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REVIEW ARTICLE

Hyperbaric oxygen therapy in acute stroke: is it time for Justitia to open her eyes?

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Abstract
Hypoxia is a critical component of neuronal death in patients with stroke. Therefore increasing oxygenation of brain tissue seems to be a logical therapy against cerebral ischemia. Oxygen therapy exists in two modalities: normobaric hyperoxia therapy and hyperbaric oxygen therapy (HBO). HBO is a therapeutic procedure in which pure (100%) oxygen is administered at greater than atmospheric pressure in HBO therapy chambers. In this review article, we aimed to summarize the current knowledge regarding the therapeutic use of HBO in acute stroke patients. Literature review and electronic search were performed using PubMed, Medscape, and UpToDate with the keywords stroke, acute stroke, hyperbaric oxygen therapy, and hyperoxia. According to the reviewed literature, the use of HBO as routine stroke therapy cannot be justified in acute stage of stroke. More randomized, controlled studies are needed regarding safety and especially effectives of HBO in stroke patients. Also, standardized definition of HBO should be proposed and used in all future studies.

Keywords Stroke · Hyperoxia · Normobaric hyperoxia therapy · Hyperbaric oxygen therapy

Introduction

For many years, stroke was the third leading cause of death in the USA. However, in the last decade, stroke dropped down to the fourth place in 2008, while today, it holds the fifth place among all causes of death in the USA, when considered separately from other cardiovascular diseases [1]. The reason for this success is probably multifactorial and includes improved prevention and care of stroke patients in the USA. However, stroke burden is still devastating especially in less developed countries. According to a recent study from 2018, stroke accounts for 10% of all deaths worldwide, making stroke the second leading global cause of death, just behind heart diseases [2].

Hypoxia is considered to be a critical component of neuronal death in patients with ischemic stroke. Increasing oxygenation of brain tissue therefore seems to be a logical therapy against cerebral ischemia. Oxygen is a medical gas, used as a neuroprotective, non-drug therapeutic agent and has several advantages over pharmaceutical medications [3]. Oxygen easily diffuses through the blood-brain barrier; it is well tolerated and relatively safe with almost negligible dose-limiting side effects [4, 5]. Oxygen therapy exists in two modalities: normobaric hyperoxia therapy and hyperbaric oxygen therapy.

Normobaric hyperoxia therapy (NHT) was extensively studied in several animal models. These studies showed that NHT reduced ischemic brain injury and improves functional outcome [6]. The neuroprotection of NHT can be explained by synergism of many potential mechanisms. NHT improves cerebral tissue oxygenation and metabolism, therefore reducing acidosis and ATP depletion caused by ischemia. It also induces neuroprotection against stroke by attenuating the blood-brain barrier leakage, upregulation and the expression of MMP-9, inhibiting NADPH oxidase, and decreasing free radical production (ROS/RNS), i.e., reducing oxidative stress [6, 7].

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Moreover, NHT is a low-cost therapy, simple to administer, and can be started immediately after stroke onset in the ambulance during patient transport to a hospital [6]. It is important to mention that recent breakthroughs in technical and chemical engineering have resulted in the formation of oxygen micro-particles that provide direct administration of O_2 molecules to the bloodstream, significantly decreasing hypoxemia in animal models [8]. The capability to administer oxygen directly to the bloodstream may represent a technique to augment oxygen delivery to a brain tissue at risk in stroke patients. However, more studies about neuroprotective effects of these micro-particles are needed.

