HBO Therapy in Neurosurgery

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K.K. Jain

Abstract

This chapter covers the applications of HBO in various conditions encountered in neurosurgical practice. These include traumatic brain injury (TBI) as well as its sequelae, and spinal cord injury (SCI). HBO has an important role in management of cerebral edema. HBO is a useful adjunct to management of ischemic and compressive lesions of the spinal cord as well as rehabilitation of the patient with SCI. HBO has important applications in cerebrovascular surgery based on its beneficial effect in cerebral ischemia including sequelae of ruptured intracranial aneurysms. In addition to its neuroprotective effect in procedures involving interruption of cerebral circulation, HBO has as an important application in selecting patients who are likely to benefit from cerebral revascularization procedures. Experimental studies as well as clinical applications are described. HBO is used either as a primary therapy or adjunct to other treatments such as radiotherapy of brain tumors and management of various complications of neurosurgery such as postoperative infections.

Keywords

Carotid endarterectomy • Cerebral edema • Cerebrovascular surgery • Extra-intracranial bypass • Hyperbaric oxygen • Neurosurgery • Postoperative complications • Spinal cord injury (SCI) • Stroke • Traumatic brain injury (TBI)

Introduction

Investigations of applications of hyperbaric oxygenation (HBO) in neurosurgery continue to evolve. A number of new publications have confirmed the efficacy of HBO in cerebral edema, which was initially reported over 40 years ago. Uncertainty among clinicians about using HBO in the therapy of cerebral pathology because definitive established mechanisms of action are still lacking has been addressed (Calvert et al. 2007).

The use of hyperbaric oxygenation (HBO) for diseases of the central nervous system is based on the ability of HBO to increase oxygenation and reduce cerebral blood flow. The pathophysiological sequelae of both head and spinal cord trauma include hypoxia and hyperemia. However, the complexity of central nervous system trauma involves events at multiple levels: cellular integrity and metabolism, blood flow, enzymatic disruption, and all their implications. Consequently, not only is multimodality therapy essential in central nervous system trauma, but also the specific effects must be carefully monitored inasmuch as the treatment of the brain and spinal cord with HBO is somewhat paradoxical, and carries with it the potential for therapeutic success as well as aggravation.

Role of HBO in the Management of Traumatic Brain Injury: TBI

Therapy for traumatic brain injury (TBI) must address the cascade of events that occurs subsequent to brain injury. The rationale for success must first be based on the potential of the

K.K. Jain, MD, FRACS, FFPM (✉)
Blaesiring 7, Basel 4057, Switzerland
e-mail: jain@pharmabiotech.ch

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damaged brain for recovery. This must be followed by the use of agents to prevent the cyclical events of ischemia, edema, elevated intracranial pressure (ICP), cellular disruption, and the metabolic and enzymatic derangements that occur subsequent to brain injury. The enclosure of the brain in the rigid and compartmentalized skull adds an additional challenge. HBO along with other non-operative care must be considered as an adjuvant to surgery or as the primary therapy in nonsurgical cases.

Osmotic and renal diuretics continue to be used for control of cerebral edema but their use is not quite satisfactory The current emphasis on treatment of TBI involves investigation of pharmacological methods and control of intracranial pressure in an effort to produce an environment that will either allow the injured brain to heal, and/or prevent the development of progressive damage. Use of various neuroprotective agents in TBI has been reviewed elsewhere (Jain 2011). There has been experimental and clinical experience with various cerebral protective agents such as calcium channel blockers, barbiturates, glutamine antagonists, free radical scavengers, steroids, receptor antagonists, and volatile anesthetics.

On a practical and accepted level, we now have very adequate monitoring facilities for TBI patients. To support our clinical judgment, we have neuro-imaging and improved methods of measuring ICP, cerebral blood flow (CBF), and cerebral metabolism. These would facilitate the development of comprehensive approaches to deal with the complexity of brain injury. Because the traumatized brain can respond to the therapeutic effects of HBO, continued efforts to develop appropriate regimes utilizing this modality are mandatory. Virtually any trauma to the central nervous system (CNS) includes the vicious cycle of interacting ischemia, hypoxia, edema, and metabolic-enzymatic disturbances. The metabolic disturbances include the production of free radicals capable of causing vasodilatation and vascular wall damage. Hypoxia causes a shift in glycolysis with the production of lactic acid and lowering of the pH. An imbalance of energy demand and availability results in the consequent ischemia-like state with loss of ATP available to the neurons and glia. In addition to the oxygen free radicals, excitatory amino acids are released as a consequence of vascular injury. The initial or subsequent loss of cellular integrity, combined with the ionic derangements and vascular dilatation effects of free radicals, and compounded by fluid and electrolyte shifts both into the interstitial spaces and extracellular components, will result in cerebral edema and increased ICP. Thus, the main therapeutic efforts of treating the head injured patient are directed toward the above noted pathophysiological changes. Agents must be used to reduce increased ICP, ischemia, and metabolic and enzymatic derangements.

Mechanism of Action of HBO in TBI

The properties of HBO that have enabled both clinical and investigational advances in the management of TBI are well known. As we have seen in previous chapters, vasoconstriction reduces cerebral blood flow, and the increased oxygenation of the blood mitigates against ischemia. The decrease in blood flow reduces a major element of ICP. However, there are additional mechanisms involved in the therapeutic effects of HBO. Studies of CBF and damaged cerebral tissue in humans demonstrate that variations of CBF are minimized by HBO. The hypothesis is that if the reduction of ICP by HBO is the result of decreased cerebral edema, then hyperoxia causes a reduction in CBF and the damaged areas manifest an increased flow after HBO. This statement does contradict the fact that hyperoxia reduces blood flow. Rather, it supports the multiple mechanisms that are present when using hyperoxia and are necessary in the treatment of cerebral trauma, a complex and multidimensional pathological entity. Variations in CBF, cerebral autoregulation have been well investigated (Jaeger et al. 2006).

Effect of HBO on ICP in Acute TBI

HBO alone has been demonstrated to reduce ICP. Even normobaric hyperoxia, defined as treatment with 100 % oxygen, has been shown to elevate brain oxygen, improve brain oxidative metabolism, and reduce intracranial pressure in TBI. ICP continues to decrease post therapy although during baseline periods there may be no difference between the control patients and those receiving 100 % oxygen. These findings provide a strong impetus for the use of oxygen in TBI. Because O_2 is being treated as a drug, dosimetry and monitoring are necessary. The correct utilization of HBO involves documentation of the patient's neurological status, measurement of ICP, and cerebral metabolism; particularly the lactate/pyruvate ratio effects an increase in the pH by decreasing the lactate level. This facilitates the decision as to when to treat, how often to treat, and what atmospheric pressure of oxygen to use. Clearly, if the same results can be obtained with normobaric oxygen (NBO), the clinician should reserve HBO for those patients that respond better to this HBO than to NBO as assessed by multimodality monitoring and neurological status. Avoidance of oxygen toxicity is paramount. The use of continuous 100 % oxygen must be accompanied by evidence of the absence of oxygen toxicity. Because HBO is dosimetry controlled, the patient's clinical status is monitored (ICP, cerebral metabolism), and if it is used intermittently, the patient has time to recover from potential O_2 toxicity with the normal indigenous anti-oxidant mechanisms. If confirmation of ICP reduction and improved metabolism aid is obtained, a combination of HBO and

"hyperoxia" should be considered for TBI. Alternate sessions of HBO and NBO can be considered. Differences in response reflect the differences and complexity of TBI. In any event, there is more than ample evidence of the need to adequately use oxygen in TBI and measure partial pressure of brain O_2 in TBI. Similarly, safety and understanding the issues of ischemia and altered metabolism continue to be stressed (Verweij et al. 2007).

