Application of hyperbaric oxygen therapy in stroke

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Content

Background and epidemiology:

Stroke may be defined as a sudden neurological deficit of presumed vascular origin (1). It is the fourth leading cause of death and major cause of disability worldwide (2-4). One in 6 people will have a stroke during their lifetime and one third of those will experience recurrence (4) . Stroke causes 9% of all deaths around the world and is the second most common cause of death after ischemic heart disease. The proportion of deaths caused by stroke is 10-12% in western countries, and 12% of these deaths are in people less than 65 years of age (5). About one-third of survivors require significant assistance in daily life at one year after the event (6). Typical estimates, largely drawn from knowledge of stroke incidence and mortality, are that about 500 people per 100000 population live with the consequences of stroke. Because stroke mortality is probably decreasing more rapidly than stroke incidence, the proportion of stroke survivors is likely to increase, which will place increased demands on health-care and social-care systems(7) .

Stroke contributes to a series of complications, such as motor and cognitive deficits (8), aphasia (9), dysphagia (10) and some psychological disorders (11), which aggravate the patient's family and socioeconomic burden (12). Worldwide, stroke consumes about 2-4% of total health-care costs, and in industrialized countries stroke accounts for more than 4% of direct health-care costs. The total costs to society have been variously estimated at £7.6 billion in the UK at 1995 prices and US$40.9 billion in the USA at 1997 prices (7, 13), which represents about US$100 per head of population per year.

Stroke is divided into two subgroups: ischemic (73-86% of the cases) and hemorrhagic (14-27% of the cases) (14). Ischemic stroke has a lower mortality rate than hemorrhagic and the acute management differs for the two subgroups (6).

Clinical presentation:

Most adult patients will have medical history with atherosclerotic risk factors including hypertension, diabetes mellitus, tobacco use, high cholesterol or the history of coronary artery disease.

Signs and symptoms of stroke often develop suddenly and then may temporarily improve or slowly worsen, depending upon the type of stroke and area of brain affected. Common signs and symptoms include the abrupt onset of any of the following: hemiparesis, monoparesis, hemi sensory deficits, monocular or binocular visual loss, diplopia, dysarthria, facial droop, ataxia, vertigo, aphasia, and decrease in the level of consciousness. Although such symptoms can occur alone, they are more likely to occur in combination. No historical feature distinguishes ischemic from hemorrhagic stroke, although nausea, vomiting, headache and sudden change in level of consciousness are more common in hemorrhagic strokes.

Pathophysiology:

Ischemic strokes are due to a reduction of perfusion. This reduction can be due to decreased systemic perfusion, severe stenosis or occlusion of a blood vessel by thrombosis or emboli (15). This reduction of blood flow to a portion or all brain tissue results in a deprivation of oxygen andglucose .

Under normal conditions, cerebral autoregulation is a phenomenon by which cerebral blood flow (CBF) is maintained at a relatively constant level despite moderate variations in perfusion pressure. During stroke, the decrease in perfusion pressure beyond the ability of the brain to compensate (by cerebral blood vessels dilatation) results in a reduction in cerebral blood flow. Initially, the oxygen extraction fraction is increased in order to maintain level of oxygen delivery to the brain tissue. At CBF of 35 ml/100g per

minute, protein synthesis ceases and glucose utilization is transiently increased. At 25 ml/100g per minute, glucose utilization drops dramatically with the onset of anaerobic glycolysis, resulting in tissue acidosis from accumulation of lactic acid. Neuronal electrical failure occurs at 16-18 ml/100 g per minute, and at 10-12 ml/100 g per minute the ion homeostasis fail, resulting in membrane potentials disruption and infarction (16-18).

Most strokes are caused by focal ischemia, affecting only a portion of the brain, typically involving a single blood vessel and its own downstream branches. The region directly surrounding the vessel is the most affected. Within this region, cells in a central core of tissue will be irreversibly damaged and die by necrosis if the duration of ischemia is long enough. At distances father from the affected vessels, a volume of cells can recieve a small amount of oxygen and glucose by diffusion from collateral vessels. These cell can be functionally impaired, but structurally intact tissue (19).This tissue is known as the ischaemic penumbra and can recover if blood flow is restored in a timely manne (19)

Within the ischaemic penumbra, a cascade of neurochemical events begins with energy energy/ adenosine triphophate (ATP) depletion, followed by ionic concentrations of sodium, potassium and calcium As a consequence, membrane potential is depolarized and excitatory amino acid glutamate is released. Activation of gluatmate receptors leads to increased calcium entering the cell. The influx of calcium is balanced by influx of water, leading to edema as well as increased glutamate release which continues the excitatory stimulation (20, 21). The ionic celular derangement leads to mitochondrial caclium overloading, which is responsible for inducing changes of inner membrane permeability with consequent malfunctioning, uncoupling of oxidative phosphorylation, over-production of reactive oxygen species (ROS), and, finally, mitochondrial swelling

and dysfunction [28]. At this stage, cell death will follow either by apoptosis or necrosis. The infarct core contains tissue that is unsalvageable and represents the terminal events of the ischemic cascade.

In addition, the release of byproducts from cellular damage activates components of the inflammatory pathway, with migration of activated leukocytes to damaged tissue. In turn, these leukocytes release cytokines which may accumulate to toxic levels (22, 23). Cerebral edema can cause secondary damage by several mechanisms including increased intracranial pressure, whcih may decrease CBF, and mass effect causing displacement of brain tissue from one compartment to another(25 ,24) .

Hemorrhagic stroke is classified as primary or secondary based on the underlying cause (26). Primary ICH is the result of spontaneous rupture of small vessels due to hypertension and cerebral amyloid angiopathy. Secondary ICH is due to a cause other than small vessel rupture (e.g., aneurysm, arteriovenous malformation, hemorrhagic transformation of ischemic stroke, and neoplasms. Following both types, direct neural and microvascular injury will occur, cerebral edema will form and perilesional blood flow will change (26). Early edema is due to the accumulation of serum proteins of the blood clot that contains osmotic activity (27). Subsequently, neural injury, ion homestasis disruption, inflammatory response (as described above) will lead to both vasogenic and cytotoxic edema (28). There is reduced regional cerebral blood flow adjacent to the hematoma, which increases as the distance from the hematoma center increased, leading to ischemic injury far larger than the hemorrhagic core (29).

In the subacute - chronic stage post stroke, the part of the brain who underwent infarction is non-viable and could not recover. However, there are brain regions which

are metabolically dysfunctional yet viable (30). These non-active (stunned) areas can persist through days, months and even years after the acute injury (31). These areas are characterized by a chronic hypoxia, which prevents proper aerobic metabolism needed for the regenerative process. The neurons within this chronic metabolic dysfunction regions have sufficient energy/oxygen for preservation of the membrane potential but not sufficient for the full action potentials and the normal neuronal activity (30, 32).

