. HBO use is limited by the need for an HBO chamber, equipment, and by some contraindications. This therapy is inconvenient for patients and presents considerable challenges in a post-stroke emergent environment. Compared with HBO, the advantages of NBHO are convenience, cost, and safety. NBHO can be delivered anywhere, even in an acute stroke setting. Moreover, NBHO can reduce the infarcted brain tissue volume and prolong the time window of thrombolytic treatment in ischemic stroke [61]. NBHO has considerable potential for the treatment of stroke as it a simple, cost-effective, non-invasive therapy that may be used at home with no toxic side effects.

A meta-analysis included four small-sample randomized controlled studies of NBHO therapy in the treatment of stroke [62]. Patients in the NBHO group inhaled 100 % oxygen for 8–12 h and researchers observed the National Institutes of Health Stroke Scale scores, modified Rankin scale scores, Barthel index scores, and the infarct volume and reperfusion rate using diffusion-weighted imaging at 4, 12, and 24 h; 1 week; and 3 and 6 months. The National Institutes of Health Stroke Scale and modified Rankin scale scores in the NBHO group in one study from India did not improve at 24 h, 1 week, or 3 months. The reperfusion rates of the NBHO groups in the other studies were significantly improved compared with the control group, which further confirmed the role of NBHO in treating acute stroke.

In acute cerebral ischemia, the treatment cost is high and there are limited treatment options, most of which fail to improve the recovery rate after stroke. Therefore, new methods for treating cerebral ischemia need to be developed urgently [63]. Recombinant tPA is an effective treatment for AIS. Liang et al. demonstrated that NBHO treatment can slow the progression of BBB damage even

during prolonged periods of cerebral ischemia (7 h), and inhibiting MMP-9 induction and TJP degradation may account for this protection. More importantly, NBHO-afforded BBB protection is sustained following tPA administration [25]. Shi et al. observed the neuroprotective effects of NBHO in AIS patients who underwent thrombolysis after admission and these benefits persisted at 3 days and 1 week, which resulted in significant reductions in the neurovascular complications associated with delayed tPA treatment and improved neurological function [24,25]. Overall, the combined use of recombinant tPA and NBHO can reduce the infarct volume more than the use of these therapies separately. A previous study confirmed the safety and effectiveness of recombinant tPA and NBHO in treating AIS [42]. In addition, experimental studies have confirmed the effectiveness of NBHO combined with other drugs in treating AIS [33,35,43–53]. NBHO alone and drug therapy alone have curative effects in AIS. However, the impact of their combined use is superior.

It has been reported that the therapeutic time window for successful NBHO is relatively narrow (approximately 30 min) [7]. Furthermore, providing oxygen supplementation immediately after the onset of ischemic stroke could reduce infarct volumes and ameliorate neurological defects; however, this protective effect may only be sustained for 72 h [16]. Mohammadi et al. found that sodium-calcium exchangers were markedly augmented in the penumbra region two days after NBHO and decreased gradually within 15 days [64]. Henninger et al. confirmed that extending the duration of NBHO to more than 3 h had a beneficial effect in severe ischemic models, and 6 h may be the optimal time course for NBHO treatment [65]. A study in rats showed that 8 h of NBHO treatment had the best neuroprotective effect compared with 2 or 4 h of treatment [66]. Therefore, further studies are necessary to determine the optimal duration of NBHO. Tiwari et al. compared NBHO treatment in models of severe ischemia and concluded that longer therapy (150 min vs. 25 min or 55 min) was more effective in reducing infarct volume at 48-h post-infarct compared to air, while the shorter (25 min) NBHO treatment only showed a trend in reducing infarct volume. Tiwari et al. demonstrated that long-time NBHO had the most significant effect in reducing infarct lesions [67]. A recent meta-analysis and systematic review showed that low-flow oxygen, mainly from the subacute phase, did not positively impact patients with acute stroke [68]. It may be necessary to further study the benefits of NBHO in the hyperacute step in treating AIS. Overall, NBHO can be used as an early treatment to reduce or slow the evolution of ischemic tissue into necrosis, thus buying time for combination therapy with other neuroprotective agents to obtain better outcomes [69,70].