The use of hyperventilation to diminish cerebral blood volume (secondary to hypocarbia causing increased pH and vasoconstriction) can be enhanced by HBO. The complexities of the use of HBO for TBI, however, must not be understated. Vasoconstriction secondary to hyperventilation can cause areas of cerebral ischemia. In addition, after 30 h of hyperventilation, the CSF pH returns to normal. Vessel diameter becomes greater than that at baseline during this time frame. It is unlikely that under hyperoxic conditions vasoconstriction itself could be deleterious. However, it has been shown that under excessive hyperoxic conditions, cerebral metabolism can be adversely affected. Thus, as in any treatment, both dosimetry and appropriate indications are essential. CBF measurements, before and after HBO, will assist in determining the efficacy of the treatment and in deciding upon dosimetry and schedules of HBO treatments. HBO is contraindicated when a stage of vasomotor paralysis has developed. In that condition, the vasoconstrictive effects of oxygen are absent and toxic hyperoxia can result. Patients receiving HBO, therefore, must show a response to hyperventilation by reduction in ICP. They must not have fixed and dilated pupils. Continuous monitoring of the neurological status when using HBO for the acute brain damaged patient is necessary. It must include jugular venous lactate and pH determinations, and periodic evaluation of cerebral blood flow. This, along with measurement of ICP and periodic neuro-imaging and clinical evaluation, will allow the appropriate application of HBO therapy. Each individual patient will require a specific dose with a specific frequency of administration during well-defined times if HBO is to be appropriately and successfully utilized.

Toxic effects of hyperoxia should be avoided (see Chap. 6). Oxygen toxicity involves metabolic production of partially reduced ROS. These oxygen free radicals include superoxide, peroxide, and hydroxyl radicals. They are produced by a univalent reduction of oxygen during aerobic metabolism. Thus, the use of HBO to reduce edema and oxygenate ischemic tissue may pose a dilemma because the original cerebral injury itself may alter cerebral metabolism, resulting in anaerobic metabolism and the production of oxygen free radicals. Free radical production in experimentally injured animals, however, has been shown to be reduced by HBO application. In spite of this observation, caution should be exercised in the use of HBO in brain injury and free radical scavengers may be used as adjuncts to HBO.

Oxygen toxicity is a dose-related phenomenon because oxygen is a drug. Dosimetry, therefore, must be appropriate. Monitoring must be continuous and accurate. HBO is administered intermittently to allow the anti-oxidant defenses to recover. Concomitant drugs that may potentiate oxygen toxicity must be avoided. These include adrenal cortical steroids which have been used in acute head injury patients. Untoward results from the use of HBO in head trauma are seen at pressures over 2 ATA. Usually HBO at 1.5–2 ATA is used in CNS disorders and is considered to be quite safe. Modifications of this will depend upon the metabolic monitoring factors and ICP measurements.

Effect of HBO Therapy in Chronic Sequelae of TBI

Most of emphasis on treatment has been in acute TBI in the past. In recent years there is increasing attention paid to chronic sequelae of TBI such as post-concussion syndrome (PCS) and possibly post-traumatic stress disorder (PTSD), which has been seen in US war veterans. Because of prevalence of PTSD in civilian population, its relation to TBI is still somewhat controversial and is the subject of ongoing investigations in war veterans. Blast-related mild TBI (mTBI) is a common injury among returning troops due to the widespread use of improvised explosive devices in the Iraq and Afghanistan Wars. Use of diffusion tensor imaging (DTI) has shown that mTBI with loss of consciousness is associated with white matter injury of the brain. The findings of a study suggest that at higher levels of PTSD symptom severity, loss of consciousness was correlated with postmortem reports of diffuse axonal injury following mTBI and that such injuries may be particularly detrimental to white matter integrity, which in turn influence neurocognitive function (Hayes et al. 2015).

In a phase I study of the safety and efficacy of HBO in 16 war veterans with chronic blast-induced mild to moderate TBI/PCS, each patient received 40 HBO sessions (1.5 ATA/60 min) in 30 days (Harch et al. 2012). Significant improvements occurred in symptoms, abnormal physical exam findings, cognitive testing, and quality-of-life measurements, with concomitant significant improvements in SPECT.

Chronic repeated trauma in sports, particularly football, is known to lead to chronic traumatic encephalopathy.

Experimental and Clinical Studies of HBO in TBI

Table 21.1 gives a brief summary of classical studies dealing with the clinical and investigative work on this topic, which indicates that HBO has an important place in the management

Table 21.1 Clinical and investigative work on HBO in traumatic brain injury: classical studies

Traumatic brain injury (TBI)
Experimental
Coe and Hayes (1966): Increased lifespan in experimentally injured rats treated with HBO
Sukoff et al. (1968): Psyllium seed-induced cerebral edema and acute epidural balloon inflation successfully treated with HBO
Wan and Sukoff (1992): Demonstrated improved neurological status and mortality in experimentally produced brain injury when HBO utilized
Clinical
Fasano et al. (1964): HBO in traumatic brain injury demonstrated to be therapeutic
Holbach et al. (1972): Acute and subacute brain injuries were demonstrated to have better results when treated with HBO. ICP and cerebral metabolism improvement documented
Mogami et al. (1969): Traumatic brain injuries and postoperative edema after brain tumor surgery successfully treated with HBO. ICP, EEG and clinical improvement most favorable in the lesser injured patients
Artru et al. (1976a): The neurological status, ICP and metabolism of certain patients with traumatic encephalopathies improved when treated with HBO. Patients under 30 without mass lesions fared better than similar control group
Országh and Simácek (1980) and Isakov et al. (1981): Positive results in patients treated with HBO for traumatic encephalopathies
Sukoff (1982): Clinical and ICP improvement seen in those patients with mid-level coma scales undergoing HBO therapy for acute head trauma
Rockswold (1992): Increased survival in acute head injury with HBO
Barrett et al. (1998): Cognitive and cerebral blood flow improvement in chronic stable traumatic brain injury by use of HBO at 1.5 ATA
Intracranial pressure (ICP)
Experimental
Miller and Ledingham (1970, 1971) and Miller (1973): HBO demonstrated to reduce ICP in experimental cerebral edema. Vasomotor changes in response to CO_2 are necessary for the vasoconstrictor effects of HBO to lower ICP. HBO and hyperventilation causes a greater reduction in ICP than hyperventilation alone. Additionally, cerebral vasoconstriction does not occur when arterial PO_2 is >1800 mmHg. Cerebral pH at 2 ATA was also shown to increase
Clinical
Mogami et al. (1969): TBI patients with the least severe symptoms had the greatest ICP reduction
Artru et al. (1976b): Improvement in patients treated with HBO for TBI
Sukoff (1982): Statistically significant reduction in ICP in all monitored TBI patients

of the severely injured but therapeutically responsive patient with TBI. A study on the effect of HBO in TBI evaluated CBF and cognitive improvement (Barrett et al. 1998). In this study five patients with TBI, at least 3 years after injury, underwent 120 HBO treatments each at 1.5 ATA for 60 min. There was a rest period of 5 months before the first set of 80 treatments and the second set of 40 treatments. Sequential studies of SPECT scanning, CBF, speech, neurological, and cognitive function were carried out. Six patients with TBI, who were not treated with HBO, served as controls. Results of SPECT scanning showed that there was no significant change over time whereas HBO-treated patients had permanent increases in penumbra area CBF. Speech fluency improved in the HBO group as well as memory and attention. The improved peaked at 80 HBO treatments. The authors concluded that HBO therapy can improve cognitive function as CBF in the penumbra in chronic stable TBI patients where no improvement would ordinarily be expected 3 years after the injury.

