Discover Medicine

Review

Understanding the biological effects of hypoxia in ischemic stroke: implications for rehabilitation and recovery

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Received: 20 July 2024 / Accepted: 22 November 2024

Abstract

Ischemic stroke can leave patients with lasting disabilities. Rehabilitation is crucial, but new approaches are needed. One promising avenue is hypoxia exposure therapy. This involves controlled exposure to low oxygen levels. While it may sound counterintuitive, this approach triggers the brain to adapt. Studies suggest hypoxia stimulates the growth of new blood vessels, boosting oxygen delivery to the damaged area. Additionally, it may promote neuroplasticity, the brain's ability to reorganize and form new connections. This can lead to the creation of new nerve cells, potentially replacing those lost in the stroke. Furthermore, hypoxia exposure might help regulate inflammation, a key contributor to stroke damage. Early research, particularly with intermittent hypoxia training, shows promise for improved motor function recovery. However, challenges remain. Stroke severity, location, and individual health vary greatly, requiring personalized treatment plans. Determining the optimal dose, timing, and frequency of hypoxia exposure is crucial for maximizing benefits. Additionally, the precise mechanisms by which hypoxia aids recovery need further investigation. Future research will focus on tailoring protocols to individual patients, exploring combinations with other rehabilitation methods, and conducting large-scale trials to solidify the safety and effectiveness of hypoxia therapy.

Keywords Ischemic stroke · Rehabilitation · Hypoxia exposure therapy

Abbreviations

DALYs	Disability-Adjusted Life-Years
EPC	Endogenous protective responses
HIF	Hypoxia-inducible factors

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Discover Medicine (2024) 1:130 | https://doi.org/10.1007/s44337-024-00161-0

IHT	Intermittent Hypoxia Therapy
LOPC	Low Oxygen Post Conditioning
MAPK/ERK	Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase
miRNAs	MicroRNAs
NO	Nitric oxide
ROS	Reactive Oxygen Species
VEGF	Vascular endothelial growth factor

1 Introduction

Stroke remains a leading cause of death and disability globally, with about 5 million deaths and a loss of 143 million Disability-Adjusted Life-Years (DALYs) annually [1, 2]. The lifetime probability of developing a stroke for an adult aged 25 years and older is 25% [3]. Of those affected, approximately one-third die, while another third suffer from permanent disabilities, leading to substantial physical, emotional, and economic burdens on patients and their families [1, 4]. The incidence of stroke is expected to rise across all demographics by 2030 [5].

Strokes are primarily classified into two types: ischemic and hemorrhagic. Ischemic stroke, responsible for about 70% of stroke cases [4], occurs due to a sudden blockage in blood flow to the brain, reducing oxygen and nutrient delivery to brain tissue [6]. In contrast, hemorrhagic stroke involves bleeding within or around the brain. This review primarily focuses on ischemic stroke, though the implications of hypoxia therapy may vary between stroke types.

Emerging therapies aim to enhance the quality of life for ischemic stroke patients. Despite significant advances, preventive strategies are still vital, particularly in resource-limited settings, to reduce ischemic stroke risk factors [7]. Ischemic stroke leads to severe impairments in cognitive, motor, and functional abilities, necessitating innovative therapeutic approaches to counteract hypoperfusion effects [8]. Effective restoration of blood flow to damaged brain regions is crucial for a favorable recovery [8].

Hypoxia, characterized by insufficient oxygen supply (with normal oxygen pressure (PaO2) ranging from 11.0–14.4 kPa and arterial oxygen saturation (SaO2) typically between 95–98%) [9, 10], has been explored in various therapeutic contexts. Initial research into hypoxia therapy began in the 1930s in the Soviet Union, evolving over time into more refined techniques, including intermittent exposure [11]. Recent studies have investigated these methods [12–14], although the precise mechanisms remain partially understood. Intermittent Hypoxia Therapy (IHT) has shown promise in improving outcomes for ischemic stroke by stimulating cerebrovascular microcirculation and promoting the formation of new blood vessels [15].

IHT, as a form of preconditioning, uses brief preischemic stimuli to enhance endogenous protective responses, offering potential benefits for functional recovery [16]. This approach aims to improve stroke-related impairments in cognition, gait, sensation, visual, and psychosocial functions [17]. Typically, IHT involves exposure to short periods of low oxygen followed by normal oxygen, with session durations ranging from 1–10 min over multiple cycles and weeks [18]. However, the relationship between hypoxia-induced biological changes and actual clinical outcomes in rehabilitation remains complex and not fully understood.

This review focuses on the biological mechanisms underlying hypoxia exposure in ischemic stroke and discusses its potential implications for rehabilitation and functional recovery. While the therapeutic potential of hypoxia is evident, further research is needed to clarify how these biological effects translate into tangible improvements in post-stroke rehabilitation outcomes.

