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Commentaries

Rejuvenation Through Oxygen, More or Less

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Abstract

Modest modulation of oxygen intake, either by inducing mild intermittent hypoxia or hyperoxia appears to induce modest rejuvenative changes in mammals, in part, by activating key regulator hypoxia-induced factor 1a (HIF-1a). Interestingly both lower oxygen and transient higher oxygen levels induce this hypoxia regulator. Hyperbaric oxygen induces HIF-1a by the hyperoxic–hypoxic paradox that results from an overinduction of protective factors under intermittent hyperoxic conditions, leading to a state somewhat similar to that induced by hypoxia. A key difference being that SIRT1 is induced by hyperoxia, whereas it is reduced during hypoxia by the activity of HIF-1a. In a recent report, a small clinical trial employing 60 sessions of intermittent hyperbaric oxygen therapy (HBOT) studying old humans resulted in increased mean telomere length of immune cells including B cells, natural killer cells, T helper, and cytotoxic T lymphocytes. Moreover, there was a reduction in $CD28^{null}$ senescent T helper and cytotoxic T cells. In a parallel report, HBOT has been reported to enhance cognition in older adults, especially attention and information processing speed through increased cerebral blood flow (CBF) in brain regions where CBF tends to decline with age. The durability of these beneficial changes is yet to be determined. These preliminary results require follow-up, including more extensive characterization of changes in aging-associated biomarkers. An interesting avenue of potential work is to elucidate potential connections between hypoxia and epigenetics, especially the induction of the master pluripotent regulatory factors, which when expressed transiently have been reported to ameliorate some aging biomarkers and pathologies.

Keywords: hypoxia, hyperbaric oxygen therapy, hyperoxic–hypoxic paradox, immunosenescence, cognitive decline

Introduction

Inducing intermittent mild cellular stress to affect aging has become a common research topic in recent years. Among the types of stress thought to be potentially beneficial are caloric restriction, potentially mediated by intermittent fasting[1] and both intermittent hypoxia and hyperoxia,[2,3] although other potential stressors such as temperature have been less well investigated in this context. Recent study on the role of oxygen in aging and lifespan has provided tantalizing hints that induced intermittent fluctuation in oxygen could have benefit in aging. Such research on mammals is complicated: although air contains 20.8% oxygen, most of the oxygen is carried by hemoglobin in the blood with low amounts of dissolved oxygen and huge variation of partial oxygen pressures throughout the body and within cells.[3]

Chronic deficits and surpluses of oxygen can be significantly detrimental, for example, prolonged high levels of oxygen are toxic to many organisms, but, however, sometimes beneficial to homeostasis and animal physiology. The key difference appears to be the extent of the alteration from normoxia and its duration. Large deviations from normal oxygen conditions are typically but not always detrimental. For example, both severe high and low oxygen conditions shorten the lifespan of adult *Drosophila melanogaster*,[4,5] but mild hypoxia actually increases the lifespan of *Drosophila*[6] and *C. elegans*.[7]

The story for chronic deviations from normoxia is more complex in mammals. Exposure of mice to 100% oxygen for 3 days after birth shortens lifespan and increases pulmonary hypertension,[8] whereas exposure to 7% oxygen for 3 weeks results in increased mortality in mice, although a 2-week regimen is actually beneficial.[9] There is at least one circumstance, wherein mild chronic hypoxia is clearly beneficial: mitochondrial diseases. It has been reported that mild hypoxia suppresses neurological damage associated

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with mitochondrial diseases based on mutations that diminish electron transport chain function, such as a Leigh's syndrome mouse model.[10,11]

Humans are naturally exposed to mild hypoxia by virtue of living at high altitudes. People living in the Himalayan mountains have lower rates of hypertension, diabetes, and obesity.[12] Lower obesity and blood lipid levels were observed in China in people living at high altitude,[13] although Tibetans at high altitude exhibited increased congenital heart disease,[14] suggesting potential developmental consequences, as well as shorter lifespans. In the Swiss Alps, people at high elevations report less coronary artery disease and stroke.[15] Given that various genetic variants that promote living at high altitudes have arisen in these populations, such as increased hemoglobin levels in people living in the Andes mountains, or decreased Hb levels in some Tibetans due to mutations in EGLN1 and hypoxia-induced factor (HIF)-2a,[16–18] as well as significant differences in diet and lifestyle, far-reaching conclusions are not possible. However, living at high altitudes may prove of benefit to humans with mitochondrial diseases as mentioned earlier.