Increased cerebral metabolic rate of oxygen and decreased level of lactate in CSF found in TBI patients treated with HBO indicate that HBO can improve cerebral metabolism. The correlation between CBF and cerebral metabolic rate and HBO is important in understanding why HBO may be useful in the treatment of severe TBI. Intracranial pressure is the sum total of brain blood volume, brain tissue volume, and water, and may be lowered by reducing blood volume. HBO can reduce blood volume. ICP responds better to HBO when the rate of CBF is lowered. There is no correlation between the response of ICP to HBO therapy and the level of CBF. In patients with elevated ICP, HBO tends to decrease it.

Experimental studies confirm some of the findings observed in earlier studies of TBI patients with HBO. In a rat model of chronic TBI, a 40-day series of 80 HBO treatments at 1.5 ATA produced an increase in contused hippocampus vascular density and an associated improvement in cognitive function as compared to controls and sham-treated animals (Harch et al. 2007). These findings reaffirm the favorable clinical experience of HBO-treated patients with chronic TBI.

A phase I/II open-label study (ClinicalTrials.gov Identifier: NCT01847755), which was on-going in 2016, will test the effect of HBO at 1.5 ATA (5 times/week) on cognitive function and CBF determined by SPECT in TBI patients. Each patient will have a SPECT scan, cognitive assessment, and physician evaluation prior to first treat-

ment and after 40, 80, and 120 treatments to document progress of the treatment. Cognitive assessment will include the Trail Making Test Parts A and B. HBO treatments may be adjusted for patient comfort. If the SPECT scan, cognitive assessment, and physician evaluation show improvement after 40 treatments, another 40 HBO treatments will be administered. Treatments will be discontinued after a 40-session interval if the SPECT scan, cognitive assessment, and physician evaluation show no improvement.

Controlled Clinical Trials of HBO for TBI

In 2012, wars in the Middle East had resulted in between 10 and 20 % of US service members with mTBI. Anecdotal reports had associated HBO with improved outcomes after mTBI, but controlled clinical trials were lacking. The Department of Defense (DoD), in collaboration with the Department of Veterans Affairs (DVA), planned a comprehensive program to examine this issue (Weaver et al. 2012). The DoD's 4 planned randomized controlled trials were to enroll a total of 242 service members with post-concussion syndrome (PCS) and expose them to a range of control, sham, and HBO conditions for 40 sessions over a period of 8–11 weeks. Compression pressures will range from 1.2 ATA (sham) to 2.4 ATA, and oxygen concentration will range from room air (sham and control) to 100 %. Outcomes measures include both subjective and objective measures performed at baseline, at exposure completion, and at 3–12 months' follow-up. This integrated program of clinical trials investigating the efficacy of HBO in service members with persistent symptoms following mTBI exposure will be important in defining practice guidelines and, if needed, for the development of definitive clinical trials in this population. However, at the time of writing this chapter in 2016, none of these planned trials could be identified. Published as well as ongoing controlled clinical trials of TBI and its sequelae (those where information is available) are listed in Table 21.2.

Table 21.2 Controlled clinical trials of HBO for TBI and sequelae

Reference/trial #	Description	Results/comments
Lin et al. (2008)	Prospective randomized trial on 44 patients with TBI half of whom received HBO after the stabilization of condition. Evaluation before and 3–6 m after HBO with Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS)	GCS of the HBO group was improved from 11.1 to 13.5 in average, and from 10.4 to 11.5 for control group. Among those patients with GOS of 4 before the HBO, significant GOS improvement was observed in HBO group 6 m after HBOT
Rockswold et al. (2010)	A prospective randomized study on 69 patients with severe TBIs were treated within 24 h of injury once/day for 3 days in 3 groups: (1) HBO, 60 m 1.5 ATA; (2) NBH, 3 h of 100 % O2 at 1 ATA; and (3) control, standard care	HBO had a more robust post-treatment effect than NBH on oxidative cerebral metabolism by producing brain tissue $PO_2 \geq 200$ mmHg. However, this effect was not all or none, but graduated
Boussi-Gross et al. (2013)	A prospective, randomized, crossover trial of 1.5 ATA HBO on 56 mTBI patients 1–5 years after injury with PCS using 40 1-h sessions (5 day/week)	HBO-induced neuroplasticity led to improvement of brain functions and quality of life at a chronic stage
Cifu et al. (2014)	Randomized, double-blind 10-week trial of effect of 40 HBO treatments (1.5–2 ATA once a day) on eye movement abnormalities in 60 war veterans with at least 1 mTBI	Neither 1.5 nor 2 ATA HBO had an effect on post-concussive eye movement abnormalities after mTBI when compared with a sham-control
Wolf et al. (2015)	Randomized trial of effect of 30 exposures of HBO at 2.4 ATA on cognitive function in TBI	No significant difference between a sham and HBO treatments but subgroups with favorable response to HBO
ClinicalTrials.gov #:NCT02089594/Completion 2015, not published yet	A phase III randomized, prospective, single-blind crossover trial of 40 treatments with HBO at 1.5 ATA versus maintenance medication on 100 patients with mTBI/PCS who have been symptomatic continuously for at least 6 months	After 8 weeks the no treatment group will be crossed over to receive 40 HBO treatments

Use of HBO for TBI in Clinical Practice

When HBO is utilized as an adjunct to the treatment of TBI, the following regime should be followed:

- A neurosurgeon is involved with the patient care.
- Treatments must be initiated within 12 h of the trauma, unless there has been a recent deterioration of the patient's condition.
- An ICP monitor must be in place.
- Concurrent methods to reduce ICP include hyperventilation for the first 48 h and consideration for barbiturate coma.
- An experienced hyperbaric team.
- The protocol must consist of exposure to HBO at between 1.5 and 2 ATA on an intermittent basis.
- Treatments can be given every 4, 6, 8, or 12 h depending upon the clinical status, ICP, and results of measurement of cerebral metabolism, neuro-imaging, and CBF measurements.
- Jugular venous glucose, pH, and lactic acid determinations are necessary. The goal is to achieve a diminished lactic acid concentration and an increased pH.
- Cerebral perfusion pressure must be adequate (70 mmHg or above).
- The patient must have therapeutic levels of an anticonvulsant.

Besides dosimetry of HBO, complete monitoring is essential including frequent neurological examinations, ICP measurements as well as analysis of CSF, blood pH, and lactic acid. Each patient must be treated according to an individual schedule, and the dose should be based on response and results. Although HBO is not established as treatment of severe TBI, therapeutic effectiveness may be established when full analysis including total monitoring of further randomized clinical trials is completed. Subgroups of appropriate patients for treatment can be identified. For these patients the ideal pressure, duration, and frequency of HBO sessions can be determined.

Conclusions

HBO has been shown both experimentally and clinically to improve the outcome of TBI. Its therapeutic effects are based on the ability of the hyperoxic environment to reduce CBF by vasoconstriction, reduce ICP, and increase oxygenation. There is supportive evidence for increasing tissue pO_2 as a consequence (tissue and microcirculation). Cerebral trauma results in a cascade of events characterized by ischemia, hypoxia, edema, increased ICP, increased CBF, and metabolic and enzymatic alterations. This results in a lowering of the pH and increase in lactic acid production, and free radical release resulting in vasodilatation, impaired carbon dioxide reactivity, and damage to the cerebral vascular endothelium. The ability of HBO to modify these pathophysiological changes is postulated, and there is sufficient experimental and clinical evidence to support this.