In terms of oxygen concentrations, Wang et al. found that compared with 33 % and 61 % oxygen content, inhalation of 45 % oxygen after ischemia/reperfusion can slow brain injury, improve neurological damage, and have a better protective effect in ischemic stroke [71]. The authors also noted that although a high oxygen concentration can theoretically increase the production of free radicals, it can also accelerate damage to the BBB and the occurrence of neuroinflammation and increase the risk of brain hypoxia, which does more harm than good in the treatment of cerebral ischemia/reperfusion injury. However, these effects have not been confirmed in experiments. In rodent experiments, many studies have demonstrated that during transient focal cerebral ischemia, delivering 100 % oxygen under normal pressure can improve diffusion and magnetic resonance imaging (MRI) abnormalities, reduce infarct volume, reduce neurobehavioral defects, and will not increase oxidative stress markers, which may be due to the persistent existence of salvageable penumbra [7,8,10,72]. In addition, studies have confirmed that NBHO treatment with 95 % oxygen during cerebral ischemia can delay the evolution of ischemic brain tissue (penumbra and core) to infarction [6]. Liu et al. confirmed that NBHO (95 % oxygen) administered during cerebral ischemia can restore the partial pressure of oxygen of penumbra tissue to the pre-ischemic level but does not affect the oxygen level of the ischemic core [9,16]. Chen et al. reported that in the delivery of NBHO in AIS, the ideal fraction of inspired oxygen could be controlled at 50–90 % [73]. The concentration range selected for NBHO treatment is generally maintained at 90–100 %, which may have a better protective effect on ischemic stroke. However, further research and clinical randomized controlled trials are required to determine the optimal oxygen concentration for NBHO treatment in the future.

Some scholars have found that intermittent NBHO (iNBHO), which is safer and more effective than continuous NBHO, can enhance the activity of anti-oxidases, reduce infarct volumes, alleviate anencephaly edema, protect the BBB, and relieve lung injury [66,74,75]. iNBHO treatment may cause oscillation of cerebral tissue oxygenation during ischemia and can then alter the patterns of reperfusion as a novel form of conditioning, thus rendering brain cells more resistant to the subsequent reperfusion insult [76]. iNBHO and ischemic post-conditioning share a common trigger for enhancing tolerance to ischemia and anoxia, protecting the brain from severe ischemic and anoxic injury [74,77]. However, further research is required to determine the inhalation frequency, length of each inhalation, and the optimal iNBHO regimen in clinical practice.

In clinical practice, whether NBHO should be delivered by mask or nasal cannula remains controversial. In clinical trials, a mask device is the most commonly used way to supplement iNBHO [41,78]. Compared with nasal equipment, venturi masks can provide a higher oxygen flow and concentration. A meta-analysis of 11 randomized controlled trials showed that mask oxygenation may be a better choice for patients with stroke [41]. In addition, Chiu et al. demonstrated that patients with severe AIS benefited more from Venturi mask-NBHO than nasal cannula-NBHO [12]. In short, compared with NBHO delivered by nasal cannula, patients with AIS preferred NBHO treatment delivered by mask.

The benefits of NBHO may be related to the pressure of oxygen therapy, length of treatment, concentration of oxygen, mode of oxygen delivery, timing of treatment, combination/reperfusion with drugs, and other factors. Although oxygen therapy has been shown to increase oxygen supply to ischemic tissues and improve prognosis after cerebral ischemia/reperfusion, NBHO has been used very sparingly in intensive care units. Moreover, the issue of NBHO applicability in AIS needs to be addressed in regard to neuroimaging studies and comorbidities. In AIS, the ischemic penumbra is defined as cerebral tissue at risk of infarction with an unpredictable fate and its salvage leading to a favorable clinical outcome. The ischemic penumbra is typically represented by the perfusion- and diffusion-weighted image (PWI/DWI) mismatch on MRI. The PWI volume represents the tissue at risk, while the DWI volume represents the infarct core. Ma et al. demonstrated that PWI/DWI mismatch exists up to 48 h, during which spontaneous salvage continues. Most importantly, tissue salvage is associated with favorable clinical outcome [79]. Further research is needed to evaluate

the importance of PWI/DWI mismatch in the clinical treatment of AIS. Whether NBHO can be used in clear-onset-time stroke (COS) only or wake-up stroke (WUS) as well needs to be further studied clinically. In addition, the mechanism of treatment and optimal therapeutic regimen for NBHO are still a matter of debate. Therefore, more multicenter clinical trials with rigorous inclusion and exclusion criteria and a larger number of populations should be conducted to obtain more reliable data aiming at validating our findings and developing the optimal regimen for using NBHO in the treatment of stroke.