The most interesting data with regard to a potential regenerative or rejuvenative role for modulating oxygen levels derive from work with mild hypoxic or hyperoxic treatments. Intermittent hyperbaric oxygen therapy (HBOT) increases wound healing rates in mice[19] and humans,[20] whereas mild hypoxia for 2 weeks promotes restoration of heart function and stimulates adult postmitotic cardiomyocytes to proliferate resulting in heart regeneration in a mouse model of myocardial infarction[9] as well as protecting rodents from reperfusion injury.[21] Of special interest to aging is that intermittent mild hypoxia (11.8%) combined with excessive carbon dioxide (CO_2), hypercapnia at 6.5%, increased the median lifespan of rats by 16% with increased cognitive, motor, and reproductive function as well as stamina. Interestingly, mice responded less significantly to this regimen,[22] which may be due to the requirement to tune such therapies for each species or even individually.

What are the mechanisms by which intermittent mild hypoxia or hyperoxia alter cellular function in similar ways? The most encompassing explanation is provided by the hyperoxic hypoxic paradox. Hypoxic conditions are sensed by prolyl hydroxylase (PHD) domain proteins of which there are three isoforms, which then hydroxylate master regulatory protein HIF-1a that under normal O_2 levels is unstable, but after hydroxylation dimerizes with HIF-1b to form active hypoxia inhibitory factor (HIF) to activate the transcription of erythropoetin to increase red blood cell formation, vascular endothelial growth factor to increase blood vessel formation, pyruvate dehydrogenase kinase 1 (PDK1) and glucose transporters to help in the transition from oxidative phosphorylation to glycolysis.[2] The benefit to regeneration may be explained by short-term hypoxia by both maintaining stem cells in their niche and in some cases stimulating proliferation and differentiation.[23–25] The story is complicated by the existence of HIF-1b and HIF-1c that lack a transcriptional activation domain. These can, respectively, dimerize with HIF-1b, HIF-2b, and HIF-3b. Nevertheless, the essential idea is that HIF-1a activation plays a key role in reprogramming cellular metabolism and inducing protective responses. Downstream, AMP kinase is activated by the increase in low energy AMP and ADP metabolites to inhibit mTORC1 by phosphorylation. This could explain the potential lifespan and health span benefits of intermittent hypoxia, as inhibition of mTOR by rapamycin is known to increase lifespan and health span in rodents.

One change associated with hypoxia that is probably counterproductive in aging is that HIF-1 interacts with and inhibits sirtuin 1 (SIRT1) that requires NAD+, which is reduced under hypoxic conditions because less NADH is consumed by the mitochondria. In general, SIRT1 tends to oppose HIF-1 by inactivating it through acetylation.[26] SIRT1 is reduced in aging and when boosted by metabolic supplementation with Nicotinamide mononucleotide (NMN) or Nicotinamide Riboside (NR), it has been reported to increase various measures of health span such as exercise capacity and muscle strength in rodents. Perhaps the most significant effect at the cellular level is that HIF-1 inhibits mitochondrial biogenesis while SIRT1 stimulates mitochondrial biogenesis.[27]

But what of the hypoxic–hyperoxic paradox? The hypothesis postulates that HBOT over several cycles induces transient high oxygen levels that induce high reactive oxygen species (ROS), whereas high ROS, in turn, induces longer lasting free radical scavenging regulators such as glutathione peroxidase, catalase, and superoxide dismutases, which persist longer than the ROS. Because the PHD enzymes that control HIF-1a levels need ROS to become activated, there is less degradation of HIF1-a, which essentially causes the hyperoxia due to HBOT to mimic hypoxia. More data would be helpful to establish the validity of this hypothesis. But the hypoxia-like state created by HBOT is different from hypoxia in at least one key way: hyperoxia increases the citric acid cycle and mitochondrial metabolism, activating SIRT1 through the presence of high NAD+, stimulating mitochondrial biogenesis.[28] In fact, intermittent hyperoxia protects against cerebral ischemia in various stroke models in rats.[29–31]