The toxic effects of oxygen itself is explained by the free radical theory of molecular oxygen toxicity and parallels the metabolic effects initiated subsequent to head injury; the release of toxic oxygen free radicals. However, when utilized appropriately as regards dosage, patient selection, CBF, and cerebral metabolic monitoring, the vasoconstrictive effect of HBO, while enabling increased tissue oxygenation, will maintain the tissue pO_2 at a level that allows the cellular antioxidant defense mechanisms to overcome the potential of hyperoxia to induce oxygen toxicity. It appears that the most favorable patients to treat are those with midlevel Glasgow coma scales using HBO pressure between 1.5 and 2 ATA, on an intermittent short-term basis. Intriguing issues in the use of HBO to manage cerebral injury include the fact that HBO has persistent effects. Additionally, the use of HBO with pharmacological agents such as oxygen radical scavengers may potentiate their therapeutic effects.

The hemodynamic phases following TBI are well defined. Autoregulation impairment after even minor brain trauma, and the importance and manner of CBF in cerebral trauma, have been well studied and are well defined. This, along with experimental and clinical success, supports the use of HBO for TBI.

Historically, cerebral vasoconstriction and increased oxygen availability were seen as the primary mechanisms of HBO in TBI. HBO now appears to improve cerebral aerobic metabolism at a cellular level, i.e., by enhancing damaged mitochondrial recovery. HBO given at the ideal treatment paradigm, 1.5 ATA for 60 min, does not appear to produce oxygen toxicity and is relatively safe (Rockswold et al. 2007). The authors believe that, by virtue of over 40 years of experimental and clinical evidence, supported by their own experience, HBO has stood the test of time and can be considered a valuable therapeutic modality in the treatment of TBI. The importance of monitoring, clinically, analysis of the ICP and metabolism, and realization that HBO is a drug, remains important. Multicenter prospective randomized clinical trials are still needed to resolve some of the controversies and to definitively define the role of HBO in severe TBI. Such clinical trials are in progress.

Role of HBO in the Management of Spinal Cord Injury

The concept of using HBO for spinal cord injury (SCI) parallels the application of this therapy for brain injuries. The ability of HBO to reduce both edema and ischemia are the key factors. Traumatic myelopathies are characterized by

ischemia and edema, which may be a consequence of vasoparalysis and direct injury to the spinal cord and its vasculature. There is compromise of spinal cord microvasculature, resulting in decreased blood flow and oxygen supply to the gray matter with surrounding hyperemia. Anatomical or physiological cellular disruption may occur as a result of the initial injury, or consequent to the pathophysiological changes that occur over a period of 2–4 h. The evolution of SCI entails gray matter ischemia and increased spinal cord blood flow with subsequent white matter edema. There are numerous publications reporting experimental work supporting the effectiveness of HBO in TBI. Clinical studies have suggested but not substantiated the potentially beneficial effects of HBO for the TBI. Encouraging reports have been anecdotal at best. However, none of the clinical studies but ours deals with patients treated within 2–4 h post-injury. This time period represents the window of opportunity that relates to the progression of pathophysiological sequelae of SCI resulting in permanent anatomical disruption of an originally physiologically functional cord. Initially, they may be indistinguishable. In our experience, patients without definite evidence of anatomical disruption of the spinal cord treated within 2–4 h of their trauma may respond to HBO treatment. Clinical monitoring of the patient must be accompanied by somatosensory-evoked potentials (SSEPs). MRI must not show evidence of anatomical disruption of the spinal cord. CT and plain X-ray films similarly must not show evidence of anatomical disruption. It is essential to begin HBO no later than 4 h post-injury. Treatment sessions are either at 1.5 or 2 ATA, depending upon the initial and subsequent clinical evaluation and pre- and post-treatment SSEPs. If there is evidence of either clinical or electrodiagnostic improvement, it is justified to continue HBO. The patient's spine must be maintained in proper alignment with traction at all times in cervical injuries. A portable traction gurney, compatible with HBO therapy as well as ground and air ambulance transfer, initial emergency hospital care, neurodiagnostic procedures, surgery, and initial nursing care, including prone and supine positioning, is used.

Effects of Spinal Cord Injury

There are two major effects of trauma to the spinal cord:

- Anatomical disruption and secondary vascular compromise following venous stasis, edema, and hypoxia. If uncorrected, it leads to tissue necrosis.
- Functional loss and paralysis below the level of the lesion.

Various surgical and drug treatments have been advanced for SCI, with little or no cure. The role of conventional surgery is confined to removal of compressive lesions and stabilization of the bony spine. Currently, research is in progress for stem cell transplantation and regeneration of the spinal cord. Major advances in SCI research during the past quarter of a century include use of SSEP, rCBF, methods to detail the morphology and content of the spinal cord tissues, and use of HBO.

Rationale of the Use of HBO in SCI

Rationale of the use of HBO in SCI is as follows:

- Some neuronal damage, due to bruising rather than laceration, is reversible by HBO.
- HBO relieves ischemia of the gray matter of the spinal cord.
- HBO reduces edema of the white matter.
- HBO corrects biochemical disturbances at the site of injury in the spinal cord substance, e.g., lactic acidosis.

Publications about research on this topic combined with clinical experience support the conclusion that HBO holds an important place in the management of the severely injured but therapeutically responsive patient with a traumatic myelopathy.

Animal Experimental Studies of HBO in SCI

The initial experimental studies suggesting the use of HBO in SCI were published by Maeda (1965). He demonstrated tissue hypoxia resulting from injury to the spinal cords of dogs induced by clamp crushing. When the animals were subjected to HBO at 2 ATA, significant elevations in spinal cord pO_2 were observed as long as 72 h after the injury. Hartzog et al. (1969) demonstrated reversibility of the neurological deficit in cord-traumatized baboons by administration of 100 % oxygen at 3 ATA during the first 24 h after trauma. Locke et al. (1971) found that lactic acid accumulates in the injured spinal cord. This supports the concept that ischemia plays a role early in the traumatic process following SCI. The lactic acid levels remain elevated up to 18 h.

Kelly et al. (1972) studied the tissue pO_2 of the normal and the traumatized spinal cord in dogs. The tissue pO_2 of the normal spinal cord rose on breathing 100 % oxygen. After trauma the tissue pO_2 dropped to near zero and did not respond to 100 % oxygen at ambient pressure. However, at 2 ATA the tissue pO_2 rose to high levels during the period of mechanical compression of the cord. The animals rendered paraplegic and then given HBO recovered to a greater degree than the untreated animals in the control group. The beneficial effects were similar to those of glucocorticosteroids and hypothermia. The authors suggested a clinical trial of HBO in patients with acute spinal cord injury.

Yeo (1976) reported the results of use of HBO therapy (3 ATA) to control the onset of paraplegia after SCI induced in sheep. Institution of HBO within 2 h of injury resulted in improved motor recovery over the following 8 weeks. Yeo's further research into the effect of HBO on experimental paraplegia in sheep, which correlated recovery of motor power and histopathology at the level of lesion after controlled contusion to the spinal cord, confirmed his earlier findings (Yeo et al. 1977). They compared the treatments used, which were prednisolone, α-methyl-*para*-tyrosine (AMT, an inhibitor of norepinephrine synthesis that produces some recovery of motor activity in SCI), mannitol, or HBO. There was significant motor recovery in the untreated (control) animals, but none regained the ability to stand or walk. There was no significant recovery with methylprednisolone. In AMT-treated as well as HBO-treated groups there was significant motor recovery. Examination at 8 weeks showed cystic necrosis of the central portion of the spinal cord at the level of the lesion in all animals, but it was least marked in those treated by HBO.