Undoubtedly, recent studies showed that NHT slows down the process of cell death after ischemic stroke. Theoretically, this allows an extension of the thrombolysis time window; combined therapy of rtPA thrombolysis and NHT was in the spotlight of several studies in recent years. In the study of Henninger et al., the effects of NHT with rtPA administration on ischemic lesion size and safety in a rat embolic stroke model were analyzed, and results showed that NHT combined with rtPA significantly reduced 24-h infarct volumes by 30%, while NHT therapy alone reduces infarct size by only 15%, which leads to a conclusion that this combined therapy may represent a safe and effective stroke treatment [9]. A similar study in rats showed that NHT after induced stroke did not raise brain levels of MMP-9 or markers of superoxide generation. Also, this therapy extends the time window for effective reperfusion. Therefore, these data provide important preliminary evidence to support the feasibility of NHT + rtPA treatment in stroke patients [10]. Also, several other animal studies showed that NHT can extend the reperfusion time window after focal cerebral ischemia, and this effect is called "freezing the penumbra." This phenomenon is explained by improved tissue oxygenation, hemodynamic effects, and complex biochemical mechanisms, which provide oxygen to the hypoxic brain tissue, delay ischemic cell death, afford more time for recanalization to occur, and finally improve outcomes after stoke. In these studies, oxidative stress due to NHT was not seen [11, 12]. In the study of Singhal et al., NHT started 12 h after onset of stroke was associated with a brief improvement in neurological status of patients [13]. In a similar study, Singhal also demonstrated transient neuroradiological improvements in diffusion/perfusion imaging and MRI spectroscopy in stroke patients receiving NHT [14]. On the other hand, the results of study conducted by Rønning et al. showed no statistical difference in 1-year neurological disability and mortality between acute stroke patients who received NHT (3 L of oxygen per minute for 24 h) after admission and those who received no treatment [15].

According to the latest "Guidelines for the Early Management of Patients With Acute Ischemic Stroke," it is not apparent that NHT is required in non-hypoxic mild or moderate stroke patients, but it may be useful in patients with severe stroke. Extrapolation of data from studies about NHT in resuscitated post-cardiac arrest patients recommends NHT to hypoxemic patients to maintain oxygen saturation over 94%. Also, these guidelines recommend NHT when indicated to achieve normoxia with the use of the least invasive technique (nasal cannula, nonrebreather mask, venturi mask, continuous positive airway pressure, bi-level positive airway pressure, or endotracheal intubation with mechanical ventilation). However, the final recommendation of Jauch et al. is that data about NHT in acute stroke patients are still inconclusive, and further studies are necessary [1].

An important study of Chan et al. conducted in patients with clinically suspected stroke before hospital admission (in prehospital settings or emergency department) showed that these patients routinely receive NHT, and this therapy appears to be safe; however, effects of NHT on stroke outcome were not analyzed [16]. This is an important study regarding NHT safety, which allows new studies to be conducted in stroke patients, that should focus on effects of NHT in prehospital settings on stroke outcome, and not just on the risk of this therapy.

Hyperbaric oxygen therapy (HBO) is a therapeutic procedure in which pure (100%) oxygen is administered at greater than atmospheric pressure in HBO therapy chambers [17]. These chambers were developed at the end of the nineteenth century for decompression sickness therapy of deep-water divers and caisson workers [18]. However, some pieces of evidence suggest that the first well-known hyperbaric oxygen chamber was built by an English priest named Henshaw. He built a structure called the *Domicilium* that was used to treat many diseases [19]. Further on, a French surgeon Fontaine built the pressurized, mobile operating room in 1879. In1928, Dr. Orville Cunningham build a structure called "the Steel Ball Hospital" in Cleveland. It was envisaged that patients suffering from diabetes live under pressure of 3 atm. However, due to the lack of beneficial evidence, 2 years later, the hospital was closed, and a few years later, it was dismantled for scrap [20].

Although it is the leading cause of death, stroke therapy is still unsatisfactory. For majority of patients, thrombolytic therapy is the only therapy aiming a specific cause (reperfusion of occluded blood vessel), and not only the consequences. It is known that hyperglycemia, hypoxia, hypotension, dehydration, and pyrexia increase the risk of neuronal injury. Therefore, stability and control of blood glucose level, oxygen saturation, blood pressure, hydration, and temperature are possible targets of acute ischemic stroke adjuvant therapy, in order to reduce neuronal injury and improve survival and functional outcome [17]. The main goal of any therapy is to minimize primary damage and salvage penumbra tissue, which is at high risk for irreversible damage. Since hypoxia is a major component of cerebral tissue damage, therapy should aim at enhancing tissue oxygenation and improving blood flow in occluded blood vessels. HBO is one potential therapy for stroke patients [17, 18].

This article reviews and summarizes important publications regarding the physiological and clinical influence of HBO on acute stroke patients. The proposed mechanism of HBO action in the reduction of neuronal injury is summarized in Table 1.