It is worth noting that Shaw et al. examined the effect of acute hyperoxic breathing on cognition in normobaric environments (~760 mmHg) within healthy individuals and possible influencing factors. Overall, the meta-analytical findings suggest that hyperoxia can improve performance in several cognitive domains (relative to normoxia); however, the overall low quality of evidence and large range of heterogeneity diminished the reliability of the magnitude of these favorable effects. This indicates a need to better understand how acute normobaric hyperoxia can enhance general and domain-specific cognition and potential strategies for its optimization [80]. Moreover, NBHO treatment can protect neural function, and its application is simple and non-invasive; it is widely used and is mainly used early in clinical practice. Studies have confirmed that NBHO treatment may promote the recovery of neurological function after craniocerebral trauma by inhibiting mitochondrial pathway cell apoptosis, which is expected to provide a new treatment method for patients, particularly patients with severe craniocerebral trauma [81,82]. In an animal study of NBHO therapy in hemorrhagic stroke, the NBHO treatment group showed improved neurological function and reduced brain edema compared with the untreated intracerebral hemorrhage control group [34]. It is also worth noting that NBHO may also be a feasible method for cancer treatment. A study previously confirmed the role of NBHO in inhibiting the development of lung cancer by inducing apoptosis for the first time [83].

5. Conclusion

NBHO is a simple, non-invasive therapy that may be delivered early after stroke onset with promising potential for the treatment of AIS. However, there remains uncertainty regarding the optimal therapeutic regimen. More studies are needed to confirm its efficacy and safety.

Funding

Data availability statement

The datasets for this review are available upon reasonable request.

CRediT authorship contribution statement

Qijian Wang: Conceptualization, Data curation, Writing - original draft, Writing - review & editing. **Xiao Zhang:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Yijun Suo:** Data curation, Writing - original draft, Writing - review & editing. **Zhiying Chen:** Data curation, Writing - original draft, Writing - review & editing. **Moxin Wu:** Data curation, Formal analysis. **Xiaoqin Wen:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Qin Lai:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Xiaoping Yin:** Conceptualization, Data curation, Funding acquisition, Writing - original draft, Writing - review & editing. **Bing Bao:** Data curation, Formal analysis, Funding acquisition, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] H.K. Eltzschig, T. Eckle, Ischemia and reperfusion—from mechanism to translation, Nat. Med. 17 (2011) 1391–1401, https://doi.org/10.1038/nm.2507.

[2] A. Zauner, W.P. Daugherty, M.R. Bullock, D.S. Warner, Brain oxygenation and energy metabolism: part I - biological function and pathophysiology, Neurosurgery 51 (2002) 289–301.

[3] C.D. Mathers, T. Boerma, D.M. Fat, Global and regional causes of death, Br. Med. Bull. 92 (2009) 7–32, https://doi.org/10.1093/bmb/ldp028.

[4] C.M. Stinear, Prediction of motor recovery after stroke: advances in biomarkers, Lancet Neurol. 16 (2017) 826–836, https://doi.org/10.1016/s1474-4422(17)30283-1.

[5] L. Chazalviel, H.N. David, B. Haelewyn, J.-E. Blatteau, N. Vallée, J.-J. Risso, et al., The underestimated effect of normobaric hyperoxia on cerebral blood flow and its relationship to neuroprotection, Brain 139 (2016) e62, https://doi.org/10.1093/brain/aww178.

[6] J. Xu, Y. Zhang, Z.Y. Liang, T. Wang, W.P. Li, L.J. Ren, et al., Normobaric hyperoxia retards the evolution of ischemic brain tissue toward infarction in a rat model of transient focal cerebral ischemia, Neurol. Res. 38 (2016) 75–79, https://doi.org/10.1080/01616412.2015.1135558.

[7] A.B. Singhal, R.M. Dijkhuizen, B.R. Rosen, E.H. Lo, Normobaric hyperoxia reduces MRI diffusion abnormalities and infarct size in experimental stroke, Neurology 58 (2002) 945–952, https://doi.org/10.1212/wnl.58.6.945.

[8] A.B. Singhal, X.Y. Wang, T. Sumii, T. Mori, E.H. Lo, Effects of normobaric hyperoxia in a rat model of focal cerebral ischemia-reperfusion, J. Cerebr. Blood Flow Metabol. 22 (2002) 861–868, https://doi.org/10.1097/00004647-200207000-00011.

[9] S.M. Liu, H.L. Shi, W.L. Liu, T. Furuichi, G.S. Timmins, K.J. Liu, Interstitial pO(2) in ischemic penumbra and core are differentially affected following transient focal cerebral ischemia in rats, J. Cerebr. Blood Flow Metabol. 24 (2004) 343–349, https://doi.org/10.1097/01.wcb.0000110047.43905.01.

[10] H.Y. Kim, A.B. Singhal, E.H. Lo, Normobaric hyperoxia extends the reperfusion window in focal cerebral ischemia, Ann. Neurol. 57 (2005) 571–575, https://doi.org/10.1002/ana.20430.