Higgins et al. (1981) studied the spinal cord-evoked potentials in cats subjected to transdural impact injuries and treated with HBO, and demonstrated beneficial effects on the long tract neuronal function. The authors suggested that HBO may afford protection against the progression of intrinsic post-traumatic spinal cord processes destructive to long tract function if this treatment is applied early.

Sukoff (1982) reported the effects of HBO on experimental SCI. Seventeen cats were treated immediately after graded SCI by intermittent exposure to 100 % oxygen at ambient pressure. No animals treated with HBO were paralyzed, whereas six of the 13 controls were. Five treated animals recovered fully and all but one could walk. Only one of the control cats could do so.

Gelderd et al. (1983) performed spinal cord transection in rats and tested the therapeutic effects of dimethyl sulfoxide (DMSO) and/or HBO at various pressures in different groups of animals. The animals were killed 60–200 days after the treatment and the spinal cord was examined with light microscopy, scanning electron microscopy, and transmission electron microscopy. Normally, the growth of axons is aborted within a few days following transection. In animals treated with DMSO and HBO, Gelderd et al. found naked axons 90–100 days post-lesion. These findings suggest that both DMSO and HBO can prolong the regeneration process for extended periods following injury. There was less cavitation in the spinal cords of animals treated with DMSO and HBO than in the controls which did not receive any treatment.

An additional study using 20 gerbils with controlled and graded spinal cord trauma caused by aneurysm clip has confirmed the therapeutic effect of HBO, and the decrease in pathological changes has been verified histologically (Sukoff 1986).

The effects of HBO have been compared with that of methylprednisolone regarding the oxidative status in experimental SCI (Kahraman et al. 2007). Clip compression method was used to produce acute SCI in rats. HBO was administered twice daily for a total of eight 90 min sessions at 2.8 ATA. Tissue levels of superoxide dismutase and glutathione peroxidase were evaluated as a measure of oxidant antioxidant status and were elevated in untreated animals. Methylprednisolone was not able to lower these levels, but HBO administration diminished all measured parameters significantly. Thus, HBO, but not methylprednisolone, seems to prevent oxidative stress associated with SCI.

Clinical Studies of HBO in SCI

Jones et al. (1978) treated seven SCI patients with HBO within 12 h of injury. Two of these patients had functional recovery, and three patients' complete lesions became incomplete (partial recovery). One of the patients had enough motor and sensory recovery after two treatments to allow the functional use of calipers.

Gamache et al. (1981) presented the results of HBO therapy in 25 of 50 patients treated during the preceding years. HBO was generally initiated 7.5 h after injury. The patients continued to receive conventional therapy for SCI, and their pre- and post-treatment motor scores were compared with those of patients not receiving HBO. Patients paralyzed for more than 24 h failed to make any significant recovery with or without HBO. The authors concluded:

The fact that HBO patients, at 4–6 months, were closer to the 1 year results of the patients treated conventionally is a reflection of the alterations in the rate of recovery rather than a difference in the overall outcome. Ideally the HBO therapy should be initiated within 4 h of the injury. Sukoff protocol for treatment of patients with traumatic myelopathy is as follows:

- Initial evaluation, including complete neurological and systemic examination, took place in the shock-trauma unit.
- Respiratory function was assisted as necessary to maintain pO_2 above 90 mmHg. Problems outside the nervous system were treated and BP was maintained at 100–130 mmHg systolic.
- X-rays of the spine were obtained and skeletal traction was applied to maintain the alignment in cases of fracture-dislocation.
- IV mannitol was given as long as BP was above 110 mmHg systolic.
- Cisternal myelography or metrizide-assisted CT scan was promptly obtained.

- HBO treatment was performed in a Sechrist monoplace chamber. A special traction device was used in the chamber and nursing attention was maintained.
- Treatment consisted of 100 % oxygen at 2 ATA for 45 min repeated every 4–6 h for 4 days. If no response had occurred by that time, treatment was discontinued.

Motor improvement was seen in those patients who were treated within 6 h of injury. Two patients with sensory problems obtained relief. Two patients showed significant reduction of myelographic block, although neither improved clinically. In three patients there was dramatic recovery. Sukoff felt that his clinical success with HBO therapy, as well as that reported by others to date, was anecdotal. He suggested that clinical trials using double-blind techniques should be initiated on patients within 4 h of SCI. Yeo (2009) reviewed his experience with the use of HBO therapy in 45 patients with SCI over the period 1978–1982. Patients were given one, two, or three treatments, usually 90 min in duration at 2.5 ATA. Thirty-five of the patients had upper motion neuron lesions. Twenty-seven of these could tolerate two or three treatments, and 15 (56 %) of them recovered functionally. During the same period of time, 29 (46 %) of the 63 patients who did not receive HBO also recovered. The difference in the recovery rate is significant, considering that the average delay from the time of injury to the commencement of treatment was 9 h. All patients who showed recovery had incomplete lesions with some preservation of function below the level of the lesion.

Role of HBO in Rehabilitation of SCI Patients

Rehabilitation is the most important part of the management of SCI patients. The role of HBO in physical therapy and rehabilitation is discussed in Chap. 36. HBO can be a useful aid in the rehabilitation of paraplegics in the following ways:

- Capacity for physical exercise can be increased in neurologically disabled persons by using HBO at 1.5 ATA (see Chap. 4).
- Metabolic complications associated with fatigue are reduced. Quadriplegics have a reduced vital capacity. Hart and Strauss (1984) tested the effect of HBO on 22 quadriplegics with an average vital capacity of 2.38 L, as compared with the expected normal of 5.10 L for that age group. HBO at 2 ATA for 2 h per day for 3 weeks did not impair pulmonary function, vital capacity, or inspiratory and expiratory forces. The vital capacity of 41 % of the patients was improved by more than 10 %.
- Spasticity is a major hindrance in rehabilitation, but it can be reduced by HBO, particularly when combined with physical therapy.

Treatment should be instituted in the first 4 h following injury, but in practice this is difficult to achieve. Perhaps the treatment of acute spinal cord injuries in a mobile hyperbaric chamber could resolve the time factor. Such a mobile facility should have all the standard emergency equipment and a physician competent to deal with spinal injuries. Sensory-evoked potentials should be used to monitor the progress of the patient, and eventually the patient should be transferred to an SCI center where further treatment should be given, along with any surgery and rehabilitation measures deemed necessary. In the first few hours of SCI, it may be difficult to sort out the serious damage to the spinal cord from spinal cord concussion and contusions. Because time is such an important factor, we suggest that all SCI patients with any degree of neurological involvement (minor or major) be treated with HBO prophylactically during the first few hours following injury. This may possibly prevent edema at the site of contusion with spinal cord compression.

Role of HBO in Compressive and Ischemic Lesions of the Spinal Cord

Compressive Lesions of the Spinal Cord

Holbach et al. (1978) reported three patients with compressive lesions of the spinal cord: one with a protruded cervical disc, one due to arachnoidal adhesions of the spinal cord, and one due to an arachnoid cyst of the lower thoracic cord. There was no improvement of the neurological deficits of these patients in spite of surgical correction of the lesions. HBO therapy was given in the hope of correcting the ischemic process associated with the compressive lesions. The first patient improved after the first HBO session but regressed afterward. Fifteen sessions at 1.5 ATA, each lasting 35–40 min, were then given on a daily basis to all three patients, who all improved. CSF oxygen was monitored and showed a significant increase during HBO. EMG was used to obtain an insight into the mode of action of HBO on the spinal cord lesions. Recordings were taken from many muscles corresponding to the level of the lesion in the spinal cord. In all three cases there was a marked increase in the density of the muscular action potentials after each course of HBO. The improvement reverted to some extent in the new few hours but never dropped to the pretreatment level. The cumulative result of a series of treatments was progressively increased action potentials, and the record had the appearance of an ascending step-like curve.