Physiology of HBO

The laws of physics behind HBO rely on ideal gas laws. Henry's law is crucial for understanding the effects of hyperbaric oxygen physiology. This law states that the amount of dissolved gas is proportional to its partial pressure in the gas phase; e.g., the amount of gas dissolved in a liquid is equivalent to the partial pressure of the gas exerted on the surface of the liquid. By increasing the atmospheric pressure in the chamber, more oxygen can be dissolved into the plasma than would be seen at surface pressure [21]. It is important to emphasize that most oxygen in the blood is bound to molecules of hemoglobin, which is 97% saturated at normal pressure. However, some oxygen is carried in plasma, and in hyperbaric conditions, this portion is increased (according to Henry's law) [22].

Physiological mechanisms of HBO include hyperoxygenation, decreased gas bubble size, vasoconstriction, angiogenesis, fibroblast proliferation and collagen synthesis, leukocyte oxidative killing, reduced intravascular leukocyte adherence, reduced lipid peroxidation, toxin inhibition, and antibiotic synergy.

Hyperoxygenation

In the resting state and assuming normal perfusion, tissues extract around 5 mL of oxygen per 100 mL of blood. If 100% oxygen is administrated to a patient at normobaric pressure, the amount of oxygen dissolved in the blood is 1.5 mL/100 mL, and if pressure increases to 3 atm., the dissolved oxygen content is around 6 mL/100 mL, which is enough to satisfy cellular requirements in resting state, without any contribution from hemoglobin-bound oxygen. Also, since oxygen is free in solution, the molecules are smaller than those bound to hemoglobin molecules and definitely smaller than red blood cells, so it can reach areas where red blood cells may not be able to pass and can also provide tissue oxygenation in the state of impaired function or reduced hemoglobin levels [22].

Table 1 The proposed mechanism of HBO action in the reduction of neuronal injury

Inhibits leukocyte activation and infiltration
Inhibits cyclooxygenase-2 expression
Decreases cerebral edema
Reduces lipid peroxidation
Increases oxygen level at neuronal tissues
Relieves intracranial pressure
Decreases immunoreactivity of substance P
Increases level of glutathione and induces expression of antioxidant enzymes
Suppresses proliferation of macrophages and foam cells in atherosclerotic lesions
Reduces ischemia-reperfusion injury
Accelerates tissue wound healing

Hyperoxia and vasoconstriction

In normal tissues, high oxygen levels (hyperoxia) cause vasoconstriction, but this is compensated with increased plasma oxygen content and microvascular blood flow. However, the vasoconstriction reduces post-traumatic edema of the tissue, which contributes to the treatment of compartment syndromes, thermal burns, and crush injuries [23, 24]. On the other hand, Singhal and his coworkers found that hyperoxia increases cerebral blood volume, in other words increases perfusion in stroke-affected areas of the brain (hyperoxia increases relative cerebral blood volume and relative cerebral blood volume within the area of initial "mean transit time" (MTT) dysfunction). This was firstly shown in rodent experiments [25], and laterin randomized, placebo-controlled study [13]. Also, earlier clinical studies of Nakajima et al. showed unexpected dilatation of blood vessels in the ischemic brain after NHT [26], and summarizing mentioned data, Singhal et al. advocate a new neuroprotective mechanism of hyperoxia: blood shunting from nonischemic (vasoconstriction in normal brain) to ischemic brain tissue (vasodilatation in stroke affected brain tissue) [13].

Angiogenesis

Recent stroke and traumatic brain injury (TBI) studies showed some evidence that HBO can induce neuroplasticity. In the study of Tal et al., highly sensitive MRI techniques showed that HBO improves cerebral microstructures by inducing cerebral angiogenesis and nerve fiber regeneration. These structural changes correlate well with the neurocognitive improvements [27].

Reduction of lipid peroxidation

In the interesting study of Thom, effects of oxygen at 1, 2, and 3 absolute atmospheres were evaluated on brain lipid peroxidation caused by carbon monoxide poisoning in a rat model. Oxygen at 3 absolute atmospheres prevented brain lipid peroxidation, while oxygen at 1 and 2 absolute atmospheres showed no significant effect [28]. Ferretti et al. demonstrated higher levels of lipid hydroperoxides in acute stroke patients (in first 24 h after stroke onset) compared with healthy individuals, and since recent studies provide evidence that oxidative stress and impairment of the antioxidant system may play

a role in the acute phase of stroke, antioxidant activity of HBO may provide protection from neurological damage caused by stroke-associated oxidative stress in the acute phase of stroke [29].