Hyperbaric Oxygen Increases Telomere Length

In a pair of related preliminary clinical studies from Hachmo, Haddany, and Efrati, HBOT evoked rejuvenative responses in human immune systems[32] and cognitive function.[33] In an uncontrolled study, 35 older adults, at least 64 years old, with a mean age of 68 years, were treated with 100% oxygen at 2 atmospheres for 90 minutes with 5-minute breaks every 20 minutes daily for 60 days. Peripheral blood cells were isolated by standard centrifugation methods using density gradients and subjected to analysis at day 0, days 30 and 60, and then 1–2 weeks after the end of the HBOT. Hachmo et al. observed a statistically significant increase of at least 20% in the telomere lengths of B cells T-helper cells, cytotoxic T cells, and natural killer cells after HBOT treatments using hybridization of standard fluorescent DNA probe for human telomere sequences and then quantifying the fluorescence. Increased telomere length was apparent by 30 days with the effect strongest in B cells. The effect persisted for at least 1–2 weeks after HBOT was discontinued.[32] Unfortunately induction of telomerase was not measured that could help distinguish between proliferative stimulation of stem cells with relatively longer telomeres or actual induction of telomerase in B and T cells.

To study whether there was a reduction of senescent immune cells, flow cytometric analysis for immune senescence

biomarker CD28 was performed in the context of identifying immune cells based on classical biomarkers, such as CD4. $CD28^{null}$ cells were considered senescent as the absence of T cell costimulatory CD28 compromises the function of $CD4^+$ and $CD8^+$ T cells.[34,35] The number of senescent T cells has been observed to increase with aging in humans.

There was a modest statistically significant decrease in the presence of T-helper and cytotoxic T cells at the 30th session, the 60th session, and after 1–2 weeks posttreatment, suggesting the possible elimination of some senescent immune cells by HBOT treatment. CD57 was not tested as an additional biomarker for senescence. Interestingly HIF-1a levels increased during the HBOT sessions as expected for the hyperoxic–hypoxic paradox, although they returned to baseline by 2 weeks after the HBOT was ended.[32]

Amir et al. conducted a second controlled clinical trial with 63 adults >64 years old, mean age 69.7 years, without cognitive clinical decline with similar global cognitive scores. Subjects were treated similarly to the study by Hachmo et al., with the following differences: there were 60 daily sessions spread for 3 months with 5 sessions per week. Cerebral blood flow (CBF), which is altered with aging in several key regions such as the superior medial frontal gyrus and the middle frontal gyrus, was measured by MRI, and cognitive ability was measured by the Neurotrax computerized cognitive testing battery, the CANTAB computerized cognitive battery, and a variety of traditional paper and pencil tests. The primary endpoint was a global cognitive score.[33]

For the 33 people in the HBOT group, significant increases in CBF were observed in global cognitive function, attention and information processing speed, as well as executive function. The specific regions observed to have increased CBF are all associated with age-related decline and include the left middle frontal gyrus, left superior frontal gyrus, right superior parietal gyrus, right superior medial frontal gyrus, supplementary motor area, and the right middle frontal gyrus.[33]

Both of these clinical trials are in need of replication with greater number of participants, more specific primary endpoints, and measurement of an increased number of biomarkers. However, the preliminary results are tantalizing, with even some preliminary data that suggest the hyperoxic–hypoxic paradox is valid and that there could be benefit from HBOT in aging humans.

Medical Implications

HBOT and even intermittent hypoxia are attractive potential therapies because they are easily implemented. Of the two, achieving intermittent hypoxia may be as simple as short-term holding or controlling one's breath. Could lifespan or health span enhancement result from simply holding one's breath or engaging in meditative techniques focused on slowing respiration?