2 Methods

A literature search was performed in these main medical database engines: PubMed (Medline), Google Scholar, Scopus (ELSEVIER), and Cochrane library (CENTRAL). The search algorithm was generated using keywords and Boolean search operators such as: *("Hypoxia Exposure" OR "Hypoxic Exposure" OR "Intermittent Hypoxic conditioning") AND ("Ischemic Stroke Rehabilitation")*. Two independent reviewers (NA & AEB) screened titles and abstracts of all identified studies based on predefined inclusion and exclusion criteria. Studies were included if they:

- Investigated the impact of hypoxia exposure on rehabilitation outcomes following ischemic stroke.
- Reported on the mechanisms underlying the effects of hypoxia exposure, the potential benefits it offered, or its clinical applications in stroke rehabilitation.

Exclusion criteria encompassed studies that:

- Focused on hemorrhagic stroke or other neurological conditions.
- Were not peer-reviewed research articles (e.g., reviews, case reports).
- Did not directly address the research question of hypoxia exposure in ischemic stroke rehabilitation.
- Were not published in English

Any discrepancies between the reviewers regarding study selection were resolved through discussion or by consulting a third reviewer (EK) to ensure objectivity.

3 Mechanisms of hypoxia in ischemic stroke rehabilitation

3.1 Neuroplasticity mechanisms

Neuroplasticity is the brain's ability to regenerate and form new neural connections after an injury [9] Table 1. Hypoxia exposure induces neuroplasticity through angiogenetic, neurogenetic, and synaptic plasticity mechanisms [19]. An ischemic brain post-stroke recovery conditioned with hypoxia stimulates the formation of blood vessels by inducing the production of vascular endothelial growth factor (VEGF). Hypoxia adaptation is regulated by HIF factors (HIF-1, HIF-2, and HIF-3), with each subunit playing a specific role based on the induced stress type [20]. Hypoxic condition induces the activation of hypoxia-inducible factors (HIFs), by suppressing O_2-dependent hydroxylation and degradation of the HIF-1α subunit. HIF are transcription factors that upregulate the production of VEGF, which promotes the proliferation and migration of endothelial cells, culminating in the formation of new blood vessels. Increased VEGF expression in response to hypoxia enhances vascular density in the ischemic brain, improving microcirculation in the affected brain areas, reviving neuronal function, and, consequently, the overall recovery [19]. Low Oxygen Post Conditioning (LOPC) exerts proangiogenetic effects by increasing vessel density in the penumbra of an ischemic brain [21]. Pietrogrande et al. examined peri-infarct vessels using immunohistochemistry targeting CD3—a biomarker expressed on endothelial cell

Table 1 Mechanisms of hypoxia in ischemic stroke rehabilitation

Mechanism	Details
Angiogenesis	VEGF Production: Hypoxia induces VEGF production via HIFs, promoting new blood vessel formation HIF Regulation: HIFs (HIF-1, HIF-2, HIF-3) control VEGF expression, enhancing vascular density and microcirculation LOPC: Low Oxygen Post Conditioning increases vessel density in the ischemic brain penumbra
Neurogenesis	HIF Target Genes: Upregulates genes involved in neurogenesis (e.g., VEGF, EPO, BDNF) NPC Proliferation: Neural progenitor cells proliferate and migrate to ischemic regions, replacing damaged neurons BDNF: Enhances NPC differentiation and synaptic plasticity
Synaptic plasticity	LTP: Long-term potentiation improves synaptic strength Dendritic Spines: Hypoxia increases spine density and morphology, boosting synaptic connectivity NeuN and Synapsin-1: Low Oxygen exposure raises NeuN (neuron maturation marker) and synapsin-1 (synaptic vesicle marker) levels
Inflammatory responses	Pro-inflammatory Cytokines: Hypoxia reduces IL-1β, TNF-α, IL-6, which are elevated post-stroke Anti-inflammatory Mechanisms: HIF-1α promotes anti-inflammatory cytokines like IL-10 to resolve inflammation and aid tissue repair Microglial Activation: Hypoxia shifts microglia from pro-inflammatory (M1) to anti-inflammatory (M2) phenotypes
Metabolic responses	Anaerobic Metabolism: Shift to anaerobic metabolism increases glycolysis and lactate production Mitochondrial Function: Enhances mitochondrial function, increases mitochondrial number, and improves cellular resilience ROS and NO Production: Intermittent hypoxic training (IHT) increases NO and ROS, which activate neuroprotective signaling pathways MicroRNAs: HIF triggers hypoxia-sensitive microRNAs

membranes—and immunofluorescent tomato-lectin, binding to endothelial plasmalemma carbohydrates [21]. They found increased blood vessel density in the hypoxic preconditioning group after 15 days. In addition to VEGF, brain-derived neurotrophic factors (BDNF) are proangiogenetic, with endothelial cells possessing an inherent ability to produce BDNF. Preclinical studies have reported intravenous BDNF administration to improve motor outcomes following photothrombotic ischemia [22]. BDNF binds to tropomyosin receptor kinase B (TrkB) receptors and activates MAPK/ERK and PI3K/Akt signalling cascades. This cascade induces neuronal differentiation, promoting adaptive mechanisms in the injured brain [23, 24]. BDNF, induced by ROS, activates HIF-1α and nuclear factor erythroid 2–related factor 2 (Nrf2), along with their associated gene programs [19]. Angiogenesis is central to stroke recovery and rehabilitation, and the proliferation of capillary endothelial cells has been reported to have a neuroprotective role [25, 26].