[11] A.B. Singhal, T. Benner, L. Roccatagliata, W.J. Koroshetz, P.W. Schaefer, E.H. Lo, et al., A pilot study of normobaric oxygen therapy in acute ischemic stroke, Stroke 36 (2005) 797–802, https://doi.org/10.1161/01.str.0000158914.66827.2e.

[12] E.H.H. Chiu, C.S. Liu, T.Y. Tan, K.C. Chang, Venturi mask adjuvant oxygen therapy in severe acute ischemic stroke, Arch. Neurol. 63 (2005) 741–744, https://doi.org/10.1001/archneur.63.5.741.

[13] W. Liu, J. Hendren, X.J. Qin, J. Shen, K.J. Liu, Normobaric hyperoxia attenuates early blood-brain barrier disruption by inhibiting MMP-9-mediated occludin degradation in focal cerebral ischemia, J. Neurochem. 108 (2009) 811–820, https://doi.org/10.1111/j.1471-4159.2008.05821.x.

[14] D. Michalski, W. Härtig, D. Schneider, C. Hobohm, Use of normobaric and hyperbaric oxygen in acute focal cerebral ischemia - a preclinical and clinical review, Acta Neurol. Scand. 123 (2011) 85–97, https://doi.org/10.1111/j.1600-0404.2010.01363.x.

[15] A.B. Singhal, A review of oxygen therapy in ischemic stroke, Neurol. Res. 29 (2007) 173–183, https://doi.org/10.1179/016164107x181815.

[16] S. Liu, W. Liu, W. Ding, M. Miyake, G.A. Rosenberg, K.J. Liu, Electron paramagnetic resonance-guided normobaric hyperoxia treatment protects the brain by maintaining penumbral oxygenation in a rat model of transient focal cerebral ischemia, J. Cerebr. Blood Flow Metabol. 26 (2006) 1274–1284, https://doi.org/10.1038/sj.jcbfm.9600277.

[17] H.K. Shin, A.K. Dunn, P.B. Jones, D.A. Boas, E.H. Lo, M.A. Moskowitz, et al., Normobaric hyperoxia improves cerebral blood flow and oxygenation and inhibits peri-infarct depolarizations in experimental focal ischaemia, Brain 130 (2007) 1631–1642, https://doi.org/10.1093/brain/awm071.

[18] W.J. Powers, A.A. Rabinstein, T. Ackerson, O.M. Adeoye, N.C. Bambakidis, K. Becker, et al., American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 49 (2018) E46–E110, https://doi.org/10.1161/str.0000000000000158.

[19] J. Hiebert, Q. Shen, A.R. Thimmesch, J.D. Pierce, Traumatic brain injury and mitochondrial dysfunction, Am. J. Med. Sci. 350 (2015) 132–138, https://doi.org/10.1097/maj.0000000000000620.

[20] C. Kolyva, A. Ghosh, I. Tachtsidis, D. Highton, C.E. Cooper, M. Smith, Cytochrome c oxidase response to changes in cerebral oxygen delivery in the adult brain shows higher brain-specificity than haemoglobin, Neuroimage 85 Pt 1 (2014) 234–244, https://doi.org/10.1016/j.neuroimage.2013.05.070.

[21] W. Dong, Z.F. Qi, J. Liang, W.J. Shi, Y.M. Zhao, Y.M. Luo, Reduction of zinc accumulation in mitochondria contributes to decreased cerebral ischemic injury by normobaric hyperoxia treatment in an experimental stroke model, Exp. Neurol. 272 (2015) 181–189, https://doi.org/10.1016/j.expneurol.2015.04.005.

[22] G.J. del Zoppo, R. von Kummer, G.F. Hamann, Ischaemic damage of brain microvessels: inherent risks for thrombolytic treatment in stroke, J. Neurol. Neurosurg. Psychiatry 65 (1998) 1–9, https://doi.org/10.1136/jnnp.65.1.1.

[23] X.C. Jin, J. Liu, Y. Yang, K.J. Liu, Y.R. Yang, W.L. Liu, Spatiotemporal evolution of blood-brain barrier damage and tissue infarction within the first 3 h after ischemia onset, Neurobiol. Dis. 48 (2012) 309–316, https://doi.org/10.1016/j.nbd.2012.07.007.

[24] S.H. Shi, Z.F. Qi, Q.F. Ma, R. Pan, G.S. Timmins, Y.M. Zhao, Normobaric hyperoxia reduces blood occludin fragments in acute ischemic stroke rats and patients, Stroke 48 (2017) 2848–2854, https://doi.org/10.1161/strokeaha.117.017713.