Hachmo et al. report that HBOT can increase telomere length, which though not a particularly good biomarker for aging, at least tends to correlate roughly with age and health.[36] Similarly, another study reported that mild hypoxia for 7 days induces telomere elongation in the heart and lungs of rats and protects them from fatal damage.[37] That hypoxia is a key component of the HBOT effect is supported by a clinical study in which intermittent hypoxia training increased verbal learning scores in a small cohort of seven people.[38] There are numerous other preliminary clinical studies that show benefit for HBOT and intermittent hypoxia: simulating high-altitude conditions (hypoxia) for exercise improves the quality of life and physical performance in patients with heart failure,[39] using daily intermittent hypoxia increases the ability to walk after spinal cord injury,[40] and in another study intermittent hypoxia increases glucose tolerance in prediabetes patients.[41] Bayer et al. alternated hypoxia with hyperoxia as part of a complex exercise and physiological regimen to improve cognitive performance in geriatric patients.[42] You et al. used HBOT as an adjunctive therapy in combination with various more conventional therapies to modestly improve the mental state of vascular dementia patients[43] and Serebrovska et al. used an alternating intermittent hypoxia/hyperoxia regimen to improve cognitive function in Alzheimer's disease patients with mild cognitive impairment.[44] In a prospective clinical trial, HBOT improved the quality of life for fibromyalgia patients and attenuated their abnormal brain activity.[45]

Preclinical studies with similar promising results include HBOT restoring cognitive function as well as decreasing insulin resistance and hippocampal aging pathologies in aging and obese old rats,[46] reducing degeneration and apoptosis in spinal cord injured rats subjected to HBOT through upregulation of BDNF/TrkB signaling,[47] decreasing inflammation after intracerebral hemorrhage in rats by modulation of microglia,[48] and attenuating Parkinson's disease (PD) symptoms in combination with benserazide in a rat PD model.[49] Hyperbaric oxygen treatment was reported to promote the regeneration of nerves after cutting sciatica nerves in rats[50] and help regenerate contused rat muscles through macrophage and satellite cell activation,[51] and to protect against apparent accelerated neural aging-like damage by injected D-galactose in mice.[52,53]

Are there any negative consequences of intermittent hypoxia? Perhaps one of the best studied are problems that arise from chronic obstructive sleep apnea that typically results in numerous episodes of hypoxia throughout a sleep period that lead to brain aging.[54] Numerous studies suggest that sleep apnea can accelerate numerous hallmarks of aging, including telomere attrition, cell senescence,[55] and exhaustion of stem cells.[56] How can the benefits observed by intermittent hypoxia or HBOT regimens be reconciled with the detrimental effects of sleep apnea? Probably the simplest hypothesis is that sleep apnea exceeds safety thresholds for hypoxia both in quantity and duration, resulting in damage rather than benefit.

Since increased telomere length is not as good a biomarker for aging as some other measures such as DNA methylation clocks,[57,58] it would be of great benefit to extend these HBOT clinical studies to assess potential age reversal by DNA methylation clock analysis, which has become the gold standard for biological age determination. Given that HIF-1a can affect epigenetic regulatory enzymes including histone lysine and DNA demethylases,[59,60] and that HIF-1a is needed during pluripotent cell reprogramming for the required shift to glycolytic metabolism,[61] it is possible that transient hypoxic states may be able to affect DNA

methylation age. If HIF-1 activation does decrease DNA methylation-based age, it would not be surprising to find that HBOT does this by transiently or partially inducing Yamanaka master pluripotency factors that have been reported to rejuvenate adult cells.[62–64] In fact, HIF or hypoxia has been reported to induce expression of these pluripotent stem cell master regulators such as Oct4, Sox2, Kilf4, c-Myc, Nanog, and miRNA-302 in cancer cells[65,66] and to upregulate at least some of these factors, such as Klf4 and Oct4, in normal cells.[67,68] It would be of great interest to query whether expression of these master factors was transiently increased, especially in stem cells, for those undergoing HBOT therapy.

Is there any way to easily obtain most of the effects of HBOT that includes both activation of HIF-1a and SIRT1 without a special apparatus? It might be possible to couple transient intermittent hypoxia achieved by controlled breathing with supplementation of precursors such as NR or NMN to raise NAD+ levels, which has been reported to have benefit in aging-related dysfunction.[69]

Perhaps hypoxia mimetics are not really needed, given how easily hypoxia and hyperoxia can be achieved. However, there is a long history of development of drugs designed to modulate HIF-1a often by inhibiting PHDs. Interestingly they confer a variety of beneficial effects on animal models, especially relating to increased regenerative capacity. For example, FG-4497, a HIF prolylhydroxylase inhibitor, increases hippocampal memory in mice.[70] Similarly, ML228, a HIF-1A activator, attenuates inflammation and damage after transient global ischemia.[71] ML228 also promoted neural functional recovery in a spinal cord injury model in rats.[72] Of interest is that at least in the case of mitochondrial diseases such as Leigh syndrome, actual mild hypoxia is more effective at ameliorating symptoms than the small molecule drugs tested to activate HIF-1a.[10]

In the end, although such drugs may be more easily developed because financial incentives play a key role in determining which clinical studies get performed, the low cost of implementing intermittent hypoxic treatments and HBOT may win the day, contingent on finding trial sponsors, perhaps noncommercial sponsors.