HBO and stroke

Early studies regarding stroke treatment with hyperoxia began almost half a century ago. However, this therapy was considered more dangerous than beneficial, so for many years, it was totally abandoned. In the last few years, this narrowed view of HBO has shifted towards a favorable assessment of its potential application in patients with stroke as some studies revealed the ability of HBO to reduce the severity of infarct volume if administered during the time of reperfusion [30]. However, there is a very limited opportunity for effective treatment as targeting time of reperfusion is very difficult, since today's imaging modalities are performed after the narrow effective time window for HBO has likely passed [31]. On the other hand, the study of Singhal et al. showed that delayed HBO applied after the reperfusion time window resulted in worse outcomes versus the normobaric groups, probably due to the role of ROS in glutamate-induced excitotoxic cell death [25].

The use of HBO in stroke is still not sufficiently evidence-based in humans, due to a small number of randomized double-blind controlled clinical studies. To date, there are no uniform criteria for the dose and duration of administration of HBO. Also, the effects of HBO combined with drugs and other treatment strategies have been investigated only recently. Therefore, more experimental and especially clinical studies are needed to identify the mechanisms more clearly and to explore the effect of HBO on acute ischemic stroke patients [32].

Conducting an electronic search (PubMed, Medline, Embase, Scopus, Cochrane Stroke Group Trials Register) and literature review, the authors of this article accepted a wide HBO definition to cover the largest number of HBO studies. Definition: "Hyperbaric oxygenation involves the use of 100% oxygen under pressure greater than that found on earth's surface at level of sea. Several units are used to denote barometric pressure, the most common being atmospheres absolute (ATA). At sea level standard barometric pressure is 1 ATA or 101,3 kPa (760 mmHg). The treatment is applied in a specially constructed chamber. Hyperbaric air involves the use of room air, and it is used as a control group in clinical studies" [33].

There are three main types of HBO found in the literature: the first is early post-stroke therapy, second is preconditioning, and the third is therapy of chronic stroke phase (Fig. 1). The goal of early post-stroke therapy is to induce hyperoxia during the ischemic and especially reperfusion periods, and the aim of preconditioning treatments focuses on exposing the individual at risk to a mild stressor, therefore inducing tolerance to future stressors. This is known as mithridatism, or practice of protecting oneself against a poison by gradually self-administering non-lethal poison doses. The word is derived from Mithridates VI, the King of Pontus, who so feared of being poisoned that he regularly ingested small poison doses, aiming to develop immunity. On the other hand, there are promising results that HBO can be used in chronic stage of stroke patients, since some studies showed that HBO could activate neuroplasticity in patients with chronic neurologic deficiencies [32, 34].

Standardized HBO is conducted at 2.5 atm. for a period of 1 h, although protocols vary in different studies [35]. The aim of this treatment is to promote cerebral oxygenation and increase oxygen levels in the ischemic region and thus minimize hypoxic damage. However, one should be aware that if pressure increases above the recommended level, oxygen toxicity may appear, as well as increased oxidative stress. Moreover, the risk of epileptic seizures drastically increases [33, 34].

Although there are no clear guidelines for HBO regimens or number of HBO sessions, some private hyperbaric centers treat stroke patients with HBO. Health insurance and health law consider HBO as experimental therapy in humans and do not provide coverage and that is why costs to patients who choose to have treatment privately can be excessive and without wishful beneficial results [36].

Since the mid-twentieth century, more than 15 studies investigated HBO effects on experimental stroke in animal models. HBO started at different times in various studies, mostly during or immediately after ischemia. The results of 16 relevant studies are summarized in Table 2, and many of them showed promising role of HBO in acute ischemic stroke models [37–53].

In 2005, Carson et al. conducted a systematic review to identify the benefits and harms of HBO in acute and chronic stroke patients. After extensive research including 157 potentially relevant papers, they included 17 observational studies and 4controlled clinical trials from internet databases, taking into account any HBO protocol in patients with acute and chronic ischemic stroke and excluding case reports and case series with less than 10 patients, and also studies published in languages other than English. Authors also graded the overall quality of each study. The results were not promising since they showed that until 2005, no good-quality trial was conducted, and this small number of studies is insufficient to determine the effectiveness of HBO, but shown evidence does not support usage in stroke patients, neither in acute nor in chronic stage [36, 37, 54–56]. Although this paper deals mostly with HBO in acute stroke patients, it is impossible not to mention some studies regarding HBO in chronic phase of stroke. Table 3 summarizes the results of 4 controlled trials conducted until 2005.