Holbach et al. (1975) reported use of HBO in the treatment of 13 patients with compressive spinal cord lesions. The therapy was administered postoperatively when neurological deficit persisted. Six of the 13 patients improved markedly, particularly in motor function, while the others showed slight changes. There were no adverse effects.

Neretin et al. (1985) used HBO for treatment of 43 patients with dyscirculatory myelopathy in developmental anomalies and spondylosis. Regression of neurological deficits was observed in patients with spastic tetraparesis within 5–6 days, in contrast to the control group, which was given only vasodilators. There was little improvement in patients with syringomyelia.

Cervical Myelopathy

The effectiveness of HBO in predicting the recovery after surgery in patients with cervical compression myelopathy was evaluated by Ishihara et al. (1997). This is the first paper to utilize HBO as a diagnostic tool to evaluate the functional integrity of the spinal cord. The study group consisted of 41 cervical myelopathy patients aged 32–78 years. Before surgery, the effect of HBO was evaluated and was graded. The severity of the myelopathy and the recovery after surgery were evaluated by the score proposed by the Japanese Orthopedic Association (JOA score). The correlation between many clinical parameters including the HBO effect and the recovery rate of JOA score was evaluated. The recovery rate of JOA score was found to be 75.2 ± 20.8 % in the excellent group, 78.1 ± 17.0 % in the good group, 66.7 ± 21.9 % in the fair group, and 31.7 ± 16.4 % in the poor group. There was a statistically significant correlation between the HBO effect and the recovery rate of the JOA score after surgery. The effect of HBO showed a high correlation with the recovery rate after surgery as compared to the other investigated parameters. HBO can be employed to assess the chance of recovery of spinal cord function after surgical decompression.

Spinal Epidural Abscess

Ravicovitch and Spalline (1982) obtained good results with HBO as an adjunct to laminectomy for drainage of epidural spinal abscesses and to antibiotic therapy. Some of these cases are associated with osteomyelitis of the vertebrae, for which HBO has proven to be very useful.

Conclusions About Use of HBO in SCI

From the available evidence in the literature, it appears that HBO has beneficial effects in some patients with SCI. Because it is difficult to distinguish between anatomical and physiological disruption during the initial stages of spinal cord trauma, all patients should be treated in a hyperbaric chamber if seen within 4 h after a spinal cord injury, unless otherwise contraindicated (MRI, CT, or plain films). Pressures of 1.5–2 ATA are utilized. Monitoring of these patients must include SSEPs and neuro-imaging studies. Determination of spinal fluid glucose metabolism utilizing ventricular CSF samples may significantly advance the treatment of traumatic myelopathies with HBO. As in brain injury, dosimetry and periodicity of treatment will depend upon the results of clinical, electrodiagnostic, and metabolic monitoring.

Experimental studies showing positive effect of HBO on SCI continue to be published and these combined with clinical experience support the role of HBO in acute SCI.

HBO as an Adjunct to Radiotherapy of Brain Tumors

HBO has been used as an adjunct to radiotherapy (Chap. 38) of brain tumors. Chang (1977) carried out a clinical trial on the radiotherapy of glioblastomas with and without HBO. Eighty previously untreated patients with histologically proven glioblastoma were evaluated. Thirty-eight were irradiated under HBO and 42 (controls) in atmospheric air. At the end of 18 months the survival rate appeared considerably higher in the HBO group (28 %) than in the controls (10 %). After 36 months no patients in the control group survived, whereas two patients in the HBO group were alive beyond 45 and 48 months, respectively. The median survival time was 38 weeks for the HBO group and 31 weeks for the controls. Owing to the small population samples and the pilot nature of the study, the difference in the survival rate between the two groups was not statistically significant. The quality of survival in the HBO group was equal to or slightly better than that of the control group.

A study of preconditioned experimental TBI under 3 ATA HBO found a protective effect of the HBO and suggested it may be a method of limiting brain injury during invasive neurosurgery (Zhiyong et al. 2007). Experimental extradural hematoma produced in a hyperbaric chamber causes no adverse effects. However, when the same mass lesion is produced under normobaric conditions, the animal suffers seizures and does not survive.

The results of radiotherapy combined with HBO in 9 patients with malignant glioma were compared with those of radiotherapy without HBO in 12 patients (Kohshi et al. 1996). This is the first report of a pilot study of irradiation immediately after exposure to HBO in humans. All patients receiving this treatment showed more than 50 % regression of the tumor, and in 4 of them, the tumors disappeared completely. Only 4 out of 12 patients without HBO showed decreases in tumor size, and all 12 patients died within 36 months. So far, this new regimen seems to be a useful form of radiotherapy for malignant gliomas. Radiotherapy, within 15 min following HBO exposure, has been studied at several institutes and has demonstrated promising clinical results for malignant gliomas of the brain (Kohshi et al. 2013).

Role of HBO in the Management of CNS Infections

Two types of infections are of particular concern to the neurosurgeon: postoperative infections and brain abscess. HBO has a proven value in the management of infections (Chap. 14). Role of HBO in the management of these will be discussed in this section.

HBO for Postoperative Infections

A study was conducted to evaluate the clinical usefulness of HBO therapy for neurosurgical infections after craniotomy or laminectomy (Larsson et al. 2002). The study involved the review of medical records, office visits, and telephone contacts for 39 consecutive patients who were referred to a neurosurgical department in 1996–2000. Infection control and healing without removal of bone flaps or foreign material, with a minimum of 6 months of follow-up monitoring, were considered to represent success. Successful results were achieved for 27 of 36 patients; one patient discontinued HBO therapy because of claustrophobia, and two could not be evaluated because of death resulting from tumor recurrence. In Group 1 (uncomplicated cranial wound infections), 12 of 15 patients achieved healing with retention of bone flaps. In Group 2 (complicated cranial wound infections, with risk factors such as malignancy, radiation injury, repeated surgery, or implants), all except one infection resolved; three of four bone flaps and three of six acrylic cranioplasties could be retained. In Group 3 (spinal wound infections), all infections resolved, five of seven without removal of fixation systems. There were no major side effects of HBO treatment. The study concluded that HBO treatment is an alternative to standard surgical removal of infected bone flaps and is particularly useful in complex situations. It can improve outcomes, reduce the need for reoperations, and enable infection control without mandatory removal of foreign material such as that used for the reconstruction of cranial operative defects. HBO therapy is a safe, powerful treatment for postoperative cranial and spinal wound infections, it seems cost-effective, and it should be included in the neurosurgical armamentarium.

The prevalence of postoperative wound infection in patients with neuromuscular scoliosis surgery is significantly higher than that in patients with other spinal surgery. A review of six high-risk pediatric patients with neuromuscular spine deformity who received HBO therapy for postoperative infections 2003–2005 revealed that infection resolved in all cases and healing occurred without removal of implants or major revision surgery (Larsson et al. 2011). A retrospective review of effect of effect of HBO on postoperative infections involved 42 neuromuscular scoliosis cases in addition to cerebral palsy or myelomeningocele, operated between 2006 and 2011 (Inanmaz et al. 2014). HBO prophylaxis (30 sessions, 2.4 ATA for 90 min/day) was used in 18 patients and 24 formed the control group. All patients received standard antibiotic prophylaxis. The overall incidence of infection in the whole study group was 11.9 % (5/42). The infection rate in the HBO and the control group were 5.5 % (1/18) and 16.6 % (4/24), respectively. The use of HBO was found to significantly decrease the incidence of postoperative infections.