It would be remiss not to mention that solid tumors often have hypoxic cores in which induction and activation of HIF-1a play a key role in helping tumors resist therapeutic intervention, in part, by suppressing apoptotic cell death. However, activation of HIF-1a by HBOT and intermittent hypoxia is unlikely to contribute much additional protection to pre-existing tumors because they are already hypoxic, but in theory such regimens could help promote early tumorigenesis by activating HIF-1a, a possibility that should be studied epidemiologically should such regimens become popular.

What about safety? Despite all the potential benefits already listed, HBOT does have known side effects, which include dental damage, sinus damage, middle ear damage, lung damage, and rarely seizures through lipid peroxidation.[20] However, overall, HBOT and especially self-directed intermittent hypoxia therapies (by controlling breathing) appear relatively safe, especially when exposure to high oxygen levels is kept <2 hours and <3 atmospheres of pressure is applied. They appear to be promising treatments to potentially ameliorate some of the consequences of growing old, but more study is needed to carefully elucidate the optimal protocols and potential benefits, as well as potential problems.

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References

1. Martin B, Mattson MP, Maudsley S. Caloric restriction and intermittent fasting: Two potential diets for successful brain aging. Ageing Res Rev 2006;5:332–353.
2. van Vliet T, Casciaro F, Demaria M. To breathe or not to breathe: Understanding how oxygen sensing contributes to age-related phenotypes. Ageing Res Rev 2021;67:101267.
3. Hadanny A, Efrati S. The hyperoxic-hypoxic paradox. Biomolecules 2020;10:958.
4. Rascón B, Harrison JF. Lifespan and oxidative stress show a non-linear response to atmospheric oxygen in Drosophila. J Exp Biol 2010;213:3441–3448.
5. Zhao HW, Ali SS, Haddad GG. Does hyperoxia selection cause adaptive alterations of mitochondrial electron transport chain activity leading to a reduction of superoxide production? Antioxid Redox Signal 2012;16:1071–1076.
6. Li QF, Wang H, Zheng L, et al. Effects of modest hypoxia and exercise on cardiac function, sleep-activity, negative geotaxis behavior of aged female drosophila. Front Physiol 2020;10:1610.
7. Leiser SF, Fletcher M, Begun A, Kaeberlein M. Life-span extension from hypoxia in *Caenorhabditis elegans* requires both HIF-1 and DAF-16 and is antagonized by SKN-1. J Gerontol 2013;68:1135–1144.
8. Yee M, White RJ, Awad HA, Bates WA, McGrath-Morrow SA, O'Reilly MA. Neonatal hyperoxia causes pulmonary vascular disease and shortens life span in aging mice. Am J Pathol 2011;178:2601–2610.
9. Nakada Y, Canseco DC, Thet S, et al. Hypoxia induces heart regeneration in adult mice. Nature 2017;541:222–227.
10. Jain IH, Zazzeron L, Goli R, et al. Hypoxia as a therapy for mitochondrial disease. Science 2016;352:54–61.
11. Ferrari M, Jain IH, Goldberger O, et al. Hypoxia treatment reverses neurodegenerative disease in a mouse model of Leigh syndrome. Proceed Natl Acad Sci 2017;114:E4241–E4250.
12. Negi PC, Bhardwaj R, Kandoria A, et al. Epidemiological study of hypertension in natives of Spiti Valley in Himalayas and impact of hypobaric hypoxemia; a cross-sectional study. J Assoc Phys India 2012;60:21–25.
13. Huang X, Hu Y, Du L, et al. Metabolic syndrome in native populations living at high altitude: A cross-sectional survey in Derong, China. BMJ Open 2020;10:e032840.
14. Chun H, Yue Y, Wang Y, et al. High prevalence of congenital heart disease at high altitudes in Tibet. Eur J Prev Cardiol 2019;26:756–759.
15. Faeh D, Gutzwiller F, Bopp M. Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. Circulation 2009;120:495–501.
16. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. Proc Natl Acad Sci U S A 2007;104:8655–8660.