Neurogenesis is another crucial constituent of neuroplasticity. Hypoxic conditions upregulate the expression of HIFs, which in turn activate HIF target genes such as VEGF, FLT-1, EPO, transferrin, IGF-, IGFBP-1 &3, transforming growth factor (TGF)β, glucose transporters 1, 2 & 3, adrenomedullin, pyruvate kinase and others involved in energy metabolism which potentiates neurogenesis [27–30]. Enhanced neurogenesis in the ischemic brain replaces damaged neurons and supports functional recovery. This neuronal regeneration is stimulated by neural progenitor cells (NPC), which proliferate into various types of neurons and glial cells, contributing to brain repair and regeneration [19]. NPC proliferation and their migration from the periventricular zone to the ischemic region support post-stroke recovery [19]. Prolonged conditioning with hypoxia increases the expression of BDNF, which stimulates the differentiation of NPCs into mature neurons and facilitates synaptic plasticity [21]. These newly developed neurons often migrate to ischemic regions to further regenerate more neurons, integrate into the existing neural networks, and support functional and motor recovery. In addition to neurogenesis, the hypoxic state also induces synaptic plasticity by long-term potentiation (LTP). Enhancing LTP sustains the opening and influx of calcium into neuronal cytoplasm, leading to the activation of signalling pathways [31]. Hypoxia-induced synaptic plasticity also involves the remodelling of dendritic spines [32]. Enhanced dendritic spine density and morphology improve synaptic connectivity and communication. These mechanisms support the growth and differentiation of new synapses and foster learning and memory development while mitigating cognitive impairment. Low oxygen exposure for stroke recovery has shown neuroprotective effects by inducing the production of NeuN and synapsin-1 proteins [21]. NeuN is a biomarker for assessing the maturation of neurons, whereas synapsin-1 is found in abundance in the membrane of actively transmitting synaptic vesicles. A study assessing LOPC as a nonpharmacological technique for motor function recovery in stroke found that preconditioning with low oxygen substantially increased NeuN levels at both 15 and 28 days after a stroke incidence and synapsin-1 levels at 30 days after [21].

3.2 Inflammatory and metabolic responses

Inflammation plays a dual role in stroke; it contributes to both injury and repair processes. However, controlled hypoxia can modulate inflammatory responses, influencing the balance between detrimental and beneficial effects. Hypoxia potentially enhances stroke rehabilitation by reducing the expression of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumour necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [33]. There is an exaggerated production and release of these cytokines during and shortly after a stroke has occurred. This further exacerbates brain damage by causing cell death and the blood–brain barrier disruption. Also, HIF-1α activates an anti-inflammatory mechanism, which can mop up free radicals post-stroke [19]. Under hypoxic conditions, HIF-1α promotes the expression of anti-inflammatory genes and pathways by stimulating the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) [19, 33], to resolve inflammation and promote tissue repair. Although hypoxia triggers diverse components of the ischemic injury cascade, including excess ROS production, severe ATP depletion, overload of intracellular calcium, and inflammation [19], intermittent hypoxia training induces neuroprotective effects such as synthesis of antioxidant and ATP-generating enzymes, and a shift in microglia from pro- to anti-inflammatory phenotypes [19].

The extent of neuroinflammation in stroke is often assessed using changes in microglial morphology, particularly referencing their degree of ramification [34, 35]. Microglia are one of the different resident immune cells of the brain that often adopt different activation states in response to hypoxia [36]. Hypoxia can induce a shift from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype in microglia, reducing neuroinflammation and supporting tissue repair and neuroprotection. Studies have identified increased microglia ramification as a neuroprotective mechanism [37]. Pietrogrande et al. reported that stroke reduced microglial ramifications with additional reduced complexity [21]. They hypothesise that LOPC improves microglial ramification, promoting the abundance of microglia typified by reduced inflammation. Metabolic adaptations are critical for the brain's survival and recovery following an ischemic stroke. Under hypoxic conditions, cells shift from aerobic to anaerobic metabolism, increasing the production of glycolytic enzymes and enhancing glucose utilisation. The shift to anaerobic metabolism increases glycolysis and the production of lactate, providing an alternative energy source for neurons' survival during a hypoxic state. Also, hypoxia preconditioning enhances mitochondrial function [29]. This facilitation helps reduce oxidative stress and improve cellular resilience to ischemic injury. Intermittent hypoxic training (IHT) or preconditioning increases the number of mitochondria, reduces structurally altered organelles, forms micromitochondria (microMt), and promotes energetically active mitochondria with vesicular cristae. The excessive reactive ROS in mitochondria, which oxidise proteins, lipids, and DNA, are central to cell damage during hypoxia and reoxygenation. LOPC and IHT induces the production of nitric oxide (NO), ROS, and hypoxia itself to trigger transcription factors into producing neuroprotective proteins to initiate kinase signalling which ultimately activates intracellular protective mechanisms against severe ATP depletion, more oxidative stress and worsening neuroinflammation [19]. Furthermore, low ROS levels induce protective adaptive responses. In addition, IHT reprograms mitochondrial metabolism to ensure adequate ATP production and activates potassium transport in the mitochondrial matrix to protect against Ca2 + overload from acute hypoxia. Numerous studies have shown that HIF is involved in various signaling pathways that modulate the hypoxic response. Specifically, HIF triggers the expression of hypoxia-sensitive microRNAs (miRNAs), which are crucial in regulating the aftermath of hypoxic stress [38].