Standard management and outcome

In the acute setting, time is of the essence in the evaluation and treatment of stroke patients. Patients are examined using a structured neurologic exam and score – National Institutes of Health Stroke Scale (NIHSS) to assist in prognosis and therapeutic selection. Non-contrast CT is used to differentiate between stroke types. Advanced imaging techniques (CT Angiography, MRI, MRI Perfusion,

Therapy of ischemic stroke focuses in restoring brain perfusion. Timely restoration of blood flow is the most effective maneuver for salvaging ischemic brain tissue that is not already infracted. There is a narrow time window during which this can be accomplished, since the benefit of reperfusion therapy for ischemic stroke decreases in a continuous fashion over time. Thus, it is crucial to determine if the patient is eligible for intravenous thrombolysis or mechanical thrombectomy. Intravenous thrombolytic therapy with alteplase (rtPTA) improves outcomes in patients with acute ischemic stroke who can be treated within 3-4.5 hours from stroke onset. Intravenous thrombolysis improves outcome rates by 1.26-1.7 unfortunately with considerably increase risk (6.8%) for symptomatic intracranial hemorrhage (33). Due to the limited

time window and exclusion related to high hemorrhagic risk, only 2-5% of the patients fulfill criteria for treatment (34).

Intra-arterial mechanical thrombectomy improves outcomes for patients with ischemic stroke caused by a large artery occlusion in the proximal anterior circulation with a significant proportional treatment benefit across by 1.56 compared to intravenous thrombolysis (35). Approximately 4-5% of ischemic stroke patients undergo endovascular thromectomy even thoghtit is estimated to be applicable in up to 10% of patients (36).

In the acute setting of hemorrhagic stroke, therapy focuses on minimization of secondary injury by ensuring adequate oxygenation, hemodynamic stability, control of intracranial pressure, and strategies to reduce the expected cellular injury (37, 38). Many the neuroprotective agents shown to be promising results in animal experiments, failed to be confirmed the expected efficacy in humans (39, 40).

In the subacute setting, several interventions (antithrombotic therapy, lipid lowering therapy, blood pressure reduction and smoking cessation) are associated with reduced stroke recurrence rates. About a quarter of stroke patients may die within a month, third within 6 months, and a half within a year (41). Prognosis is even worse for those with intracerebral and subarachnoid haemorrhage because the 1-month mortality approaches 50%. The major cause of early mortality is neurological deterioration with contributions from other causes such as infections secondary to aspiration (if not managed aggressively), but later deaths are more commonly caused by cardiac disease or complications of stroke (41). After minor stroke, the risk of further stroke is substantially higher than previously thought, reaching as high as 30% within the first month in some subgroups (42).

During the subacute-chronic phase, patients are usually advice to participate in intensive rehabilitation programs in order to improve independent function and quality of life. These rehabilitation programs helps the patients to adapt to their disabilities. Rehabilitation includes a multidisciplinary approach conducted by physiotherapy, speech and language therapy, cognitive rehabilitation therapy, medications and others.

Motor deficits are one of the most common and challenging consequences of a stroke (43). An estimation of 50% of survivors have hemiparesis, 30% are unable to walk without assistance, and 25% are dependent for activities of daily living (44). A variety of interventions can improve aspects of occupational performance in stroke survivors who have residual motor impairments. Currently, occupational therapists use multiple interventions to remediate motor impairments. However, no consensus has been reached regarding which interventions are most effective for improving occupational performance and from the biological perspective none of these interventions target the basic brain pathology responsible for clinical presentation (45).

In addition to motor disabilities, 35% - 50% of stroke survivors develop depression, the most common psychological sequel of stroke (46). The evidence is inconclusive for using multicomponent exercise programs to combat depression after stroke and for the use of stroke education and care support and coordination interventions to address poststroke anxiety (47). One study provided support for an intensive multidisciplinary home program in improving depression, anxiety, and health-related quality of life (47).

The rate of cognitive impairment after stroke is reported between 37-46% (44, 48).The evidence regarding interventions for executive dysfunction and memory loss is limited. There is insufficient evidence regarding impairments of attention and mixed evidence regarding interventions for visual field deficits. The effective interventions have some

commonalities, including being performance focused,and using a compensatory stimulation as opposed to a remediation approach.

In general, spontaneous recovery from stroke occurs mainly within the first 30 days, though moderate and severe stroke survivors continue to improve for at least 90 days (49)

Rationale for HBOT use

The brain receives 15% of the cardiac output, consumes 20% of the total body oxygen, and utilizes 25% of the total body glucose. The energy thus supplied is sufficient to keep only 5-10% of the neurons active at any given time. At a standard healthy condition, the brain utilizes almost all the oxygen/energy delivered to it so there is no reserve left neither for re-circulating during the acute hypoxic setting or for the regenerative processes needed at the delayed post stroke setting.

In the acute phase of stroke, the reduced supply of oxygen and glucose initiate the vicious cascade resulting in brain injury. Hyperbaric oxygen therapy (HBOT), by increasing the oxygen delivery to the ischemic tissue can reduce the expected damage. Many animal studies revealed the beneficial effects of HBOT in acute stroke, early HBOT can reduce cerebral edema, infarct volume (50) and improve CBF (51). HBOT can also revererse the blood-brain-barrier permabiility caused by activation of matrix metalloproteinases, one of the mechanisms responsible for the hemorrhagic transformation (52). That was confirmed by another study where HBOT decreases hemorrhagic transformation and decreased mortality in an animal model of focal cerebral ischemia (53).

In the delayed chronic stage, HBOT improves penumbral oxygenation through modification of the transcription factor hypoxia-inducible factor-1 alpha (HIF 1α) and its downstream targets. Oxygenation improves energy metabolism in the border zones of focal cerebral ischemia represented by significant reduction of areas with tissue acidosis and areas with ATP depletion (54)(55) . HBOT can also decrease the post ischemic inflammatory response by reducing blood-brain-barrier damage (56), inflammatory cytokines release (50) and supresses the aggravated response of astrocytes and microgliosis (57). In addition, HBOT inhibits polymorphonuclear cells infiltration, sequestration and activity in the injured brain (58, 59) (60).

HBOT reduces apoptosis which enables to preserve more brain tissues and promote neurologic functional recovery (61). Opening of mitochondrial ATP-sensitive potassium channel plays a role in this antiapoptotic effect of early hyperbaric oxygenation (62). Other mechanisms involve increased nitric oxide levels, reduced formation of hydroxylfree radicals and decreased glutamate release (63).

The bottom line is that HBOT promotes neurogenesis which correlates with neurocognitive recovery. In addition to the above mention mechanism, one of the most intriguing is related to HBOT effect on stem cells. HBOT increases mobilization of bone marrow stem cells to the ischemic tissue in addition to stimulating trophic factors that improve neurogenesis and gliosis (64).