17. Beall CM, Cavalleri GL, Deng L, et al. Natural selection on EPAS1 (HIF2α) associated with low hemoglobin concentration in Tibetan highlanders. Proc Natl Acad Sci U S A 2010;107:11459–11464.
18. Lorenzo FR, Huff C, Myllymäki M, et al. A genetic mechanism for Tibetan high-altitude adaptation. Nat Genet 2014;46:951–956.
19. Zhang Q, Gould LJ. Hyperbaric oxygen reduces matrix metalloproteinases in ischemic wounds through a redox-dependent mechanism. J Invest Dermatol 2014;134:237–246.
20. Heyboer M, Sharma D, Santiago W, McCulloch N. Hyperbaric oxygen therapy: Side effects defined and quantified. Adv Wound Care 2017;6:210–224.
21. Cai Z, Dominador JM, Guo W, et al. Hearts from rodents exposed to intermittent hypoxia or erythropoietin are protected against ischemia-reperfusion injury. Circulation 2003;108:79–85.
22. Kulikov VP, Tregub PP, Osipov IS, Trukhanov AI. Hypercapnic hypoxia as a potential means to extend life expectancy and improve physiological activity in mice. Biogerontology 2019;20:677–686.
23. Mohammad K, Dakik P, Medkour Y, Mitrofanova D, Titorenko VI. Quiescence entry, maintenance, and exit in adult stem cells. Int J Mol Sci 2019;20:2158.
24. Peña-Villalobos I, Casanova-Maldonado I, Lois P, et al. Hyperbaric oxygen increases stem cell proliferation, angiogenesis and wound-healing ability of WJ-MSCs in diabetic mice. Front Physiol 2018;9:995.
25. Das R, Jahr H, van Osch GJVM, Farrell E. The role of hypoxia in bone marrow–derived mesenchymal stem cells: Considerations for regenerative medicine approaches. Tissue Eng Part B 2009;16:159–168.
26. Chen R, Dioum EM, Hogg RT, Gerard RD, Garcia JA. Hypoxia increases sirtuin 1 expression in a hypoxia-inducible factor-dependent manner *. J Biol Chem 2011; 286:13869–13878.
27. Bonkowski MS, Sinclair DA. Slowing ageing by design: The rise of NAD(+) and sirtuin-activating compounds. Nature Reviews. Mol Cell Biol 2016;17:679–690.
28. Yan W, Fang Z, Yang Q, et al. SirT1 mediates hyperbaric oxygen preconditioning-induced ischemic tolerance in rat brain. J Cerebral Blood Flow Metabol 2013;33:396–406.
29. Xue F, Huang J, Ding P, et al. Nrf2/antioxidant defense pathway is involved in the neuroprotective effects of Sirt1 against focal cerebral ischemia in rats after hyperbaric oxygen preconditioning. Behav Brain Res 2016;309:1–8.
30. Hu Q, Liang X, Chen D, et al. Delayed hyperbaric oxygen therapy promotes neurogenesis through reactive oxygen species/hypoxia-inducible factor-1α/β-catenin pathway in middle cerebral artery occlusion rats. Stroke 2014;45: 1807–1814.
31. Hu Q, Manaenko A, Bian H, et al. Hyperbaric oxygen reduces infarction volume and hemorrhagic transformation through ATP/NAD+/Sirt1 pathway in hyperglycemic MCAO rats. Stroke 2017;48:1655–1664.
32. Hachmo Y, Hadanny A, Abu Hamed R, et al. Hyperbaric oxygen therapy increases telomere length and decreases immunosenescence in isolated blood cells: A prospective trial. Aging (Albany NY) 2020;12:22445–22456.
33. Amir H, Malka D-K, Gil S, et al. Cognitive enhancement of healthy older adults using hyperbaric oxygen: A randomized controlled trial. Aging (Albany NY) 2020;12:13740–13761.