4 Benefits of hypoxia exposure in ischemic stroke rehabilitation

The potential benefits of hypoxic exposure are not limited to the heart and are also very useful in the brain [39]. When given in a secure and therapeutic setting, hypoxia exposure has proven to be a useful intervention for patients recuperating from ischemic strokes. The notion that hypoxia conditioning can bolster the brain's defenses against ischemic stroke is supported by a number of clinical studies [40, 41]. Numerous studies [42, 43] have also revealed that people with a history of spontaneous transient ischemic episodes in humans have lower stroke severity and better functional outcomes. Exposure to hypoxia during ischemia events provides a number of advantages since it can start a variety of cellular and physiological processes that enhance neuroprotection and recovery. See Table 2.

Hypoxia exposure has been demonstrated to play an important function in neuroprotection. Because of the fact that the brain needs oxygen and glucose to perform a variety of biological processes, including bladder control and creative thinking. However, when a stroke happens, the nervous system's chemical and electrical connection is immediately disturbed due to a shortage of oxygen and glucose. Despite its sophisticated structure, the human brain uses ancient homeostatic systems to combat hypoxia and ischemia. According to Ratan et al. [44], the transcription factor hypoxia-inducible factor-1 (HIF1-1) activates a number of genes that assist neurons to survive in low-oxygen situations following a stroke. Thus, adopting pharmacological or molecular approaches to stimulate hypoxia adaptation, such as blocking HIF prolyl 4 hydroxylases, can significantly maintain brain tissue and enhance good recovery [44, 45].

Hypoxia exposure has also been found to improve neuroplasticity. This is especially useful in stroke rehabilitation since it can help restore functions that were lost due to the ischemic event [46]. Mild intermittent hypoxia (MIH) can activate pathways that boost synaptic plasticity, making it easier to rewire brain circuits and improve motor and cognitive skills [46]. Another notable advantage of hypoxia exposure is its capacity to stimulate angiogenesis. This procedure is critical in ischemic stroke rehabilitation because it increases blood circulation to the afflicted brain regions, which improves oxygen and nutrition delivery. According to Marti et al. [47], they studied the claim that hypoxia causes angiogenesis, which could mitigate the damaging effects of stroke on the nervous system by using hypoxia marker nitroimidazole EF5. They discovered that when they expressed vascular endothelial growth factor and receptors (VEGF/VEGFR) system, which is activated by hypoxia, promotes the formation of new blood vessels after brain ischemia. As a result, increased angiogenesis can lead to greater tissue repair and functional recovery, mitigating the long-term effects of the stroke.

Additionally, Hypoxia exposure can increase mitochondrial biogenesis and improve mitochondrial function. This is important in stroke rehabilitation because greater mitochondrial activity can result in more energy production, which is required for the repair and regeneration of injured brain structures. According to Piao et al. [48], brief mild hypoxia treatment following global ischemia injury surprisingly increased myocardial mitochondrial respiration and metabolism, as well as improved physiological recovery and survival in mouse animals. Finally, hypoxia exposure can be combined with other rehabilitation interventions to improve their effectiveness. Combining hypoxic exposure with physical, occupational, or pharmaceutical therapies can result in more significant changes in patient outcomes [49].

Table 2 Potential benefits of hypoxia exposure in ischemic stroke rehabilitation

Benefit	Mechanism	
Neuroprotection	Hypoxia induces the expression of hypoxia-inducible factor-1 (HIF-1), which activates genes that enhance neuronal survival under low-oxygen conditions	[44, 45]
Improved neuroplasticity	Mild intermittent hypoxia (MIH) activates pathways that boost synaptic plasticity, aiding in the rewiring of brain circuits and improvement in motor and cognitive skills	[46]
Increased angiogenesis	Hypoxia stimulates the vascular endothelial growth factor (VEGF) pathway, promoting the formation of new blood vessels and enhancing blood flow to ischemic brain regions	[47]
Enhanced mitochondrial function	Hypoxia exposure can increase mitochondrial biogenesis and improve mitochondrial function, leading to greater energy production crucial for brain repair and regeneration	[48]
Synergistic effects with other therapies	Combining hypoxia exposure with physical, occupational, or pharmaceutical therapies lead to more significant improvements in patient outcomes	[49]

5 Clinical applications of hypoxia in ischemic stroke rehabilitation

Hypoxia therapy, also known as hypoxic conditioning or training, has emerged as a promising option for stroke rehabilitation [16]. By exposing individuals to low oxygen levels, hypoxia initiates and potentiates adaptive neuronal changes, enhancing neuroplasticity, neuroprotection and angiogenesis [17, 18]. While these neuroadaptive changes of hypoxic conditioning have been leveraged for use in other conditions, its clinical application in stroke rehabilitation has gained more traction in recent years [16–19, 50, 51].