Preconditioning with hyperbaric oxygen prior to stroke was found as neuroprotective. Thus, generating tolerance against brain ischemia-reperfusion injury improving recovery rate and lowering mortality rate. HBOT reduce the infarct size (65), reduce neuroinflammation (66, 67), activated angiogenesis by upregulation of HIF-1α and its target EPO gene (68) (69), decrease anaerobic metabolism and lactate levels, inhibited

toxic excitatory glutamate release (70), regulated striatal metabolites (such as dopamine) (71) (72), supressed mitocondrial apoptotic pathways (73) (74), and upregulated of anti-oxidant enzymes (catalase and superoxide dismutase) (75)

The optimal HBOT protocol in the acute stroke setting was not be determined in animals' models. Even thought that a dose response effect could be demonstrated (76), the timing for intervention is inconclusive. For instance, application of HBOT within 6 hours of injury could benefit the patient but that applying HBOT 12 h or more after injury may increase the injured tissue (77). In another trial, applying HBOT even after both 9 and 18 hours reduced infarct size and improved neurological recovery, however the results of 9 hours delay treatment were superior than the18 hours delay(78). Moreover, several studies showed efficacy of HBOT only if there was a successful recanalization of the occluded artery recanalization (79). In addition to reduction of infarct size, the use of HBOT cominbed with thrombolysis yielded decreased post thrombolytic intracerebral hemorrahage which may suggest the combined use (80). Longer (3 weeks compared with 2 days) course of HBOT achieved higher improvements in neurological function (81).

In the subacute-chronic delayed stage, several animal studies have revealed the beneficial effect of HBOT on the chronically injured brain tissue and on the resultant neuro-cognitive dysfunction in animal models (82-84). By increasing oxygen content in the blood and injured tissue (85-87), HBOT can supply the energy needed for the brain regenerative processes of neuroplasticity.

HBOT induces neuroplasticity by stimulating cell proliferation (88), promotes neurogenesis of endogenous neural stem cells (89), regenerates axonal white matter (90), improves maturation and myelination of injured neural fibers (91, 92), and stimulates axonal growth thus increasing the ability of neurons to function and communicate with

each other (93, 94). At the cellular level, HBOT can improve cellular metabolism, reduce apoptosis, alleviate oxidative stress and increase levels of neurotrophins and nitric oxide through enhancement of mitochondrial function (in both neurons and glial cells) ,89 ,87) (95. Moreover, the effects of HBOT on neurons can be mediated indirectly by glial cells, including astrocytes (57). The common denominator to all repair and regeneration mechanisms is that they are all oxygen dependent.

HBOT was also found to have a significant role in initiation and facilitation of angiogenesis, which is required for axonal regeneration (96-100). By inducing angiogenesis, HBOT improves the cerebral vascular flow necessary for neurogenesis and synaptogenesis (101, 102).

Evidence-Based review of HBO use

Acute stroke

There were 4 RCTs, 3 prospective studies,2 cohort studies, 3 case reports and one meta-analysis evaluating the clinical effects of HBOT in acute stroke. The studies had different HBOT protocols for hyperbaric pressure, different time delay to HBOT, inclusion/exclusion of thrombolysis, severity of injury, type of stroke, number of sessions, as well as different methods of evaluation.

Low level evidence:

Meta-analysis done at 2014 (103) was set to pool 7 randomized controlled trials on acute ischemic stroke treated with HBOT. Base on 4 trials, it concluded there were no significant differences in case fatality rates in receiving HBOT compared to sham therapy (p=0.96). However, only one out of the 7 studies study was included in efficacy analysis (p=0.12). Therefore this meta-analysis could not be considered valid.

Chen et al. reported on a patient who suffered acute ischemic stroke unqualified for thrombolysis who received HBOT started 3 days later (104). He received 10 sessions in total. Post HBOT, the patient had improved neurological scores (NIHSS, BI, mRS) at completion of HBOT and at 3 months follow up. SPECT and CT-perfusion imaging showed improved CBF and penumbra areas

Gibon et al. collected a case series of 12 patients with acute ischemic strokes as a result of cardiac surgery (105). Patients were treated with HBOT within 4-48 hours from surgery for 1-3 sessions. Eight (66%) patients had partial or complete resolution of neurological symptoms. The main limitations lies within the fact that although these cases could be considered as ischemic strokes, at least some of these cases may be related to air embolism rather than thrombo/embolic origin. In addition, this was a relative small case series, without an objective imaging and a control group.

McCormick's retrospective study reevaluated 22 patients with acute stroke treated with HBOT in 1966 (106). In the one- to five-hour post-stroke group of 13 patients, nine (41% of 22) had fully recoverd or recoverd with relapse. When HBOT started more than six hours post-stroke, only one patient (11%) had partial recovery with relapse. The other eight patients who received treatment after six hours had no recovery at all. The main limitations of this study are small sample size, lack of objective imaging, lack of thrombolysis, standard of treatment in 1966, and lack of a control group.

Lim et al. reported a case of hemorrhagic stroke treated within 24 hours (107). Patient was treated with 9 daily sessions of 90 minutes of hyperbaric oxygen at 1.8 ATA. During

and post HBOT there was clinically significant neurological improvement in motor strength and GCS. Improvements were sustained at 3 and 6 months follow up. The important of this study from the pathophysiological view is that compared to baseline MRI, perfusion MRI done after first session showed increased cerebral blood volume around the hematoma.

Ingvar et al. reported on 4 patients with acute/subacute ischemic stroke treated within 2 weeks after event (108). HBOT sessions were 1.5-2.5 hours of 100% oxygen at 2-2.5 ATA. In three out of four cases, HBOT had beneficial effects on the neurological deficits. One of the cases with progressive ischemic lesions of brain stem had a dramatic change by HBOT.

Moderate/high level evidence:

Chen et al prospective study included 46 patients (of which 16 HBOT) suffering from ischemic stroke for 48 hours without thrombolysis (109). HBOT of 10 sessions of 2 ATA started 3-5 days after stroke, was compared to standard of care. There was a non significant trend in early efficacy (after 10 sessions) measured by NIHSS between the 2 groups and this treand became clinically significant at the delayed neurological consequence. At 1 month post stroke, the clinical outcome was better in the acute stroke patients treated with HBOT (p=0.024). It should be noted that all patients had mild stroke severity (NIHSS 1-14). Other limitations include relative small number of patientand lack of an objective imaging method for infract/brain metabolism.

Imai et al. RCT (110) enrolled 38 patients with anterior circulation embolic ischemic stroke within 48 hours prior to inclusion. The HBOT group was treated with 7 sessions

of 2 ATA 100% oxygen for 60 minutes in addition to Edaravone administrated intravenously before and after each session. Six patients had favourable outcomes at 90 days in the HBOT group compared to only 1 in the control group (p=0.045). No significant difference was noticed for median absolute NIHSS scores between groups within 7 days of treatment. However the median change in NIHSS score within 7 days of treatment was 5 in the HBOT group compared to 1 in the control group (p<0.01). The main limitations of the study was the relative small sample size, lack of comparing objective brain imaging and inability to assess HBOT effect alone (without Edavorone).