After reviewing several systemic review studies, it looked easy to make a conclusion that the use of HBO as a routine

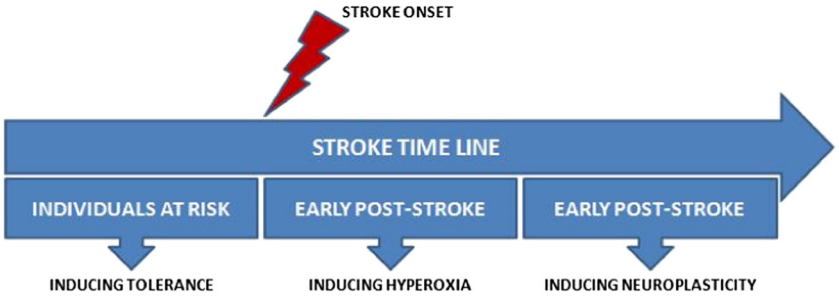

Fig. 1 Types of HBO in relation to time of therapy relative to stroke onset

stroke therapy cannot be justified in any phase of stroke. At this point, it is worth to mention the study by Efrati et al. They conducted a prospective, randomized, controlled trial including 59 patients that suffered stroke 6–36 months prior to inclusion (chronic phase) and had motor dysfunction. Life quality, NHISS, ADL, and SPECT imaging were assessed in all patients. HBO protocol included 40 dives in both groups (patient and control), 5 days per week, 90 min each dive with 100% oxygen at 2 ATA. The treated group was evaluated at baseline and after 40 dives, and the control group was evaluated three times: at baseline, after a 2-month period of no treatment, and after subsequent 2 months of 40 HBO dives. Interestingly, life quality and neurological functions of all patients in both groups were significantly improved following the HBO, while no improvement was found during the control period of the patients in the control group. These results showed that HBO can make improvements in stroke patients even at late chronic stages. Also, on the basis of neuroimaging, authors suggested that neuroplasticity can be activated in the chronic phase in the regions where SPECT/CT (anatomy/physiology) mismatch is present [57]. Although this study showed some positive results in rather small number of patients, it has important limitations: (1) It included very heterogeneous group of patients both with ischemic and hemorrhagic strokes; (2) Inclusion period was very wide, 6–36 months post ictus; (3) It did not take into account, as confounders, other treatments that the included patients received (thrombolytic therapy in patients with ischemic stroke, antidepressants, antithrombotic therapy, etc.); and (4) The main limitation of the study is that SPECT observed elevated brain activity was detected mostly in regions of live brain cells in both patient groups (with and without HBO treatment).

Similar to the study of Sarny et al. mentioned in Table 3, Shiracki et al. presented a case report and a study with a small number of post-stroke patients and suggested that HBO may potentially improve deficit in long-term aphasic patients. However, the study is of limited value since no statistical analysis was mentioned [58].

It is important to mention the "Cochrane corner" study of Bennett et al. They conducted a meta-analysis systemic review to determine the safety and effectiveness of HBO for the treatment of acute ischemic stroke. They performed a

Table 2 Experimental studies of HBO in stroke in animal models [4]

Authors	Animal	Timing of HBO	ATA	Outcome measure	Positive effect
Reitan et al. 1990	Gerbil	Immediately after	2.5	Survival	Yes
Burt et al. 1987	Gerbil	Immediately after	1.5	HP changes	Yes
Weinstein et al. 1987	Cat	1, 3, and 4 h after	1.5	NS, HP changes	Yes
Corkill et al. 1985	Gerbil	1 h after	1.5, 2.0	NS, survival	Yes
Weinstein et al. 1986	Gerbil	Immediately after	1.5	Survival, HP changes	Yes
Ruiz et al. 1986	Dog	Immediately after	2.0	NS	No
Shiokawa et al. 1986	Rat	1 and 3 h after	2.0	Survival, metabolic findings of ischemia	Yes
Kapp et al. 1982	Cat	Immediately after	1.5	EEG, metabolic findings of ischemia	Yes
Patterson et al. 1968	Dog	During	3.0	NS	Yes
Moor et al. 1966	Dog	During	3.0	NS, HP changes	Yes
McSherry et al. 1966	Dog	During	2.0, 3.0, 4.0	Survival, EEG	Yes
Thomas et al. 1966	Dog	During	3.0	NS, HP changes	Yes
Whalen et al. 1966	Dog and monkey	During	3.0	EEG	Yes
Fuson et al. 1965	Dog	During	3.0	EEG	Yes
Jacobson and Lawson 1963	Dog	During	2.0	NS, HP changes	Yes
Smith et al. 1961	Dog	During	2.0	EEG	Yes