[25] J. Liang, Z.F. Qi, W.L. Liu, P. Wang, W.J. Shi, W. Dong, Normobaric hyperoxia slows blood-brain barrier damage and expands the therapeutic time window for tissue-type plasminogen activator treatment in cerebral ischemia, Stroke 46 (2015) 1344–1351, https://doi.org/10.1161/strokeaha.114.008599.

[26] D.B. Yang, L.Y. Ma, P. Wang, D.J. Yang, Y.N. Zhang, X. Zhao, Normobaric oxygen inhibits AQP4 and NHE1 expression in experimental focal ischemic stroke, Int. J. Mol. Med. 43 (2019) 1193–1202, https://doi.org/10.3892/ijmm.2018.4037.

[27] M. Eslami, S. Oryan, M. Rahnema, M.R. Bigdeli, Neuroprotective effects of normobaric hyperoxia and transplantation of encapsulated choroid plexus epithelial cells on the focal brain ischemia, Cell J 23 (2021) 303–312, https://doi.org/10.22074/cellj.2021.7204.

[28] A.C. Kulkarni, P. Kuppusamy, N. Parinandi, Oxygen, the lead actor in the pathophysiologic drama: enactment of the trinity of normoxia, hypoxia, and hyperoxia in disease and therapy, Antioxidants Redox Signal. 9 (2007) 1717–1730, https://doi.org/10.1089/ars.2007.1724.

[29] P.D. Ray, B.W. Huang, Y. Tsuji, Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling, Cell. Signal. 24 (2012) 981–990, https://doi.org/10.1016/j.cellsig.2012.01.008.

[30] J. Weaver, K.J. Liu, Does normobaric hyperoxia increase oxidative stress in acute ischemic stroke? A critical review of the literature, Med. Gas Res. 5 (2015) 11, https://doi.org/10.1186/s13618-015-0032-4.

[31] X. Tang, K.J. Liu, J. Ramu, Q. Chen, T. Li, W. Liu, Inhibition of gp91(phox) contributes towards normobaric hyperoxia afforded neuroprotection in focal cerebral ischemia, Brain Res. 1348 (2010) 174–180, https://doi.org/10.1016/j.brainres.2010.05.082.

[32] Z.F. Qi, S.H. Yuan, K.J. Liu, X.M. Ji, Normobaric hyperoxia plays a neuroprotective role after cerebral ischemia by maintaining the redox homeostasis and the level of connexin 43 in astrocytes, CNS Neurosci. Therapy 28 (2022) 1509–1518, https://doi.org/10.1111/cns.13875.

[33] X. Jin, J. Liu, K.J. Liu, G.A. Rosenberg, Y. Yang, W. Liu, Normobaric hyperoxia combined with minocycline provides greater neuroprotection than either alone in transient focal cerebral ischemia, Exp. Neurol. 240 (2013) 9–16, https://doi.org/10.1016/j.expneurol.2012.11.018.

[34] P.D. You, M.C. Lin, K.Z. Li, X.F. Ye, J.M. Zheng, Normobaric oxygen therapy inhibits HIF-1α and VEGF expression in per and reduces neurological function defects, Neuroreport 27 (2016) 329–336, https://doi.org/10.1097/wnr.0000000000000542.

[35] X.K. Geng, S. Parmar, X.M. Li, C.Y. Peng, X.M. Ji, T. Chakraborty, Reduced apoptosis by combining normobaric oxygenation with ethanol in transient ischemic stroke, Brain Res. 1531 (2013) 17–24, https://doi.org/10.1016/j.brainres.2013.07.051.

[36] Z. Yang, H. Chen, M. Xian, X. Jiang, L. Yuan, J. Mai, Role of medical pressured oxygen injector in the rehabilitation of motor function and abilities of daily living at early stage of cerebral infarction, Chin. J. Clin. Rehabil. 8 (2004) 2414–2415.

[37] R. Zhao, C. Wang, Y. Wang, Changes in serum cellular adhesion molecule and matrix metalloproteinase-9 levels in patients with cerebral infarction following hyperbaric oxygen therapy A case and intergroup control study, Neural Regen. Res 3 (2008) 1245–1248.

[38] H.J. Helmerhorst, M.-J. Roos-Blom, D.J. van Westerloo, E. de Jonge, Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, meta-analysis, and meta-regression of cohort studies, Crit. Care Med. 43 (2015) 1508–1519, https://doi.org/10.1097/ccm.0000000000000998.

[39] N. Fujiwara, Y. Murata, K. Arai, Y. Egi, J. Lu, O. Wu, Combination therapy with normobaric oxygen (NBO) plus thrombolysis in experimental ischemic stroke, BMC Neurosci. 10 (2009) 79, https://doi.org/10.1186/1471-2202-10-79.