Rusyniak et al. RCT (111) on 33 patients with ischemic stroke within 24 hours who did not receive thrombolysis. The HBOT group (n=17) was treated with 60 minutes of hyperbaric oxygen at 2.5 ATA session, while the control group (n=16) received a sham treatment of air at 1.14 ATA session. Authors reported there were no statistical differences detected between the 2 groups in the number of patients with early improvement (p=0.44). At 3 months, the percentage of patients with good outcomes (in GCS, mRS and NIHSS) was greater in the sham group compared with the HBO-treated group. As one of the important RCTs in acute stroke, it has considerable limitations; first, the small sample size. Second, there's no objective imaging used for selection of patients as well as follow up measures. Third, authors did not report the different results in patients with short time delay from symptoms. As discussed above, and shown in animal and human studies, time is a critical factor. Patients within 6 hours from symptom onset to treatment (only 15% in this study) may benefit considerably better than after 6 and 12 hours. Fourth, since thrombolysis was excluded, the extremely short protocol of only 1 session was probably not enough to oxygenate the injured tissues. Without early recanalization, the penumbra tissues would need repeated oxygenation to

survive. In addition the exclusion of thrombolysis may be critical, as HBOT had better results in animals when recanalization occurred. Another physiological perspective can be related to the use of 2.5 ATA with 100% oxygen. With related to injured brain, and compared to other studies using much lower pressures (for example 1.3-1.5 ATA), 2.5 ATA can be consider much higher than optimal.

Nighoghossian et al. RCT on 34 patients with acute middle cerebral artery ischemic stroke within 24 hours prior to inclusion (112). Due to dropout, only 27 were included in final analysis. HBOT group (n=17) were treated with 10 sessions of hyperbaric oxygen at 1.5 ATA, 100% oxyegnfor 40 minutes, where the sham group (n=17) were treated with air at 1.2 ATA. There was a trend favoring HBOT treatment was observed at 1 year according to the statistically significant higher mean scores of the Orgogozo ($p<0.02$) and Trouillas scales ($p<0.03$). However, the mean change from pretherapeutic to posttherapeutic scores in the two groups at 6 months and 1 year did was not statistical significance. The study had several limitations. First, the small sample size which was even reduced further by dropout. Second, there was stratification of results per time to HBOT. As discussed earlier, time is a critical factor and patients treated in the first six hours may have a significant benefit. Third, there was no thrombolysis available at the year of study. Fourth, there was no imaging used as an objective measure of improvement. Lastly, the length of each session (40 minutes) can be considered too short to saturate the tissues.

Anderon et al. RCT on 39 patients with anterior circulation ischemic stroke within 2 weeks prior to inclusion (113). This study could be considered as an intervention for acute to subacute stroke. HBOT group (N=20) was treated with 60 minutes of

hyperbaric oxygen at 1.5 ATA three times a day for maximal 5 days (maximal 15 sessions). The sham group (N=19) was treated with air at hyperbaric pressure of 1.5 ATA. Due to loss of follow up and protocol violations only 27 patients were included in final analysis. Even though both groups improved significantly post treatment the difference between groups, was not significant. In addition, there was no significant difference in infarct volumes at 4 months (p=0.250). The study had considerable limitations which should be discussed. First, retrospective review of all 39 CT scans demonstrated that even though clinical severity stratifications were similar between groups, more patients with larger infarcts were randomized to the oxygen-treated group. This is a critical reinforcement for selection of patients based on brain imaging. Second, patients were treated in too large time span related to the initiation of the insult (10-148 hours), but there was no stratification of the results by time. Third, the small sample size which was further reduced in final analysis. Fourth, the time to intervention range was 10-148 hours post injury which may too late for oxygenation of penumbra tissues. Fifth, there was no thrombolysis avavilable in 1991 which can be evaluted as an adjunctive to HBOT. Lastly, the use of 1.5 ATA as sham treatment is a known problem in hyperbaric medicine. At 1.5 ATA of compressed air there is a significant increase in plasma and tissue oxygen pressure by at least 70%. It is well known that any slight increase in the partial pressure, say 1.05 ATA (at the Dead Sea), can bring on significant physiological effects (114, 115). Thus, the evidence that both groups improved considerably may be related of a non-sham treatment. 1.5 ATA may well serve as a low dosage effective treatment rather than sham control.

Kapp et al. prospective study on 22 patients with acute/subacute anterior circulation stroke treated with HBOT (116). Patients were treated with 40 minutes of hyperbaric

oxygen at 1.5 ATA for 14 daily sessions. The treatment was started within 1 hour to 2 weeks from event. Ten (45%) patients improved motor function. Out of 14 patients who had dysphasia, six (43%) had improvement in speech. Among the responders, improvement was seen in the first two session. Two patients who received HBOT within 1 hour to event had complete recovery. Authors report there's no evidence for improved results if treatment is started in the first 24 hours compared to the first week. However, none of the patients was treated between 2 and 6 hours to event. There was a positive but not absolute correlation between partial deficit and response to HBOT. There was a non absolute correlation between small infarct size and response to HBOT. The study has several limitations besides the small sample size and lack of a control group. No proper statistical analysis was provided. The hetergoneous time delay from event to treatment (1 hours-2 weeks), where most patients were treated after 6 hours from event is a major issue. In addition, the hyperbaric protocol of 40 minutes per session can be considered too short for appropriate oxygenation of the tissues.

Lebedev et al. reported on 124 patients with acute stroke treated with HBOT (117). However the article is not available and details are unknown. It was established that the depth of unconsciousness and the motor and aphasic disorders decreased during a HBOT session, but the effect was usually short-lived. Aggravation of the patients' condition in the first week of the disease, evidently caused by increase of cerebral edema, occurred much less frequently using HBOT. The number of patients with regression of the neurological symptoms was practically the same with and without the use of HBOT, but the regression of the neurological defects was most evident in patients exposed to HBOT.

In summary, the current clinical evidence is not sufficient to recommend the use of HBOT in acute stroke. All RCTs had considerable small samples (20-40 patients) with significant methodological flaws. No objective brain imaging was used as an objective measure of brain damage for patient selection and improvement. In addition, the time to treatment hasn't been stratified properly, especially in the first few hours from event to treatment.

Chronic Stroke

There were 2 RCT's, 2 prospective study, 2 cohort and 3 case reports evaluating the clinical effects of HBOT in patients suffering from stroke in the chronic stage. The studies had different HBOT protocols and evaluated different aspects of stroke consequences; neurological function, depression and cognitive functions. All RCTs showed HBOT treated groups improved significantly compared to pre-treatment state.