34. Warrington KJ, Vallejo AN, Weyand CM, Goronzy JJ. CD28 loss in senescent CD4+ T cells: Reversal by interleukin-12 stimulation. Blood 2003;101:3543–3549.
35. Bryl E, Witkowski JM. Decreased proliferative capability of CD4(+) cells of elderly people is associated with faster loss of activation-related antigens and accumulation of regulatory T cells. Exp Gerontol 2004;39:587–595.
36. Fasching CL. Telomere length measurement as a clinical biomarker of aging and disease. Crit Rev Clin Lab Sci 2018;55:443–465.
37. Wang Y, Zhao Z, Zhu Z, et al. Telomere elongation protects heart and lung tissue cells from fatal damage in rats exposed to severe hypoxia. J Physiol Anthropol 2018;37.
38. Wang H, Shi X, Schenck H, et al. Intermittent hypoxia training for treating mild cognitive impairment: A pilot study. Am J Alzheimers Dis 2020;35:1533317519896725.
39. Saeed O, Bhatia V, Formica P, et al. Improved exercise performance and skeletal muscle strength after simulated altitude exposure: A novel approach for patients with chronic heart failure. J Cardiac Fail 2012;18:387–391.
40. Hayes HB, Jayaraman A, Herrmann M, Mitchell GS, Rymer WZ, Trumbower RD. Daily intermittent hypoxia enhances walking after chronic spinal cord injury. Neurology 2014;82:104–113.
41. Serebrovska TV, Portnychenko AG, Drevytska TI, et al. Intermittent hypoxia training in prediabetes patients: Beneficial effects on glucose homeostasis, hypoxia tolerance and gene expression. Exp Biol Med 2017;242:1542–1552.
42. Bayer U, Likar R, Pinter G, et al. Intermittent hypoxic–hyperoxic training on cognitive performance in geriatric patients. Alzheimers Dement 2017;3:114–122.
43. You Q, Li L, Xiong S, et al. Meta-analysis on the efficacy and safety of hyperbaric oxygen as adjunctive therapy for vascular dementia. Front Aging Neurosci 2019;11:86.
44. Serebrovska ZO, Serebrovska TV, Kholin VA, et al. Intermittent hypoxia-hyperoxia training improves cognitive function and decreases circulating biomarkers of Alzheimer's disease in patients with mild cognitive impairment: A pilot study. Int J Mol Sci 2019;20:5405.
45. Efrati S, Golan H, Bechor Y, et al. Hyperbaric oxygen therapy can diminish fibromyalgia syndrome—Prospective clinical trial. PLoS One 2015;10:e0127012.
46. Shwe T, Bo-Htay C, Ongnok B, et al. Hyperbaric oxygen therapy restores cognitive function and hippocampal pathologies in both aging and aging-obese rats. Mechan Ageing Dev 2021;195:111465.
47. Ying X, Tu W, Li S, et al. Hyperbaric oxygen therapy reduces apoptosis and dendritic/synaptic degeneration via the BDNF/TrkB signaling pathways in SCI rats. Life Sci 2019;229:187–199.
48. Yang L, Tang J, Chen Q, et al. Hyperbaric oxygen preconditioning attenuates neuroinflammation after intracerebral hemorrhage in rats by regulating microglia characteristics. Brain Res 2015;1627:21–30.
49. Pan X, Chen C, Huang J, Wei H, Fan Q. Neuroprotective effect of combined therapy with hyperbaric oxygen and madopar on 6-hydroxydopamine-induced Parkinson's disease in rats. Neurosci Lett 2015;600:220–225.
50. Ince B, Arslan A, Dadaci M, Oltulu P, Bilgen F. The effect of different application timings of hyperbaric oxygen treatment on nerve regeneration in rats. Microsurgery 2016; 36:586–592.