Table 3 Summarized findings of 4 controlled clinical trials on HBO in stroke patients

Authors	No. of patients	Stroke	Patients/control treatment	Measurements	Results	Conclusion
Rusyniak et al. USA 2003	Randomized, prospective, double-blind, sham-controlled pilot study/33 patients	Acute ischemic stroke without thrombolytics over a 24-month period	60 min/2.5 ATA 60 min/1.14 ATA	NHISS at 24 h; NIHSS, Barthel index, modified Rankin scale, Glasgow Outcome Scale at 90 days; and mortality at 90 days	After 24 h: no differences ($p = 0.44$); At 90 days: NIHSS, 80% vs 31.3%; $p = 0.04$; Barthel index, 81.8% vs 50%; $p = 0.12$; modified Rankin scale, 81.8% vs 31.3%; $p = 0.02$; Glasgow Outcome Scale, 90.9% vs 37.5%; $p = 0.01$	Although our HBO protocol appears feasible and safe, it does not appear to be beneficial and may be harmful in patients with acute ischemic stroke
Nighoghossian et al. France 1995	Double-blind, randomized controlled study/34 patients	Acute ischemic stroke within 24 h of middle cerebral artery occlusion	40 min /1.5 ATA/10 dives every day 40 min/1.5 ATA/ room air /10 dives every day	Orgogozo, Rankin, and Trouillas scale at 24 h, 6 months, 1 year	The mean score of the HBO group was significantly better on the Orgogozo scale at 1 year ($p < 0.02$). However, the difference at 1 year between pre-therapeutic and post-therapeutic scores was not significantly different in the two groups ($p < 0.16$). No significant differences on Orgogozo, Rankin, and Trouillas scale at 6 months and 1 year	HBO might be safe. HBO might improve outcome after stroke, since outcome trend favoring HBO therapy was observed
Anderson et al. USA 1991	Double-blind, prospective, randomized controlled study/39 patients	Within 2 weeks of ischemic stroke – chronic stage	60 min / 1.5 ATA every 8 h / 15 dives 60 min / 1.5 ATA / room air/ every 8 h / 15 dives	Neurological exam (graded 0–100) at 5th day, 6 week, 4 month, 1 year	Baseline, 45.5 vs 44.6 Day 5, 43.8 vs 38.5 ($p = 0.54$) Week 6, 38.5 vs 28 3 ($p = 0.25$) Month 4, 34.5 vs 25.6 ($p = 0.33$) Year 1, 31.4 vs 25.8 ($p = 0.53$)	Study was interrupted when authors noticed what appeared to be a trend favoring the air-treated patients. The trend was probably an artifact of the randomization process.
Sarno et al. USA 1972	Double-blind, prospective, randomized controlled study/32 patients	Over 3 months after stroke – chronic stage	90 min / 2.0 ATA / 1 dive 90 min / 2.0 ATA / 10.5%O_2 / 1 dive	Communication testing Cognitive and perceptual testing	No significant difference in communication skills 24 h before vs immediately after HBOT treatment	HBO does not improve the communication (language) and cognitive-perceptual (intellectual) function of post-stroke patients

sensitive electronic search of multiple databases in 2014 and included 11 randomized controlled trials with a total of 705 participants with acute ischemic stroke. Results showed that there is no statistically significant difference in fatality rate during the first 3 to 6 months after stroke in patients receiving HBO. Three out of 7 studies found improvements in 4 out of 19 scale measures of function, disability, or daily activities after HBO. One year after stroke, mean Trouillas Disability Scale showed lower values with HBO, and the mean Orgogozo Scale was higher, but according to Bennett et al., these improvements were not apparent in earlier assessments in the relevant studies. One study also reported an early benefit from HBO in neurological function assessed by unstandardized deficit score, as well improvement in the Barthel index at 3 weeks after stroke. The authors concluded that the clinical data are limited and the evidence is insufficient to confirm that HBO significantly affects outcomes after acute ischemic stroke, so usage of HBO as a routine therapy in stroke cannot be justified by current data [59].