Low level evidence:

Hadanny et al. evaluated 11 patients with anoxic brain injury (even thought not classical stroke it represent systemic and brain hypoperfusion) due to cardiac arrest with cognitive impairments for an average of 2.6 years post injury (118). HBOT induced modest but significant improvement in memory (12%), attention (20%) and executive function (24%). Clinical improvements correlated with increased brain activity in relevant brain areas as assessed by SPECT imaging. Study limitations: a relatively small sample, lack of control group and not classical stroke.

Boussi-Gorss et al. retrospective analysis of 91 patients with either hemorrhagic or ischemic stroke at the late stages (3-180 months) treated with HBOT (119). Patients were treated with 2ATA 100% oxygen for 40-60 sessions. Compared to baseline evaluation, HBOT induced significant improvements in all memory measures (verbal, nonverbal, delayed, and immediate) ($p<0.0005$). The clinical improvements were well correlated with brain metabolism improvements measured by SPECT, mainly in temporal areas. Main limitations include lack of control group and the retrospective method.

Churchill published a prospective study (120) that included 22 patients at least one year after stroke. Even though a year or more had elapsed since the acute insult, HBOT induced improvement in symptoms (51% memory, 51% attention/concentration, 48% balance/coordination, 45% endurance, 20% sleep). However, on standardized evaluations of cognition and questionnaires no significant changes were reported. A small subset of the patients had brain imaging, and of those more than 50% showed significant improvements in brain perfusion. The study has several limitations due to the small sample size, vague inclusion criteria and no control group. In addition, the statistics were calculated for the entire group of chronic brain injury and not specifically for post stroke patients.

Lee et al. reported on a case of a patient treated with HBOT 20 days after ischemic stroke (121). The patient received 8 sessions of 90 minutes hyperbaric oxygen at 2 ATA. Even though it is only one case the strength relates to the use MR spectroscopy. Post HBOT, there was clinical improvement in addition to normalization of lactate level at MR spectroscopy.

Neubauer reported a patient with chronic brain ischemia treated successfully with HBOT (122). The patient presented with symptoms of gross mental confusion, memory loss, both recent and remote, irrational speech and occasional violence. After series of HBOT at 1.5-2 AT the patient improved significantly to well functioning. Improvement was was maintained for four years with intermittent HBOT sessions.

Hart et al. reported on a patient treated with HBOT 2 months after ischemic stroke (123). HBOT protocol included 2 hours of 100% oxygen at 2.5ATA for 15 sessions, 1 month break and another 15 sessions. There was a significant improvement in right hand motor function, as well as EEG changes.

Moderate/high level evidence:

Yan et al. RCT (124) on 90 patients (30 HBOT, 30 HBOT+ fluoxetine, 30 fluoxetine) one month after stroke. HBOT protocol included 20 sessions of 2 ATA for 70 minutes 100% oxygen. HBOT had significant reduced post stroke depression measured when administrated on top of fluoxetine when compared to fluoxetine alone by Hamilton's depression ($p<0.05$) compared to the other groups. The combined treatment reached 90% clinical efficacy, compared to 70-76% in the other groups. The main limitations in this study were lack of negative control and small sample size. In addition, no objective imaging/assessment was performed. When considering treatment in the chronic stage of stroke, 4 weeks of HBOT may be not enough time for repair mechanisms mentioned above to take place.

Efrati et al. RCT included 59 patients who suffered a stroke (both ischemic and hemorrhagic) 6-36 months prior to inclusion (125). Study was designed as cross-over study where patients in the treated group were evaluated twice; at baseline and after 40 HBOT sessions. Patients in the cross group were evaluated three times: at baseline, after a 2-month control period of no treatment, and after subsequent 2-months of 40 HBOT sessions. Patients were treated with 90 minutes of 2 ATA HBOT for 40 sessions. HBOT improved neurological function group (measured in NIHSS) in both the treated group and treated-cross group ($p=0.004$ and $p<0.0001$, respectively). This was further noticeable since there was no improvement was found during the control period of the patients in the cross group ($p=0.43$). The same pattern was seen in the quality of life score (measured in ADL) ($p<0.001$ in HBOT treated and $p<0.0001$ in the HBOT treated cross group). Results of SPECT imaging were well correlated with clinical improvement, especially in regions of noticeable discrepancy between anatomy (CT/MR) and physiology (SPECT). The crossover design afforded a triple comparison for proper evaluation of the HBOT effect. The major limitation in this study was the selection of patients by their brain SPECT, which may not always be feasible for all. However, this limitation and the results of this study should guide the proper use of HBOT on selected stroke patients that have a well-defined metabolic brain injury.

Vila et al. prospective study on 26 patients (18 HBOT) with neurological disabilities and cognitive decline due to cerebrovascular disease (126). Two thirds of the patients had history to clinical strokes and all patients had signs of brain ischemic changes in imaging. HBOT group was treated with 2.5 ATA hyperbaric oxygen for 45 minutes while the control group was exposed to 1.1 ATA breathing air. There was a statistically significant improvement in all scales (neurologic disabilities, cognitive function assays

and quality of life) for the HBOT group compared with the placebo group and in the placebo group after receiving HBOT months ($p<0.05$). Neurological improvement persisted in the majority of patients for up to 6 months. In addition, subjects who were originally in the control group showed significant improvement after receiving HBOT. The main limitations include relative small sample size and the lack of follow up objective brain imaging. Each session included only 45 minutes of hyperbaric oxygen. A minimum of a 1 hour HBOT exposure at 2 ATA is required to saturate the mixed venous hemoglobin return to the right atrium in normal resting males. In addition the protocol included only 10 sessions, which may be too short to gain the full benefits from the induced repair mechanisms as discussed above. However this study shows the importance of patient selection by an objective method as well as the superiority over a sham treatment.

In summary, all RCTs as well as the other studies excluding one, favor the use of HBOT in the chronic stage of stroke. The use of an objective brain imaging method is of highly importance as criteria of patients' selection and as an objective measure of the treatment results. The studies that were done with a proper control group and objective measurable endpoints showed significant improvement in cognitive function, neurological function, quality of life and brain metabolism.

- **Patients selection for HBOT**

-Acute stroke:

Considering the current literature, HBOT could not be recommended for acute stroke settings. Most studies had significant methodological flaws. In addition to small sample size, the main issues were patients' selection and timing of intervention. Currently, there is no clinical evidence regarding the optimal time to HBOT. There is not enough evidence to differentiate between ischemic and hemorrhagic strokes.

-Subacute/Chronic stroke:

Most of the studies in the delayed-chronic setting evaluated the effects of HBOT 3 months to 3 years post injury. The data before one month and after 3 years is lacking. No study has shown the importance or rational for delaying HBOT latter than 3 months. However, since most intensive rehabilitation programs treat stroke patients within the first 3 months, it problematic from sample size statistical consideration to have a control group during this period of time.