Over the years, various strategies for inducing hypoxia have been employed in clinical strategies for stroke rehabilitation [52]. One of them is intermittent hypoxia training (IHT) using acute intermittent hypoxia (AIH), an approach that has proven beneficial in stroke recovery, particularly for improving locomotor function [52]. In a phase II RCT done to study the efficacy of AIH for stroke rehabilitation, it was found that AIH produces greater gains in locomotor parameters when combined with high-intensity training (HIT) compared to normoxia [52]. This impressive finding is not only limited to clinical efficacy, as several other studies on IHT showed that the technique is not only effective in improving strength and mobility recovery but also safe for use in modulating training-induced neuroplasticity [53].

Hypoxic preconditioning (HPC) is another approach that has been used mostly in preclinical settings on animal models of stroke [54]. By exposing rat models of cerebrovascular ischemia to short and repeated episodes of hypoxia before an anticipated ischemic cerebrovascular event, hypoxic conditioning provides neuroprotection and improves tolerance to neuronal ischemic insults [54, 55]. While HPC protocols also vary, they typically involve alternating bouts of hypoxia (for 2–5 min with oxygen levels around 10–15%) and normoxia. The sessions are usually conducted once to three times daily over days to weeks [54, 55].

Lately, hypobaric hypoxia using reduced atmospheric pressure has also produced positive results in preclinical studies [56]. In this approach, the subject is exposed to reduced atmospheric pressure, mimicking high-altitude scenarios. The lower atmospheric pressure reduces the partial pressure of oxygen, creating a hypoxic state which helps stimulate autoregulatory and neuroprotective changes [57]. This technique was studied by Yaqi et al. (2021), using rat models with middle cerebral artery occlusion. After exposing the rats to 2-h sessions of hypobaric hypoxia for 10 days, the ultrastructural changes in the brain were studied. Proteomic tests and western blotting were also carried out on the preconditioned group. It was found that the preconditioned group had a lower infarct volume compared to control. In addition, the level of cleaved-caspase-3, a marker of cellular injury, was also lesser in the preconditioned group compared to the control [56].

Although hypoxia therapy has shown significant promise from clinical and preclinical studies, an obvious drawback to its implementation is the lack of unified procedure protocols. Thus, further research needs to be done to provide a unified and optimal protocol for understanding the efficacy, safety and side effect profiles of each treatment approach [17]. Standardized protocols on dosing duration and frequency need to be provided [17, 18]. Furthermore, more research needs to be done to understand the applicability and role of hypoxia therapy for stroke rehabilitation in patients with underlying respiratory and cardiovascular comorbidity.

6 Challenges and future directions

A fundamental obstacle relating to patients requiring stroke therapy remains the significant variability in age, stroke site, presence of comorbidities, and severity [58, 59]. This complicates the standardization of hypoxia protocols and outcome prediction.

Furthermore, the scale between therapeutic intermittent hypoxia and potentially toxic hypoxia requires careful balance [60]. As a result, it is difficult to determine the optimal level, timing, and frequency of hypoxia exposure to provide therapeutic benefit.

Although there is some understanding that intermittent hypoxia promotes neuroplasticity and angiogenesis [19], the precise mechanisms through which hypoxia exposure relates to stroke rehabilitation is not fully understood. Consequently, safety concerns exist in terms of individual variability in response to hypoxic exposure due to factors such as genes, environment, and lifestyle.

Future research in this field should factor in individual patient characteristics in the development of hypoxia protocols to yield the best outcomes. The synergistic effect of other rehabilitation methods such as physical therapy and pharmacological intervention should also be explored by later works.

As determining the precise timing and frequency of hypoxia exposure remains a complicated knot, it is a matter of necessity for future work to investigate different hypoxia models to determine the safest and most effective therapeutic approach.

Studies should seek to further bridge the gap in the current understanding of the mechanisms of how hypoxia controls neuroplasticity, angiogenesis, and other processes involved in stroke recovery.

There is also a need for large-scale, multicenter, and multidisciplinary clinical trials to not only validate the efficacy and safety of hypoxia exposure in diverse stroke populations but to also develop standardized guidelines and protocols for clinical use.

Any such studies should also keep an eye on the future through the assessment of long-term effects as it pertains to the quality of life, and secondary stroke prevention.

By addressing these challenges and pursuing these future directions, the field can better understand and harness the potential benefits of hypoxia exposure in ischemic stroke rehabilitation.