A retrospective clinical study included 19 cases of iatrogenic spinal infection between 2008 and 2013 where adjuvant HBO therapy was applied because there was no improvement in clinical and laboratory findings despite medical treatment for at least 3 weeks (Onen et al. 2015). Iatrogenic spinal infections were most frequent in the lumbar region and occurred after spine instrumentation in 12 cases and after microdiscectomy in 7 cases. The average number of HBO therapy sessions applied was 20 (range: 10–40). Wound discharge and clinical and laboratory findings recovered in all cases at the end of the therapy course. HBO therapy is considered to be a safe and efficient as an adjuvant therapy in the treatment of infections. It was found to be effective in the prevention of revision procedures and instrumentation failures in iatrogenic osteomyelitis cases, which had occurred following spinal instrumentation.

HBO for Brain Abscess

Brain abscesses may stem from a variety of infective organisms, but anaerobic organisms predominate, which make the abscess difficult to treat by antibiotics, normally the first mode of treatment. Surgical drainage is reserved for encapsulated abscesses that do not resolve and situations where increased intracranial pressure occurs. Brain abscesses are associated with a high mortality and the survivors have severe neurological sequelae. Lampl et al. (1989) treated a series of ten unselected consecutive patients with brain abscess using HBO as an adjunct. All the patients recovered and only one had residual neurological disability. HBO therapy in children with brain abscesses seems to be safe and effective, even when they are associated with subdural or epidural empyemas (Kurschel et al. 2006). It provides a helpful adjuvant tool in the usual multimodal treatment of cerebral infections and may reduce the intravenous course of antibiotics and, consequently, the duration of hospitalization. The rationale of the use of HBO for treatment of brain abscesses is based on the following:

- HBO has a bactericidal effect on predominantly anaerobic organisms.
- HBO has a synergistic effect with the antibiotics used for the treatment of the brain abscess.
- Intermittent opening of the blood–brain barrier (BBB) as an effect of HBO facilitates entry of the antibiotics into the abscess cavity.

- HBO reduces cerebral edema surrounding the abscess and reduces the intracranial pressure.

Experimental studies in the rat have shown that BBB is damaged in staphylococcal cerebritis and that there is surrounding edema in the early stage of the formation of the brain abscess (Lo et al. 1994). This would provide an additional rationale for the use of HBO in the early stages of human brain abscesses, because oxygen entry into the area of cerebritis would be facilitated and brain edema would also be reduced.

In an experimental study, 80 female Wistar rats with brain abscess induced by inoculation of *Staphylococcus aureus* were randomized into groups and treated either with antibiotics, HBO, or with a combination of both (Bilic et al. 2012). Beneficial effect of HBO was evident in groups treated with HBO or with a combination of antibiotic + HBO, which was mainly manifested on days 3 and 5 of the experiment and was evident as statistically significant increase of a number of newly formed blood vessels, increase in mean vascular density, and smaller abscess necrotic core.

Although patients with supratentorial listerial brain abscesses showed a longer survival with surgical drainage, the standard therapy for patients with subtentorial lesions has not been established. In a patient with supra- and subtentorial brain abscesses caused by *L. monocytogenes* infection, which did not respond to antibiotics and the symptoms gradually worsened, HBO treatment was used along with antibiotics, because drainage was not indicated for subtentorial lesions (Nakahara et al. 2014). HBO dramatically reduced the volume of abscesses and improved the symptoms. In a rare case of cerebellar abscess produced by anaerobic bacteria where CT and MRI showed the presence of a multiloculated cerebellar abscess and *Fusobacterium nucleatum* was cultured on aspiration of the abscess (Shimogawa et al. 2015). The patient was administered antibiotic treatment combined with HBO. The symptoms were briefly relieved but the cerebellar abscess recurred, which required a second aspiration. The combined treatment with antibiotics and HBO was maintained after the second operation. After 6 weeks of treatment, the cerebellar abscess was completely controlled. It was concluded that antibiotic treatment combined with HBO is useful for treatment of cerebellar abscesses caused by infection with anaerobic bacteria.

A population-based, comparative cohort study included 40 consecutive adult patients with spontaneous brain abscess treated with surgery and antibiotics between 2003 and 2014; 20 of them received adjuvant HBO, while the remaining patients received only standard therapy (Bartek et al. 2016). Resolution of brain abscesses and infection was seen in all patients. Two patients had reoperations after HBO initiation (10 %), while nine patients (45 %) in the non-HBO group underwent reoperations. Of the 26 patients who did not receive HBO after the first surgery, 15 (58 %) had one or several recurrences that lead to a new treatment: surgery, surgery + HBO or just HBO. In contrast, recurrences occurred in only 2 of 14 (14 %) who did receive HBO after the first surgery. A good outcome (Glasgow Outcome Score [GOS] of 5) was achieved in 16 patients (80 %) in the HBO cohort versus 9 patients (45 %) in the non-HBOT group. Prospective studies are warranted to establish the role of HBOT in the treatment of brain abscesses.

Role of HBO in Cerebrovascular Surgery

The use of HBO for primary cerebral ischemia remains controversial in spite of many clinical and experimental demonstrations of its effectiveness. The rationale for increased tissue and microcirculatory oxygenation has been presented in previous chapters. Role of HBO for acute ischemic stroke is described in Chap. 19. Potential of combination of HBO with thrombolysis by tPA has been discussed. Direct thrombolysis of the clot by intraarterial administration of streptokinase and urokinase is also under clinical investigation. This involves manipulation of the clot and has the advantage of a lesser dose of the thrombolytic and less risk of intracerebral hemorrhage. HBO may be used as an adjunct during the preparation of the patient for the procedure which may be performed by a neuroradiologist/neurosurgeon and also in the postoperative period to reduce cerebral edema and possible reperfusion injury. This chapter deals with neurosurgical aspects of cerebral ischemia. HBO has a role as an adjunct in the following situations in cerebrovascular surgery:

- As a measure for cerebral protection during cerebral vascular procedures requiring vascular occlusion. Complicated neurosurgical procedures requiring lasers and electrocoagulation cannot be performed in a hyperbaric operating room; simpler procedures such as endarterectomy of the cervical portion of the carotid artery can be carried out.
- HBO should be particularly considered in the high-risk carotid endarterectomy patients to afford cerebral protection from stroke during preoperative waiting period.
- Postoperative complications of cerebrovascular surgery; particularly those associated with surgery of intracranial aneurysms.
- As a decision-making measure to select patients for carotid endarterectomy and extracranial/intracranial (EC/IC) bypass operation.
- For cerebral protection during the preoperative waiting period for patients with cerebrovascular occlusive disease.