[40] H.N. David, B. Haelewyn, M. Degoulet, D.G. Colomb, J.J. Risso, J.H. Abraini, Prothrombolytic action of normobaric oxygen given alone or in combination with recombinant tissue-plasminogen activator in a rat model of thromboembolic stroke, J. Appl. Physiol. 112 (2012) (1985) 2068–2076, https://doi.org/10.1152/japplphysiol.00092.2012.

[41] J.Y. Ding, D. Zhou, M. Sui, R. Meng, A. Chandra, J. Han, The effect of normobaric oxygen in patients with acute stroke: a systematic review and meta-analysis, Neurol. Res. 40 (2018) 433–444, https://doi.org/10.1080/01616412.2018.1454091.

[42] N. Li, L.F. Wu, W.B. Zhao, D. Dornbos, C.J. Wu, W.L. Li, Efficacy and safety of normobaric hyperoxia combined with intravenous thrombolysis on acute ischemic stroke patients, Neurol. Res. 43 (2021) 809–814, https://doi.org/10.1080/01616412.2021.1939234.

[43] W. Li, Z. Qi, Q. Ma, J. Ding, C. Wu, H. Song, Normobaric hyperoxia combined with endovascular treatment for acute ischemic stroke patients: a randomized controlled clinical trial, Neurology 99 (2022) e824–e834, https://doi.org/10.1212/wnl.0000000000200775.

[44] S.M. Desai, R.M. Jha, I. Linfante, Collateral circulation augmentation and neuroprotection as adjuvant to mechanical thrombectomy in acute ischemic stroke, Neurology 97 (2021) S178–S184, https://doi.org/10.1212/wnl.0000000000012809.

[45] Y. Nonaka, A. Koumura, K. Hyakkoku, M. Shimazawa, S. Yoshimura, T. Iwama, Combination treatment with normobaric hyperoxia and cilostazol protects mice against focal cerebral ischemia-induced neuronal damage better than each treatment alone, J. Pharmacol. Exp. Therapeut. 330 (2009) 13–22, https://doi.org/10.1124/jpet.109.151548.

[46] S.Y. Park, J.H. Lee, C.D. Kim, W.S. Lee, W.S. Park, J. Han, Cilostazol suppresses superoxide production and expression of adhesion molecules in human endothelial cells via mediation of cAMP-dependent protein kinase-mediated maxi-K channel activation, J. Pharmacol. Exp. Therapeut. 317 (2006) 1238–1245, https://doi.org/10.1124/jpet.105.098509.

[47] K. Wakida, N. Morimoto, M. Shimazawa, I. Hozumi, H. Nagase, T. Inuzuka, Cilostazol reduces ischemic brain damage partly by inducing metallothionein-1 and -2, Brain Res. 1116 (2006) 187–193, https://doi.org/10.1016/j.brainres.2006.07.125.

[48] Y. Nonaka, M. Shimazawa, S. Yoshimura, T. Iwama, H. Hara, Combination effects of normobaric hyperoxia and edaravone on focal cerebral ischemia-induced neuronal damage in mice, Neurosci. Lett. 441 (2008) 224–228, https://doi.org/10.1016/j.neulet.2008.06.033.

[49] N. Zhang, M. Komine-Kobayashi, R. Tanaka, M. Liu, Y. Mizuno, T. Urabe, Edaravone reduces early accumulation of oxidative products and sequential inflammatory responses after transient focal ischemia in mice brain, Stroke 36 (2005) 2220–2225, https://doi.org/10.1161/01.str.0000182241.07096.06.

[50] Y. Liu, W.-C. Liu, Y. Sun, X. Shen, X. Wang, H. Shu, Normobaric hyperoxia extends neuro- and vaso-protection of N-acetylcysteine in transient focal ischemia, Mol. Neurobiol. 54 (2017) 3418–3427, https://doi.org/10.1007/s12035-016-9932-0.

[51] M.C. Beker, A.B. Caglayan, T. Kelestemur, B. Caglayan, E. Yalcin, B. Yulug, Effects of normobaric oxygen and melatonin on reperfusion injury: role of cerebral microcirculation, Oncotarget 6 (2015) 30604–30614, https://doi.org/10.18632/oncotarget.5773.

[52] X.K. Geng, P. Fu, X.M. Ji, C.Y. Peng, V. Fredrickson, C. Sy, Synergetic neuroprotection of normobaric oxygenation and ethanol in ischemic stroke through improved oxidative mechanism, Stroke 44 (2013) 1418–1425, https://doi.org/10.1161/strokeaha.111.000315.