7 Conclusion

This review expounded on the impact and benefit of hypoxia exposure either as preconditioning or with intermittent training in the rehabilitation of patients post-ischemic stroke. Our findings identified the substantial benefit of hypoxia exposure in this process. Clinical studies support hypoxia exposure to upscale the brain's defences against ischemic stroke, as it serves to bolster neuroprotection, facilitating a recovery post-ischemic stroke. The mechanism for this is diverse, leveraging angiogenetic and neuroplastic measures, where hypoxia induces the production of HIF and subsequent stimulation of VEGF for the formation of new blood vessels. Additionally, hypoxia condition favours neuroplasticity in diverse ways, including the activation of HIF target genes such as FLT-1, EPO, transferrin, IGF-, IGFBP-1 &3, transforming growth factor (TGF)β, glucose transporters 1, 2 & 3 and adrenomedullin which support neuronal regeneration via proliferation of neuronal progenitor cells. Regulating the extent of neuroinflammation, supporting tissue repair, and increasing microglia ramification are other mechanisms that promote neuronal regeneration and mitigation of further damage in stroke. In care, intermittent hypoxia has shown potential, boosting the regain of motor functions more than using high-intensity training or normoxia. Hypobaric oxygen is showing traction as a potential therapeutic technique, having shown promising outcomes in preclinical trials. Challenges in effectively utilising this technique to rehabilitate stroke patients are not limited to stroke site, presence of comorbidity or disease severity but extend far to include challenges in using optimal hypoxia levels and precise therapeutic exposure frequencies to prevent complications of toxic hypoxia and harness clinical benefits. Further research should be directed at developing a treatment protocol that adopts a patient-centric approach while harnessing the potential of complementary therapeutic modalities for effective patient outcomes.

Author contributions N.A conceptualised the study; NA, GO, EK, BU, AEB, IJO, AM, IAY, AOO, ATO, OO, YAA were involved in the literature review. A.E.B, and N.A extracted the data from the reviewed studies; NA, GO, EK, BU, AEB, IJO, AM, IAY, AOO, ATO, OO, YAA wrote the final and first drafts. NA, GO, EK, BU, AEB, IJO, AM, IAY, AOO, ATO, OO, YAA read and approved the final manuscript.

Funding No funding was received for this study.

Data availability No datasets were generated or analysed during the current study.