51. Oyaizu T, Enomoto M, Yamamoto N, et al. Hyperbaric oxygen reduces inflammation, oxygenates injured muscle, and regenerates skeletal muscle via macrophage and satellite cell activation. Sci Rep 2018;8:1288.
52. Chen X, Li Y, Chen W, Nong Z, Huang J, Chen C. Protective effect of hyperbaric oxygen on cognitive impairment induced by d-galactose in mice. Neurochem Res 2016;41:3032–3041.
53. Chen C, Huang L, Nong Z, et al. Hyperbaric oxygen prevents cognitive impairments in mice induced by d-galactose by improving cholinergic and anti-apoptotic functions. Neurochem Res 2017;42:1240–1253.
54. Weihs A, Frenzel S, Wittfeld K, et al. Associations between sleep apnea and advanced brain aging in a large-scale population study. Sleep 2021;44:zsaa204.
55. Polonis K, Becari C, Chahal CAA, et al. Chronic intermittent hypoxia triggers a senescence-like phenotype in human white preadipocytes. Sci Rep 2020;10:6846.
56. Gaspar L, Alvaro A, Moita J, Cavadas C. Obstructive sleep apnea and hallmarks of aging. Trends Mol Med 2017;23: 675–692.
57. Breitling LP, Saum K-U, Perna L, Schöttker B, Holleczek B, Brenner H. Frailty is associated with the epigenetic clock but not with telomere length in a German cohort. Clin Epigenet 2016;8:21.
58. Liu Z, Leung D, Thrush K, et al. Underlying features of epigenetic aging clocks in vivo and in vitro. Aging Cell 2020;19:e13229.
59. Matuleviciute R, Cunha PP, Johnson RS, Foskolou IP. Oxygen regulation of TET enzymes. FEBS J. [Epub ahead of print]; DOI: 10.1111/febs.15695.
60. Anand C, Hemanta A, William GW, Kyle KB. Insights into the function and regulation of Jumonji C Lysine demethylases as hypoxic responsive enzymes. Curr Prot Peptide Sci 2020;21:642–654.
61. Mathieu J, Zhou W, Xing Y, et al. Hypoxia-inducible factors have distinct and stage-specific roles during reprogramming of human cells to pluripotency. Cell Stem Cell 2014;14:592–605.
62. Sarkar TJ, Quarta M, Mukherjee S, et al. Transient non-integrative nuclear reprogramming promotes multifaceted reversal of aging in human cells. Nat Commun 2020;11:1545.
63. Rodríguez-Matellán A, Alcazar N, Hernández F, Serrano M, Ávila J. In vivo reprogramming ameliorates aging features in dentate gyrus cells and improves memory in mice. Stem Cell Rep 2020;15:1056–1066.
64. Ocampo A, Reddy P, Martinez-Redondo P, et al. In vivo amelioration of age-associated hallmarks by partial reprogramming. Cell 2016;167:1719–1733.e12.
65. Mathieu J, Zhang Z, Zhou W, et al. HIF induces human embryonic stem cell markers in cancer cells. Cancer Res 2011;71:4640–4652.
66. Bae K-M, Dai Y, Vieweg J, Siemann DW. Hypoxia regulates SOX2 expression to promote prostate cancer cell invasion and sphere formation. Am J Cancer Res 2016;6: 1078–1088.
67. Shan F, Huang Z, Xiong R, Huang Q-Y, Li J. HIF1α-induced upregulation of KLF4 promotes migration of human vascular smooth muscle cells under hypoxia. J Cell Physiol 2020;235:141–150.
68. Firth AL, Yao W, Remillard CV, Ogawa A, Yuan JX-J. Upregulation of Oct-4 isoforms in pulmonary artery smooth muscle cells from patients with pulmonary arterial hypertension. Am J Physiol 2010;298:L548–L557.
69. Yoshino J, Baur JA, Imai S. NAD+ intermediates: The biology and therapeutic potential of NMN and NR. Cell Metabol 2018;27:513–528.
70. Adamcio B, Sperling S, Hagemeyer N, Walkinshaw G, Ehrenreich H. Hypoxia inducible factor stabilization leads to lasting improvement of hippocampal memory in healthy mice. Behav Brain Res 2010;208:80–84.
71. Xing J, Lu J. HIF-1α Activation attenuates IL-6 and TNF-α pathways in hippocampus of rats following transient global ischemia. Cell Physiol Biochem 2016;39:511–520.
72. Chen H, Li J, Liang S, et al. Effect of hypoxia-inducible factor-1/vascular endothelial growth factor signaling pathway on spinal cord injury in rats. Exp Ther Med 2017;13: 861–866.

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