In April 2016, the Tenth European Consensus Conference on Hyperbaric Medicine revisited the European Committee on Hyperbaric Medicine list of accepted indications for HBO. Mathieu et al. summarized the data, and according to these consensuses, HBO is not recommended for use in acute phase of ischemic stroke (type 1 recommendation, level C evidence). Also, they stated that it would be reasonable to consider HBO in an investigational clinical study in highly selected patients with chronic stroke who have clear finding of metabolically dysfunctional regions of the brain that are mismatching with the necrotic brain regions (type 2 recommendations, level C evidence) [60].

Apart from the mentioned studies, which are randomized controlled trials, Zhai et al. summarized data from several latest clinical studies in order to better understand the current usage of HBO. As reviewers before, they concluded that the effectiveness of HBO in stroke patients has not been proven due to the lack of good-quality randomized controlled trials, and therefore, more studies are needed to find uniform standards of HBO, for each specific phase (acute/chronic) [32]. Micarelli et al. investigated regional cerebral blood flow distribution during HBO in 7 healthy subjects exposed to HBO at a pressure of 2.5 ATA. They found an increased regional cerebral blood flow mainly on the dominant hemisphere in sensory/motor area, premotor area, posterior cingulated and visual cortex, some parts of temporal gyrus, superior frontal gyrus, angular gyrus, and cerebellum. This study unfolds a possible mechanism of HBO beneficial effects on the motor and cognitive improvement in stroke patients [61]. In 2011, McCormic et al. conducted a regression retrospective statistical analysis of the Heyman et al. study of 22 acute stroke patients treated with HBO, examining the influence of treatment time window, time in chamber, and dose of HBO, and found that only time window after stroke affects the recovery efficacy, and they concluded that the most promising time window is during the first 3 h after stroke (earlier HBO, better efficacy) [62]. The sometimes seen post-stroke depression affects functional recovery and quality of life of these patients. Antidepressants combined with HBO have a supplementary beneficial effect, and a prospective clinical study of Yan et al. showed that combination of fluoxetine and HBO has a significantly better effect than HBO or fluoxetine alone, but further bigger investigations are needed to verify this synergistic effect [63].

Due to the lack of convincing evidence that HBO is effective for stroke, and also because of the lack of proof that HBO is ineffective, as mentioned, Carson et al. conducted a systematic review of the current evidence of HBO for stroke. They found only four randomized controlled trials, one controlled clinical trial and 17 observational studies. They identified major flaws in most of the studies, especially in observational studies. Although all 17 observational studies had poor quality, they are frequently cited by proponents of HBO as a proof of its efficiency. Also, after analysis, they rated all randomized control studies as fair or poor quality [36]. Different methodology used in these studies makes generalization of results almost impossible. Also, confusion created by this approach has diminished interest in HBO for stroke, so one can notice that all studies are outdated. Carson et al. concluded that current studies do not support the use of HBO in acute stroke patients; however, no good-quality study was conducted. Their review of current studies' limitations provided information about gaps in the evidence that can be used to guide future studies. They propose that if good-quality observational studies suggest a benefit of HBO, randomized controlled trials should be conducted. They also proposed methods for minimizing bias in randomized controlled trials: (1) defining and using objective outcome measures; (2) using masked outcome assessment; (3) assigning control group patients to sham treatment; (4) baseline stability of patients should be established to avoid confounding with the natural course of the disease; (5) better randomization; (6) all patients must receive the same course of therapy; (7) better attention to adverse events [36]. So, to bring back interest in HBO, experts in this field must define the standard protocol for HBO in acute stroke patients. This protocol must be used in large, good-quality observational and afterwards in randomized controlled trials, after which the results will be more reliable.

Adverse effects and disadvantages of HBO

HBO is considered safe with adverse effects rarely seen if chamber pressures are below 3 ATA. Sometimes, extreme hyperbaric condition or long therapy duration can result in oxygen toxicity, especially central nervous system toxicity, pulmonary and middle ear barotraumas, and rarely retinopathy and prematurity [32, 64]. Higher pressures (over 5 ATA)

can cause agitation or epileptic seizure, probably due to the upregulation of free radicals in the brain tissue [65]. Thus, guidelines for HBO recommend maximum pressure no greater than 3.0 ATA [32, 66]. Also, HBO can be stressful for claustrophobic patients [67].