Code availability Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

1. Stroke, Cerebrovascular accident. In: WHO. 2024. https://www.emro.who.int/health-topics/stroke-cerebrovascular-accident/index.html. Accessed 11 Jul 2024.
2. Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021;20:795–820.
3. Gorelick PB. The global burden of stroke: persistent and disabling. Lancet Neurol. 2019;18:417–8.
4. Ding Q, Liu S, Yao Y, Liu H, Cai T, Han L. Global, regional, and national burden of ischemic stroke, 1990–2019. Neurology. 2022;98:e279–90.
5. Pu L, Wang L, Zhang R, Zhao T, Jiang Y, Han L. Projected global trends in ischemic stroke incidence, deaths and disability-adjusted life years from 2020 to 2030. Stroke. 2023;54:1330–9.
6. Walter K. What is acute ischemic stroke? JAMA. 2022;327:885.
7. eClinicalMedicine. The rising global burden of stroke. eClinicalMedicine. 2023. https://doi.org/10.1016/j.eclinm.2023.102028.
8. Phipps MS, Cronin CA. Management of acute ischemic stroke. BMJ. 2020;368: l6983.
9. Ferdinand P, Roffe C. Hypoxia after stroke: a review of experimental and clinical evidence. Exp Transl Stroke Med. 2016;8:9.
10. Williams AJ. ABC of oxygen: assessing and interpreting arterial blood gases and acid-base balance. BMJ. 1998;317:1213–6.
11. Serebrovskaya TV. Intermittent hypoxia research in the former soviet union and the commonwealth of independent states: history and review of the concept and selected applications. High Alt Med Biol. 2002;3:205–21.
12. Monson NL, Ortega SB, Ireland SJ, et al. Repetitive hypoxic preconditioning induces an immunosuppressed B cell phenotype during endogenous protection from stroke. J Neuroinflamm. 2014;11:22.
13. Ren C, Han R, Hu J, Li H, Li S, Liu Y, Cheng Z, Ji X, Ding Y. Hypoxia post-conditioning promoted glycolysis in mice cerebral ischemic model. Brain Res. 2020;1748: 147044.
14. Selvaraj UM, Ortega SB, Hu R, Gilchrist R, Kong X, Partin A, Plautz EJ, Klein RS, Gidday JM, Stowe AM. Preconditioning-induced CXCL12 upregulation minimizes leukocyte infiltration after stroke in ischemia-tolerant mice. J Cereb blood flow Metab Off J Int Soc Cereb Blood Flow Metab. 2017;37:801–13.
15. Guan Y, Gu Y, Shao H, et al. Intermittent hypoxia protects against hypoxic-ischemic brain damage by inducing functional angiogenesis. J Cereb Blood Flow Metab. 2023;43:1656–71.
16. Dirnagl U, Becker K, Meisel A. Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use. Lancet Neurol. 2009;8:398–412.
17. Kuriakose D, Xiao Z. Pathophysiology and treatment of stroke: present status and future perspectives. Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21207609.
18 Burtscher J, Mallet RT, Pialoux V, Millet GP, Burtscher M. Adaptive responses to hypoxia and/or hyperoxia in humans. Antioxidants redox Signal. 2022;37:887–912.
19. Sprick JD, Mallet RT, Przyklenk K, Rickards CA. Ischaemic and hypoxic conditioning: potential for protection of vital organs. Exp Physiol. 2019;104(3):278–94. https://doi.org/10.1113/EP087122.
20. Mankovska IM, Serebrovska TV. Mitochondria as a target of intermittent hypoxia. Int J Physiol Pathophysiol. 2015;6:347–62.
21. Pietrogrande G, Zalewska K, Zhao Z, et al. Low oxygen post conditioning as an efficient non-pharmacological strategy to promote motor function after stroke. Transl Stroke Res. 2019;10:402–12. https://doi.org/10.1007/s12975-018-0656-5.
22. Schabitz WR, Steigleder T, Cooper-Kuhn CM, Schwab S, Sommer C, Schneider A, et al. Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis. Stroke. 2007;38(7):2165–72.
23. Numakawa T, Suzuki S, Kumamaru E, Adachi N, Richards M, Kunugi H. BDNF function and intracellular signaling in neurons. Histol Histopathol. 2010;25(2):237–58.
24. Huang EJ, Reichardt LF. Trk receptors: roles in neuronal signal transduction. Annu Rev Biochem. 2003;72(1):609–42.
25. Ergul A, Alhusban A, Fagan SC. Angiogenesis: a harmonized target for recovery after stroke. Stroke. 2012;43(8):2270–4.
26. Li Y, Lu Z, Keogh CL, Yu SP, Wei L. Erythropoietin-induced neurovascular protection, angiogenesis, and cerebral blood flow restoration after focal ischemia in mice. J Cereb Blood Flow Metab. 2007;27(5):1043–54.
27. Ratcliffe PJ, O'rourke JF, Maxwell PH, Pugh CW. Oxygen sensing, hypoxia-inducible factor-1 and the regulation of mammalian gene expression. J Exp Biol. 1998;201(8):1153–62.
28. Semenza GL, Nejfelt MK, Chi SM, Antonarakis SE. Hypoxia-inducible nuclear factors bind to an enhancer element located 3′to the human erythropoietin gene. Proc Natl Acad Sci. 1991;88(13):5680–4.
29. Sharp FR, Ran R, Lu A, Tang Y, Strauss KI, Glass T, Ardizzone T, Bernaudin M. Hypoxic preconditioning protects against ischemic brain injury. NeuroRx. 2004;1(1):26–35.
30. Wang R, Li J, Duan Y, Tao Z, Zhao H, Luo Y. Effects of erythropoietin on gliogenesis during cerebral ischemic/reperfusion recovery in adult mice. Aging Dis. 2017;8(4):410.
31. Migaud M, Charlesworth P, Dempster M, Webster LC, Watabe AM, Makhinson M, He Y, Ramsay MF, Morris RG, Morrison JH, O'Dell TJ, Grant SG. Enhanced long-term potentiation and impaired learning in mice with mutant postsynaptic density-95 protein. Nature. 1998;396(6710):433–9. https://doi.org/10.1038/24790.
32. Aderinto N, AbdulBasit MO, Olatunji G, Adejumo T. Exploring the transformative influence of neuroplasticity on stroke rehabilitation: a narrative review of current evidence. Ann Med Surg. 2023;85(9):4425–32. https://doi.org/10.1097/MS9.0000000000001137.
33. Zhu H, Hu S, Li Y, Sun Y, Xiong X, Hu X, Chen J, Qiu S. Interleukins and ischemic stroke. Front Immunol. 2022;31(13): 828447.