The correlation between metabolic brain imaging (eg. SPECT) and clinical outcome promises better results and affords objective evaluation of the patients. Therefore, patients should have brain metabolic imaging in addition to anatomical imaging at baseline as part of the pre post HBOT evaluations. Patients that can benefit the most from the treatment are those considerable metabolism defects without matched necrotic/anatomical damage.

- **HBOT protocol**

Acute stroke :

No protocol could be recommended based on current literature.

Chronic stroke:

Most evidence for HBOT in the chronic stroke settings was gained with a protocol of 90 minutes of 100% oxygen at 2 ATA.

The optimal number of sessions for specific patients is not clear. 20-40 sessions were used in the different study protocols, and in the authors' opinion 40 daily sessions should be the minimum number of sessions. It seems reasonable to assume that in order to gain full benefit from the neuroplastic/ regenerative brain processes 60 session can be recommended. However there is no study that compared different HBOT protocols.

It is highly recommended that all patients should undergo brain SPECT or PET-CT evaluation, in addition to MRI, for metabolism defects before and after the treatment. This may serve as an adjunctive tool for the decision whether to continue the treatment further. It should be well recognized by the physician and the expectation should be set with the patient that HBOT cannot have any effect on the necrotic brain regions.

Cognitive evaluations should be standardized, with preference to automated objective evaluations. Tests should have several versions with high test-retest reliability.

Neurological functions and depression should be evaluated properly and objectively.

Cost impact:

Financially:

The average cost for the first year for a stroke post stroke is about $17,080(127). The corresponding average yearly cost of medication was $ 5,392(128), while the average cost of yearly rehabilitation service utilization was $11,689 (127). Studies

showed that the annual costs of care for a patient with ischemic stroke at 10 years were did not decrease and were similar to the costs between 3 and 5 years after event (128). However, for hemorrhagic stroke, annual costs increase significantly in the long term and are considerably higher at 10 years (128). When considering a 40-60 sessions of HBOT, the cost would be $12,000-24,000, which is cost effective by all means even in the first year after treatment. In addition, these numbers do not take into account the loss of work due to disability and the return to work after HBOT of those who can improve/recover with the treatment.

Safety: In a recent retrospective analysis, patients suffering from chronic stroke did not have a higher complication rate compared to other HBOT patients. The usual risks of 40-60 sessions in HBOT are mild and reversible.

Conclusions:

Acute stroke: based on the data available today, HBOT cannot be recommended in the acute setting of stroke. Further multicenter studies are needed in order to evaluate the optimal treatment protocol for the different types of injuries.

Chronic Stroke: Based on the data available today, HBOT may be recommended in chronic stroke for a selected group of patients who have clear evidence of metabolically dysfunctioning brain regions that are mismatching with the necrotic brain regions. Patients who are candidates for HBOT should be properly evaluated prior to therapy by standardized cognitive tests and by a functional imaging of the brain.

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of session)	Results	Conclusion / comment
Hadanny (2015) (118)	**Case series**	**11 patients**	**Cognitive: Neurotrax computerized tests of memory, attention, executive function, information processing speed including: verbal memory, non-verbal memory, go-no-go test, Stroop, staged information processing test, catch game.** **Brain imaging: SPECT**	**Patients with anoxic brain damage due to cardiac arrest for at least 6 months with who have completed two SPECT imaging and two cognitive evaluations**	**60 min of 100% oxygen at 1.5 ATA X 60 sessions**	**Significant improvement in the global cognitive scores with a mean relative change of 8% (p=0.006). The most prominent improvement was in executive functions indices, with 24% mean relative change (p=0.011).**	**Favors the use of HBOT in anoxic brain damage (systemic hypoperfusion)** **Small sample** **No control group**

						Attention indices improved by mean relative change of 20% (p=0.06). Memory indices by mean relative change of 12% (p=0.08). The mean relative changes of all patients revealed significant improvement (higher than 10%) in brain activity in the cingulate gyrus, inferior frontal gyrus,	

						perirhinal cortex, primary visual cortex and parietal lobe (BA 7)	
Chen (2012) (109)	**Prospective study**	**46 patients (16 HBOT)**	**NIHSS score**	**Acute mild ischemic stroke (NIHSS 0-14) within 48 hours after onset without evidence of hemorrhage and no thrombolytic therapy recieved**	**60 mins of 100% oxygen at 2 ATA X 10 sessions Started within 3-5 days of stroke**	**The difference of basal NIHSS scores between the HBOT group and control group was not statistically significant (P = 0.647) and there was no statistically significant difference on early efficacy**	**Favors the use of HBOT in acute stroke Small sample Mild severity patients only No objective imaging Short follow up**

						between the groups (P = 0.140). However, comparison of late efficacy showed a statistically significant difference between the groups (P = 0.024)	
Yan (2015) (124)	**RCT**	**90 patients (30 HBOT, 30 HBOT+Fluoxetine)**	**Depression: Hamilton depression scale (HAMD)** **Neurological function: Scandinavian stroke scale (SSS)**	**Patients within 4 weeks after stroke**	**70 mins of 100% oxygen at 2 ATA X 20 sessions**	**the HAMD scores also showed better improvement in the hyperbaric oxygen combined group than the other two groups (p < 0.05). There**	**Favors the use of HBOT in the subacute-chronic stage of stroke** **Small sample size** **Lack of negative control** **No objective imaging** **Small number of sessions/short time of treatment**

						were no differences in SSS scores between the three groups at the end of the study (p > 0.05) The score reduction rates of the fluoxetine treatment group, HBO treatment group, and combined HBO treatment group were 70%, 76.7%, and 90%, respectively (p<0.05)	
Bennett (2014) (103)	**Meta-analysis**	**70-144 patients**	**Mortality Efficacy –**	**Acute stroke**	**1.5-2 ATA With different**	**No significant differences**	**No conclusion due to:** **- No true pooling of RCTs** **- No conclusion could be drawn**

			different scales of functional outcome		**protocols**	**in case fatality rates were noted (six deaths (8%) in those receiving HBOT versus six (8.5%) among those given sham therapy). In the HBOT group, three of 38 participants (8%) were judged to have received 'no effect' from therapy and were unable to care for**	

						themselves, compared with seven of 32 cases (22%) in the control group (p=0.12)	
Boussi-Rahav (2014) (119)	**Retrospective analysis**	**91 patients**	**Cognitive functions: Delayed memory, immediate memory, verbal memory, nonverbal memory Total memory index Brain imaging: SPECT**	**>3 months post stroke with 2 cognitive evaluations**	**90 mins of 100% oxygen at 2 ATA X 40-60 sessions**	**There was a significant improvement in all memory scores after HBO2 therapy compared with baseline (p<0.0005). The percentages of relative change for each memory measure**	**Favors the use of HBOT in chronic stroke -retrospective analysis -no control group -no strict protocol of 40-60 sessions**