[53] P. Rodriguez, J. Zhao, B. Milman, Y.V. Tiwari, T.Q. Duong, Methylene blue and normobaric hyperoxia combination therapy in experimental ischemic stroke, Brain Behav 6 (2016) e00478, https://doi.org/10.1002/brb3.478.

[54] D. Zhou, R. Meng, S.J. Li, J.Y. Ya, J.Y. Ding, S.L. Shang, Advances in chronic cerebral circulation insufficiency, CNS Neurosci. Ther. 24 (2017) 5–17, https://doi.org/10.1111/cns.12780.

[55] R. Alva, M. Mirza, A. Baiton, L. Lazuran, L. Samokysh, A. Bobinski, Oxygen toxicity: cellular mechanisms in normobaric hyperoxia, Cell Biol. Toxicol. 39 (2023) 111–143, https://doi.org/10.1007/s10565-022-09773-7.

[56] A. Pagano, C. Barazzone-Argiroffo, Alveolar cell death in hyperoxia-induced lung injury, Ann. N. Y. Acad. Sci. 1010 (2003) 405–416, https://doi.org/10.1196/annals.1299.074.

[57] E.G. Wolf, J. Prye, R. Michaelson, G. Brower, L. Profenna, O. Boneta, Hyperbaric side effects in a traumatic brain injury randomized clinical trial, Undersea Hyperb. Med. 39 (2012) 1075–1082.

[58] J.V. Brugniaux, G, B. Coombs, O.F. Barak, Z. Dujic, M.S. Sekhon, P.N. Ainslie, Highs and lows of hyperoxia: physiological, performance, and clinical aspects, Am. J. Physiol. Regul. Integr. Comp. Physiol. 315 (2018) R1–R27, https://doi.org/10.1152/ajpregu.00165.2017.

[59] G.D. Satyarthee, Hyperbaric oxygen therapy in ischemic stroke management: standardized consensus-based therapeutic protocol, Neurol. India 67 (2019) 653–654, https://doi.org/10.4103/0028-3886.263205.

[60] B. Gonzales-Portillo, T. Lippert, H. Nguyen, J.-Y. Lee, C.V. Borlongan, Hyperbaric oxygen therapy: a new look on treating stroke and traumatic brain injury, Brain Circ 5 (2019) 101–105, https://doi.org/10.4103/bc.bc_31_19.

[61] Z.L. Ji, K.Y. Liu, L.P. Cai, C.Y. Peng, P.Q. Xin, Z. Gao, Therapeutic effect of tPA in ischemic stroke is enhanced by its combination with normobaric oxygen and hypothermia or ethanol, Brain Res. 1627 (2015) 31–40, https://doi.org/10.1016/j.brainres.2015.08.019.

[62] Z. Deng, W. Chen, J. Jin, J. Zhao, H. Xu, The neuroprotection effect of oxygen therapy: a systematic review and meta-analysis, Niger, J. Clin. Pract 21 (2018) 401–416, https://doi.org/10.4103/njcp.njcp_315_16.

[63] R.H.C. Lee, M.H.H. Lee, C.Y.C. Wu, A. Couto E. Silva, H.E. Possoit, T.-H. Hsieh, Cerebral ischemia and neuroregeneration, Neural Regen. Res 17 (2018) 373–385, https://doi.org/10.4103/1673-5374.228711.

[64] E. Mohammadi, M.R. Bigdeli, Time course of neuroprotection induced by normobaric hyperoxia and NCX1 expression, Brain Inj. 28 (2014) 1127–1134, https://doi.org/10.3109/02699052.2014.896472.

[65] N. Henninger, J. Bouley, J.M. Nelligan, K.M. Sicard, M. Fisher, Normobaric hyperoxia delays perfusion/diffusion mismatch evolution, reduces infarct volume, and differentially affects neuronal cell death pathways after suture middle cerebral artery occlusion in rats, J. Cerebr. Blood Flow Metabol. 27 (2007) 1632–1642, https://doi.org/10.1038/sj.jcbfm.9600463.

[66] Z.R. Yuan, R. Pan, W.L. Liu, K.J. Liu, Extended normobaric hyperoxia therapy yields greater neuroprotection for focal transient ischemia-reperfusion in rats, Med. Gas Res. 4 (2014) 14, https://doi.org/10.1186/2045-9912-4-14.

[67] Y.V. Tiwari, Z. Jiang, Y. Sun, F. Du, P. Rodriguez, Q. Shen, Effects of stroke severity and treatment duration in normobaric hyperoxia treatment of ischemic stroke, Brain Res. 1635 (2016) 121–129, https://doi.org/10.1016/j.brainres.2016.01.030.