34. Zalewska K, Ong LK, Johnson SJ, Nilsson M, Walker FR. Oral administration of corticosterone at stress-like levels drives microglial but not vascular disturbances post-stroke. Neuroscience. 2017;352:30–8.
35. Karperien A, Ahammer H, Jelinek HF. Quantitating the subtleties of microglial morphology with fractal analysis. Front Cell Neurosci. 2013;7:3.
36. Kanazawa M, Ninomiya I, Hatakeyama M, Takahashi T, Shimohata T. Microglia and monocytes/macrophages polarization reveal novel therapeutic mechanism against stroke. Int J Mol Sci. 2017;18(10):2135.
37. Vinet J, et al. Neuroprotective function for ramified microglia in hippocampal excitotoxicity. J Neuroinflamm. 2012;9:27.
38. Zhang G, Chen L, Liu J, Jin Y, Lin Z, Du S, Fu Z, Chen T, Qin Y, Sui F, Jiang Y. HIF-1α/microRNA-128-3p axis protects hippocampal neurons from apoptosis via the Axin1-mediated Wnt/β-catenin signaling pathway in Parkinson's disease models. Aging. 2020;12(5):4067.
39. Verges S, Chacaroun S, Godin-Ribuot D, Baillieul S. Hypoxic conditioning as a new therapeutic modality. Front Pediatr. 2015;3(June):1–14.
40. Sitzer M. Transient ischaemic attack preceding anterior circulation infarction is independently associated with favourable outcome. J Neurol Neurosurg Psychiatry. 2004;75(4):659–60. https://doi.org/10.1136/jnnp.2003.015875.
41. Castillo J, Moro MÁ, Blanco M, Leira R, Serena J, Lizasoain I, et al. The release of tumor necrosis factor–α is associated with ischemic tolerance in human stroke. Ann Neurol. 2003;54(6):811–9. https://doi.org/10.1002/ana.10765.
42. Weih M, Kallenberg K, Bergk A, Dirnagl U, Harms L, Wernecke KD, et al. Attenuated stroke severity after prodromal TIA. Stroke. 1999;30(9):1851–4. https://doi.org/10.1161/01.STR.30.9.1851.
43. Moncayo J, de Freitas GR, Bogousslavsky J, Altieri M, van Melle G. Do transient ischemic attacks have a neuroprotective effect? Neurology. 2000;54(11):2089–94. https://doi.org/10.1212/WNL.54.11.2089.
44. Ratan RR, Siddiq A, Smirnova N, Karpisheva K, Haskew-Layton R, McConoughey S, et al. Harnessing hypoxic adaptation to prevent, treat, and repair stroke. J Mol Med. 2007;85(12):1331–8. https://doi.org/10.1007/s00109-007-0283-1.
45. Davis CK, Jain SA, Bae ON, Majid A, Rajanikant GK. Hypoxia mimetic agents for ischemic stroke. Front Cell Dev Biol. 2019;6(January):1–12.
46. Mukandala G, Tynan R, Lanigan S, O'Connor J. The effects of hypoxia and inflammation on synaptic signaling in the CNS. Brain Sci. 2016;6(1):6.
47. Marti HJH, Bernaudin M, Bellail A, Schoch H, Euler M, Petit E, et al. Hypoxia-induced vascular endothelial growth factor expression precedes neovascularization after cerebral ischemia. Am J Pathol. 2000;156(3):965–76.
48. Piao L, Fang YH, Wu R, Hamanaka R, Mutlu G, Archer S, et al. Mild hypoxia as therapy for post-ischemic mitochondrial injury. Physiology. 2023. https://doi.org/10.1152/physiol.2023.38.S1.5734904.
49. Yuan H, Liu J, Gu Y, Ji X, Nan G. Intermittent hypoxia conditioning as a potential prevention and treatment strategy for ischemic stroke: current evidence and future directions. Front Neurosci. 2022;16(November):1–17.
50. Lo EH, Albers GW, Dichgans M, et al. Circadian biology and stroke. Stroke. 2021;52:2180–90.
51. Esposito E, Li W, Mandeville ET, et al. Potential circadian effects on translational failure for neuroprotection. Nature. 2020;582:395–8.
52. Hornby TG, Plawecki A, Lotter JK, Shoger LH, Voigtmann CJ, Inks E, Henderson CE. Acute intermittent hypoxia with high-intensity gait training in chronic stroke: a phase II randomized crossover trial. Stroke. 2024;55:1748.
53. Pearcey G, Barry A, Sandhu M, Roth E, Carroll TJ, Rymer WZ. Acute intermittent hypoxia in people living with chronic stroke-a preliminary study to examine safety and efficacy as a neurorehabilitation intervention. medRxiv. 2023:2023–12.
54. Wacker BK, Park TS, Gidday JM. Hypoxic preconditioning-induced cerebral ischemic tolerance: role of microvascular sphingosine kinase 2. Stroke. 2009;40(10):3342–8.
55. Tang Y, Pacary E, Fréret T, Divoux D, Petit E, Schumann-Bard P, Bernaudin M. Effect of hypoxic preconditioning on brain genomic response before and following ischemia in the adult mouse: identification of potential neuroprotective candidates for stroke. Neurobiol Dis. 2006;21(1):18–28.
56. Wan Y, Huang L, Liu Y, Ji W, Li C, Ge RL. Preconditioning with intermittent hypobaric hypoxia attenuates stroke damage and modulates endocytosis in residual neurons. Front Neurol. 2021;15(12): 750908.
57. Subudhi AW, Panerai RB, Roach RC. Effects of hypobaric hypoxia on cerebral autoregulation. Stroke. 2010;41(4):641–6.
58. Gottesman RF, Seshadri S. Risk factors, lifestyle behaviors, and vascular brain health. Stroke. 2022;53(2):394–403.
59. Kayser B, Verges S. Hypoxia, energy balance, and obesity: an update. Obes Rev an Off J Int Assoc Study Obes. 2021;22(Suppl 2): e13192.
60. Serebrovskaya TV, Xi L. Intermittent hypoxia training as non-pharmacologic therapy for cardiovascular diseases: practical analysis on methods and equipment. Exp Biol Med. 2016;241(15):1708–23.