Advances in the treatment of stroke in the last two decades are enormous, but a significant decline in interest for HBO is evident. It can be noticed that 2 out of 4 controlled clinical studies that dealt with HBO in stroke patients were conducted in the pre-thrombolysis/thrombectomy era; the study of Nighoghossian et al. was published in 1995, but few months before the NINDS trial; and the study of Rusyniak et al. was performed in 2003 but only in patients in whom thrombolysis was not indicated. The introduction of rtPA thrombolysis made a revolution in the stroke treatment, and today, this therapy represents a pillar of every acute stroke guideline around the world. It has been 25 years since the publication of the randomized controlled NINDS (the National Institute of Neurological Disorders and Stroke) tissue-type plasminogen activator trial which showed that intravenous rtPA thrombolysis started within 3 h after the onset of ischemic stroke symptoms improved clinical outcome at 3 months. Also, a meta-analysis published in 2014 emphasized the generalized efficacy of rtPA in the first 4.5-h time window, regardless of age or stroke severity, but confirmed a relationship with treatment time; e.g., no trial has confirmed benefit after 4.5 h. On the other hand, it has been more than 15 years since the Food and Drug Administration approved the first endovascular device for mechanical endovascular thrombectomy [68–70]. Both of these procedures are performed in specialized institutions and must be carried out immediately after the stroke onset, making the study of HBO in acute stroke patients technically impossible. In addition to being technically demanding to examine the effect of HBO on acute stroke patients, it is ethically, morally, and also legally impossible to examine the isolated effect of HBO on stroke patients who are indicated for thrombolysis/thrombectomy given that these treatments are standardized and accepted. In order to be able to conduct a HBO efficacy study, it is necessary to find a way to simultaneously apply standardized therapy (thrombolysis/thrombectomy) and HBO in patients with acute stroke.

Fig. 2 Lady Justice (Latin, *Justitia*), appropriate symbol for HBO

Since hyperbaric oxygen chambers are usually measuring 7 ft by 2 ft by 2 ft, they are designed to fit only one person, enabling the presence of another person inside the chamber if necessary (e.g., a nurse or a doctor) [67]. This is one of the problems that can occur in HBO treatment of patients with acute stroke, and with a long exposure time (1 h or 90 min), as well as additional 30 min required to depressurize following therapy, it is almost impossible to leave the stroke patient alone for so long, especially since patient cannot make a quick escape if necessary (for example due to breathing problems, epileptic seizure, need for additional analysis).

There are some practical limitations in performing MRI in acute stroke patients, such as standard MRI contraindications (presence of a pacemaker), diminished level of consciousness, agitation, vomiting, and hemodynamic compromise [71]. Since MRI imaging takes time similar to the HBO, one can predict that diminished level of consciousness, agitation, vomiting, and hemodynamic instability can prevent the use of HBO therapy in stroke patients with these symptoms. Also similar to MRI imaging, approach to patient is difficult due to HBO chamber structure. Unlike in MRI imaging, abrupt stopping of therapy is not possible, due to the need for decompression; e.g., there is a significant risk of barotrauma if treatment is stopped abruptly. More studies on the topic of practical disadvantages and limitations of HBO are needed.

Conclusion

Lady Justice (Latin, *Justitia*) is a symbol for the virtue of justice mainly seen in books dealing with law and justice. However, it seems appropriate to compare this goddess from Roman mythology with HBO in stroke patients (Fig. 2). There are several symbols regarding this, since Justitia is blindfolded and holds a sword in one and scales in the other hand. In our case, the sword represents time and manner of action e.g. therapy, while scales hold for uncertainty whether therapy is effective or even harmful. The blindfold represents impartiality, e.g., a principle that decisions should be based on objective criteria, and according to the current literature, more studies are needed for Justitia to take of the blindfold and open her eyes to see clearly.

Compliance with ethical standards

Conflict of interest Authors have no potential conflicts of interest do disclose.

Ethical approval Not applicable.

Research involving human participants and/or animals Not applicable

Informed consent Not applicable

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