						are presented in Figure 4. The change percentages were found to be as follows: 18% for the TMI measure, 43.5% for IVM, 48.6% for DVM, 17.5% for INVM and 18% for DNVM. **There were 35–46% of the patients who achieved significant clinical improvement in the**	

						different memory measures, out of which a very high percentage (78.9 – 100%) recovered, that is, passed the cutoff score differentiating between impaired and unimpaired populations in their posttreatment assessment. **These clinical changes were**	

						found to be in good agreement with metabolic brain changes assessed by SPECT brain imaging.	
Churchill 592012 (120)	**Prospective study**	**22 patients**	**Neuropsychological measures, questionnaires, neurologic exams, physical functioning measures** **Brain imaging: Auditory MRI, MRI Spectroscopy, CT-angio**	**Stroke at least 1 year prior to inclusion**	**60 min of 100% oxygen at 1.5 ATA X 60 sessions**	**Participants reported improvements in symptoms, such as memory and balance/ coordination.** **No standardized testing showed clinically important improvement.**	**No conclusion due to:** **Small sample size** **Vague inclusion criteria** **No control group**

Efrati (2013) (125)	**RCT**	**59 patients (29 HBOT)**	**Neurological function: NIHSS** **Quality of life: ADL, EQ5D, EQ-VAS** **Brain imaging: SPECT**	**Stroke within 6-36 months prior to inclusion**	**90 minutes of 100% oxygen at 2ATA X 40 sessions**	**Clinical evaluations revealed statistically significant improvements in the NIHSS measures following treatment both in the HBOT-treated group (p=0.004) and in the HBOT-treated cross group (p<0.0001). The significance of these improvements is further noticeable when compared**	**Favors the use of HBOT in chronic stroke** **Randomized controlled trial with control group and crossover design** **Selection of patients with proper functional imaging**

						to the control (non-treatment) period of the cross group during which the scores did not change at all (p=0.43). Clinical evaluations revealed statistically significant improvements in the ADL score following treatment both in the HBOT-treated group (p<0.001) and the cross group	

						after the cross to the HBOT-treated ($p<0.0001$). The significance of these improvements is further noticeable when compared to the control (non-treatment) period of the cross group during which there was no change in the ADL scores ($p=0.42$ compared to baseline	

						EQ-5D score significantly improved following treatment, both for the HBOT-treated group (p<0.0001 compared to baseline) and the HBOT-treated cross group (p<0.0001 compared to pre-HBOT), while there was no improvement following	

						the control period (p=0.122 compared to baseline, p=0.009 for comparison between the groups). Comparison of brain activity improvement following the HBOT revealed that 55% of the treated group had significant improvement after HBOT and 35% had mild improvement. In the	

						cross group, during the first (control) period 36% had mild improvement and only 6.2% had significant improvement (p<0.001). After HBOT, the cross group demonstrated 43% significant improvement and 29% mild improvement (p<0.001) (data not shown in tables).	

Chen (2011) (104)	**Case report**	**1 patient**	**Neurological function: NIHSS, mRS, MMSE, GCS, BI, MoCA** **Brain imaging: SPECT CT perfusion**	**None : ischemic stroke 3 days prior to treatment**	**60 mins of 100% oxygen at 2 ATA X 10 sessions**	**neurological function, showed prominent improvement immediately after HBC^T and also at one and three months . His regional cerebral blood flow (rCBF) with 99mTc-ethyl cysteinate dimmer (99Tc ECD) brain single-photon emission computed tomograph**	**No conclusion due to: Case report**

						y (SPECT) did show the ameliorati on.Improv ed penumbra areas were also noted in the computed tomograph y perfusion (CTP) image study.	
Gibson (2010) (105)	**Case series**	**12 patients**	**Neurological exam**	**Neurologic al signs after cardiac surgery**	**Table RN62 followed by 1-3 2 ATA sessions**	**8/12 patients had partial or complete resolution of neurologic al signs. 3 patients demonstra ted minimal neurologic al**	**Could not conclude due to : -Air embolism as an origin in several cases -retrospective analysis -small sample size -lack of control group -no objective imaging**

						improvement and one died a rapid neurological death.	
Imai (2006) (110)	**RCT**	**38 patients**	**Neurological function: NIHSS, mRS**	**Acute anterior circulation embolic ischemic stroke within 48 hours prior to inclusion, NIHSS>4**	**60 minutes of 100% oxygen at 2 ATA X 7 sessions**	**No significant differences were present in median NIHSS scores at baseline or at 7 days (NS). On the other hand, median intergroup improvement in NIHSS was 5 in the HBOT group compared to 1 in the control group ($p<0.01$).**	**Favors the use of HBOT in acute embolic ischemic stroke** **-combination of Edavorone – true effect of HBOT unknown** **-small sample size** **-lack of objective imaging in analysis**

						6 had favorable outcome at 90 days in the HBOT groups compared to only 1 in the control group (p=0.045). No difference in mortality rate at 90 days between the 2 groups (p=0.302)	
McCormick (2011) (106)	**Retrospective analysis**	**22 patients**	**Neurological examination**	**Acute stroke within hours**	**2-3 ATA X 1 session**	**In the one- to five-hour post-stroke group of 13 patients, nine (41% of 22) had**	**Favors the use of HBOT in acute ischemic stroke -lack of control group -small sample size -retrospective analysis -No thrombolysis available in 1966**

						recovery or recovery with relapse. Only two of the nine had permanent recovery. Past six hours post-stroke, only one patient (11% +/- 21% SE) had partial recovery with relapse. The other eight patients who received treatment past six hours had no	

						recovery at all. With each passing hour decreasing the chance of at least partial transient recovery by 62% - odds ratio: 0.38 (95% CI: 0.150.95), p=0.039	
Lee (2008) (121)	**Case report**	**1 patient**	**Neurological examination** **Brain imaging: MRI, MR spectroscopy**	**Subacute ischemic stroke – 20 days post insult**	**90 minutes of 100% oxygen at 2 ATA X 8 sessions**	**MRI and 1 H-MRS detected neither new ischemic lesions nor lactate peaks in the same areas and the patient showed clinical improvem**	**Could not conclude from case report**