[68] A. Mahmood, S. Neilson, V. Biswas, K. Muir, Normobaric oxygen therapy in acute stroke: a systematic review and meta-analysis, Cerebrovasc. Dis. 51 (2022) 427–437, https://doi.org/10.1159/000521027.

[69] W. Liu, J. Hendren, X.J. Qin, K.J. Liu, Normobaric hyperoxia reduces the neurovascular complications associated with delayed tissue plasminogen activator treatment in a rat model of focal cerebral ischemia, Stroke 40 (2009) 2526–2531, https://doi.org/10.1161/strokeaha.108.545483.

[70] A.B. Singhal, Oxygen therapy in stroke: past, present, and future, Int. J. Stroke 1 (2006) 191–200, https://doi.org/10.1111/j.1747-4949.2006.00058.x.

[71] J. Wang, G. Jin, Y. Zhang, Study on the optimal scheme of normobaric oxygen therapy for ischemic stroke patients, Chin. J. Practical Neurol. Dis 18 (2015) 52–54.

[72] E.P. Flynn, R.N. Auer, Eubaric hyperoxemia and experimental cerebral infarction, Ann. Neurol. 52 (2002) 566–572, https://doi.org/10.1002/ana.10322.

[73] Z.Y. Chen, Y.C. Ding, X.M. Ji, R. Meng, Advances in normobaric hyperoxia brain protection in experimental stroke, Front. Neurol. 11 (2020) 1–6, https://doi.org/10.3389/fneur.2020.00050.

[74] M.R. Bigdeli, B. Rasoulian, A.A. Meratan, In vivo normobaric hyperoxia preconditioning induces different degrees of antioxidant enzymes activities in rat brain tissue, Eur. J. Pharmacol. 611 (2009) 22–29, https://doi.org/10.1016/j.ejphar.2009.03.034.

[75] M.R. Bigdeli, S. Hajizadeh, M. Froozandeh, B. Rasulian, A. Heidarianpour, A. Khoshbaten, Prolonged and intermittent normobaric hyperoxia induce different degrees of ischemic tolerance in rat brain tissue, Brain Res. 1152 (2007) 228–233, https://doi.org/10.1016/j.brainres.2007.03.068.

[76] C. Liu, J. Weaver, K.J. Liu, Rapid conditioning with oxygen oscillation neuroprotection by intermittent normobaric hyperoxia after transient focal cerebral ischemia in rats, Stroke 43 (2012) 220–226, https://doi.org/10.1161/strokeaha.111.625756.

[77] M.R. Bigdeli, M. Asheghabadi, A. Khalili, Time course of neuroprotection induced by normobaric hyperoxia in focal cerebral ischemia, Neurol. Res. 34 (2012) 439–446, https://doi.org/10.1179/1743132812y.0000000013.

[78] S.H. Shi, Z.F. Qi, Y.M. Luo, X.M. Ji, K.J. Liu, Normobaric oxygen treatment in acute ischemic stroke: a clinical perspective, Med. Gas Res. 6 (2016) 147–153, https://doi.org/10.4103/2045-9912.191360.

[79] H. Ma, P. Wright, L. Allport, T.G. Phan, L. Churilov, J. Ly, Salvage of the PWI/DWI mismatch up to 48 h from stroke onset leads to favorable clinical outcome, Int. J. Stroke 10 (2015) 565–570, https://doi.org/10.1111/ijs.12203.

[80] D.W. Shaw, P.W. Bloomfield, N. Gant, The effect of acute normobaric hyperoxia on cognition: a systematic review, meta-analysis and meta-regression, Physiol. Behav. 267 (2023), 114208, https://doi.org/10.1016/j.physbeh.2023.114208.

[81] S.J. Zhu, C. Liu, J. Shen, J. Wang, C. Tang, H. Shan, Protective effect and mechanism of early normobaric hyperoxia therapy on brain injury in rats, Chin. J. Crit. Care Med 24 (2015) 17–23.

[82] Y. Li, G. Cheng, J. Zhang, Research progress of normobaric hyperoxia therapy in the treatment of craniocerebral trauma, Chin. J. Neurosurg 34 (2018) 214–216.

[83] S.W. Kim, I.K. Kim, J.H. Ha, C.D. Yeo, H.H. Kang, J.W. Kim, Normobaric hyperoxia inhibits the progression of lung cancer by inducing apoptosis, Exp. Biol. Med. 243 (2018) 739–748, https://doi.org/10.1177/1535370218774737.