						ent.	
Vila ((2005) (126)	**Prospective study**	**26 patients (18 HBOT)**	**Neurological function: Gait and Equilibrium scale (GES) Barthel scale (BS) Unified scale for parkinson's diseae (UPDRS) Quality of life Instrumental Activities of daily life (IADL)** **Cognitive functions: Mini Mental state examination (MMSE)**	**Patients with cerebrovascular disease by the combination of at least 2 neurological deficits and objective cerebrovascular changes in CT**	**45 minutes of 100% oxygen / 21% air at 2 ATA / 1.1 ATA X 10 sessions**	**There was a statistically significant improvement in all scales for the HBO2 group compared with the placebo group and in the placebo group after receiving HBO2 ($p<0.05$) including: MMSE, BS, IADL, GES, UPDRS,** **Neurological improvement**	**Favors the use of HBOT in chronic stroke:** **-small sample size** **-lack of randomization** **-lack of follow up objective imaging** **-short HBOT protocol: both time of sessions and number of sessions** **-selection of patients based on objective imaging**

						persisted in the majority of patients for up to 6 months	
Rusyniak (2003) (111)	**RCT**	**33 patients (17 HBOT, 16 sham)**	**Neurological functions: mRS, NIHSS** **Mortality**	**Acute ischemic stroke within 24 hours prior to inclusion** **Thrombolysis was excluded**	**60 minutes of 100% oxygen/21%air at 2.5ATA /1.14 ATA**	**There were no statistical differences detected between the 2 groups in the number of patients with early improvement (sham, 31.3%; HBO, 17.7%; P=0.44). At 3 months, the percentage of patients with good outcomes was**	**Although unfavor use of HBOT in acute ishcmiec stroke, could not conclude due to :** **-small sample size** **-no report of results in short time delay of stroke to treatment** **-most patients (85%) >6 hours from symptoms** **-lack of objective imaging** **-very short protocol** **-thrombolysis excluded**

						greater in the sham group compared with the HBO-treated group, reaching significance in GCS,mRS and NIHSS.	
Lim (2001) (107)	**Case report**	**1 patient**	**Neurological examination** **Perfusion MRI**	**Acute hemorrhagic stroke within 24 hours from symptoms**	**90 minutes of 100% oxygen at 1.8 ATA X 9 sessions**	**By the third treatment, her GCS had improved to 15/15. Motor power improved to 4/5 after the fourth treatment. Improvement was sustained at 3- and at 6-**	**Could not conclude due to case report**

						months follow-up. HBOT shows an increase in rCBV immediately around the hematoma after HBOT	
Nighoghossian (1995) (112)	**RCT**	**34 patients (17 HBOT, 17 Sham) Only 24 patients in analysis (14 vs.13)**	**Neurological function: Modified Rankin score, Trouillas scale, Orgogozo scale**	**Acute middle cerebral artery ischemic stroke within 24 hours**	**40 minutes of 100% oxygen at 1.5 ATA X 10 sesisons**	**There was a significant difference between the two groups at the 1-year follow-up according to the mean scores on the Orgogozo (P<0.02) and Trouillas (P<0.03) scales,**	**Could not conclude due to:** **-small sample size** **-lack of objective imaging measure** **-short session time** **-no thrombolysis at 1995** **-no time to treatment stratification**

						whereas the Rankin scale score did not show any difference (P<0.11). Conversely, the comparison of the pretherapeutic and posttherapeutic differences in the two groups at 6 months and 1 year did not show any statistical significance	
Anderson (1991) (113)	**RCT**	**39 (20 HBOT, 19 Sham). 27 included in final analysis**	**Neurological examination Brain imaging: infarct size on CT**	**Acute/subacute anterior circulation ischemic stroke**	**60 minutes of 100% oxygen at 1.5 ATA three**	**At 4 months, air-treated patients had improved**	**Could not conclude due to: -non objective imaging based selection of patients – HBOT patients had larger infracts in CT. -lack of time to treatment stratification**

				within 2 weeks prior to inclusion	**daily up to 15 sessions, Compared with 60 minutes of 21% oxygen at 1.5 ATA three daily up to 15 sessions**	**by 15.9±3.2 points (mean+SEM, p< 0.0003) and oxygen-treated patients by 12.2±4.8 points (p<0.03). The difference between groups, although not significant. Based on CT scan data from 12 air-treated patients and 15 oxygen-treated patients, infarct volumes at**	**-small sample size -no thrombolysis in 1991 -1.5 ATA as sham treatment**

						4 months were 29.0±12.2 and 49.2+11.7 cm3 , respectively (two-tailed / test, p=0.25).	
Neurbauer (1983) (122)	**Case report**	**1 patient**	**Neurological examination**	**Chronic ischemia – small vessels stenosis**	**100% oxygen at 1.5-2 ATA X unknown number of sessions**		**Could not conclude from case report**
Kapp (1981) (116)	**Uncontrolled prospective study**	**22 patients**	**Neurological examination**	**Anterior circulation acute/subacute stroke**	**100% oxygen at 1.5 ATA for 40 minutes X 14 sessions**	**Ten (45%) patients improved motor function. Out of 14 patients who had dysphasia, six (43%) had improvement in speech.**	**Favors the use of HBOT in acute/subacute HBOT:** **-small sample size** **-lack of control group** **-hetergonous time delay to treatment** **-no treatment within 2-6 hours from event** **-no proper statistical analysis** **-short HBOT protocol**

						Among the responders, improvement was seen in the first two session. Two patients who received HBOT within 1 hour to event had complete recovery. Authors report there's no evidence for improved results if treatment is started in the first 24 hours compared to the first week.	

						However, no patients were treated between 2 and 6 hours to event. There was a positive but not absolute correlation between partial deficit and response to HBOT. There was a non absolute correlation between small infarct size and response to HBOT.	
Lebedev (1983) (117)	**Unknown design**	**124 patients**	**Unknown**	**Unknown**	**Unknown**	**It was established that the depth of**	**Could not conclude to lack of details of study**

						unconsciousness and the motor and aphasic disorders decreased during a HBOT session, but the effect was usually short-lived. Aggravation of the patients' condition in the first week of the disease, evidently caused by increase of cerebral edema, occurred much less frequently using	

						HBOT. The number of patients with regression of the neurologic al symptoms was practically the same with and without the use of HBO, but the regression of the neurologic al defects was most evident in patients exposed to HBOT.	
Sarno (1972)	**Case series**	**16 patients**	**Neurological examination** **Cognitive evaluation**	**Unknown**	**Unknown**	**No improvem ent in auditory comprehe**	**Could not conclude from small case series without control and lack of details**

						nsion or functional communcation post HBOT	
Hart (1971) (123)	**Case report**	**1 patient**	**Neuological examination** **EEG**	**Chronic stroke 2 months after event**	**120 minutes of 100% oxygen at 2.5 ATA X 30 sessions**	**There was a significant improvement in motor function of the upper limb. EEG changes were interpreted as sign of improvement.**	**Could not conclude from case report**
Ingvar (1965) (108)	**Case reports**	**4 patients**	**Neurological examination** **EEG**	**Unknown**	**1.5-2.5 hours of 100% oxygen at 2-2.5 ATA for unknown number of sessions**	**3 out 4 patients had beneficial effects from HBOT.**	**Could not conclude from 4 case reports and lack of details**

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