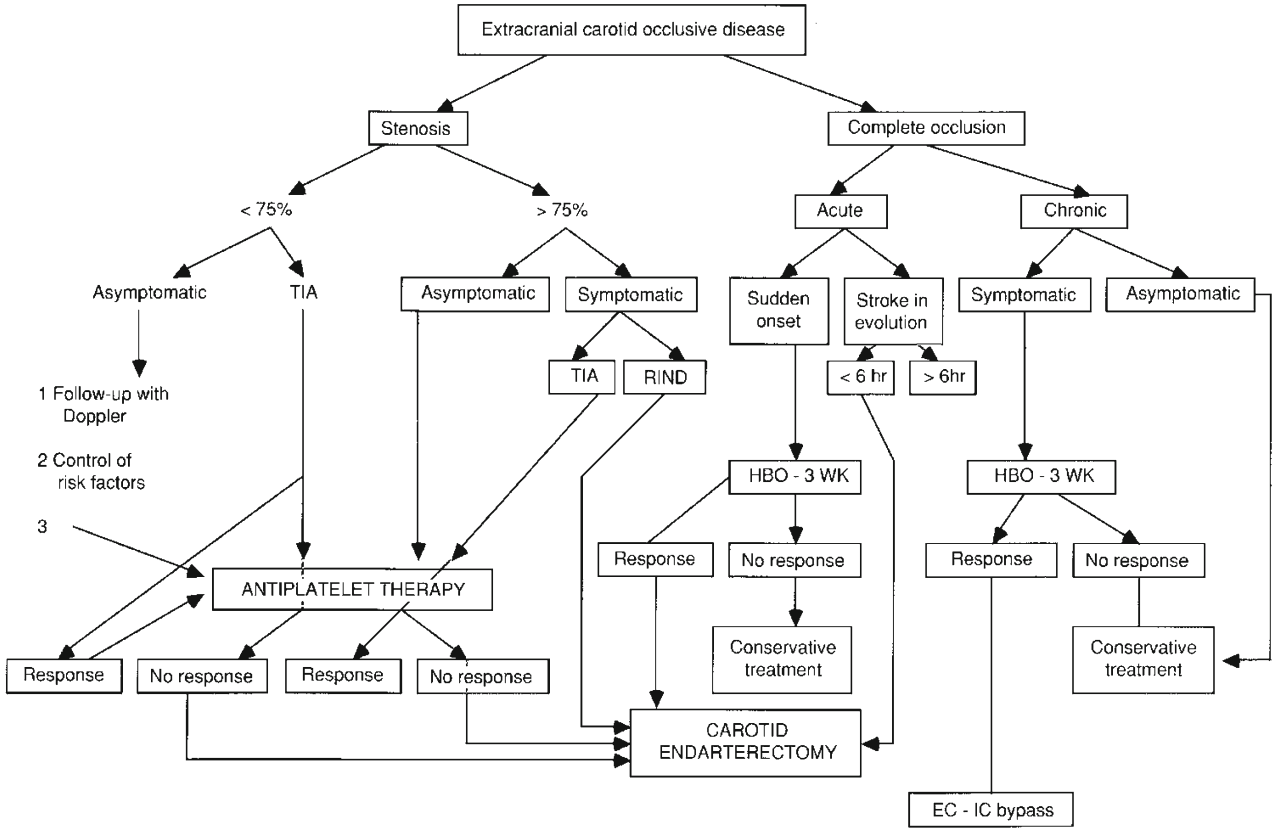

Fig. 21.1 Decision-making for conservative versus surgical management of extracranial carotid occlusive disease. *HBO* hyperbaric oxygen, *EC/IC* extracranial–intracranial bypass, *TIA* transient ischemic attack, *RIND* reversible ischemic neurological deficit, *TPA* tissue plasminogen activator, *asterisk* not eligible for TPA cerebral oxygenation

Use of HBO in Relation to Carotid Endarterectomy

Early attempts to employ HBO as an adjunct to cerebrovascular surgery were made by Illingworth (1962) and Jacobson et al. (1963a). Oxygen at 2 ATA was used during carotid endarterectomy, but it did not afford protection against temporary carotid occlusion, and an intraluminal bypass had to be used. There was, however, an increase in cerebral oxygenation. McDowall et al. (1966) believed that Jacobson's failure was due to cerebral vasoconstriction from HBO and halothane anesthesia, and they subsequently performed a carotid endarterectomy under HBO using chloroform anesthesia, which had a vasodilating effect on cerebral vessels. The procedure was successful.

Lepoire et al. (1972) described the beneficial effect of HBO in six cases of post-traumatic thrombosis of the terminal part of the internal carotid artery. Those lesions are amenable to surgical procedures—direct or bypass—but it is important to give supportive treatment to prevent brain damage from infarction and edema in the acute stage before the surgery can be performed.

Carotid endarterectomy is the most commonly performed surgical procedure for stroke. HBO can be included in the decision tree for the management of a patient with carotid occlusion, as shown in Fig. 21.1. Reversibility of neurological deficit can be determined by response to HBO and improvement seen on SPECT scan. As an alternative to carotid endarterectomy, a less invasive procedure—percutaneous angioplasty with stenting—is being carried out. An incidence of 5% of minor strokes and 1% major strokes has been reported to be associated with this procedure. It is feasible to reduce this complication rate by the use of HBO which has a beneficial effect in cerebral ischemia (see Chap. 18).

Use of HBO for Postoperative Complications of Surgery for Intracranial Aneurysms

Neurological deficits after aneurysm surgery stem from a number of causes, including vasospasm, vascular occlusion, and cerebral edema. Holbach and Gött (1969a) used HBO in a patient with a large middle cerebral artery aneurysm who developed hemiplegia and seizures after surgical repair of the aneurysm. The patient recovered. Several surgeons have used HBO

in managing the postoperative complications of intracranial aneurysm surgery and found that HBO prevented the development of severe and fixed neurological deficits in many cases.

Kitaoka et al. (1983) tried HBO treatment in 25 patients with postoperative mental signs after direct operations on anterior communicating aneurysms. Ischemia and edema of the frontal lobes occurred due to spasm of the anterior cerebral arteries. The HBO treatments were started in the "chronic phase" after cerebral edema had subsided. The effects of HBO were marked in three cases, moderate in six cases, slight in 11 cases, and insignificant in four cases. Generally, the results were favorable. The degree of efficacy of HBO was closely related to the previous condition of the patient. HBO was distinctly effective in patients who did not have marked spasm of the anterior cerebral arteries or infarction of the frontal lobes before or after the operation. In contrast, the treatment was ineffective in patients who were in a poor condition (grade) before surgery, e.g., coma. Many patients improved mentally, although EEG, rCBF, and CT scan showed no changes. The authors recommended the use of HBO therapy for postoperative mental signs as soon as cerebral edema disappears.

Isakov and Romasenko (1985) also used HBO in the postoperative care of patients with complications of aneurysm surgery. They used oxygen at 1.6–2.0 ATA. The course of 47 patients treated with HBO was compared with that of 30 patients not subjected to HBO (control group). The conclusions were that in patients with HBO therapy:

1. The serious phase was less prolonged
2. The duration of meningeal syndrome (fever, headache) was shorter by 6 days
3. The number of patients with good results from surgery increased by 18 %
4. Mental disorders were prevented in patients who had no frontal lobe hematoma
5. There was a decrease of postoperative wound infections

HBO to be useful in the management of patients with neurological deficits resulting from vasospasm associated with subarachnoid hemorrhage. HBO is a useful adjunct in moderate cerebral edema, but it is not as effective in severe edema with midline shifts seen on CT scan. Kohshi et al. (1993) evaluated the usefulness of HBO in 43 patients who developed vasospasm following surgery in the acute stage following rupture of intracranial aneurysms. They found that HBO was a useful adjunct to mild hypertensive hypervolumia for the treatment of mild symptomatic vasospasm.

HBO has been shown to ameliorate disturbances following experimental subarachnoid hemorrhage in rats: decreased Na+, K+, and ATPase activity and impaired function of cerebrocortical cell membrane proteins (Yufu et al. 1993). This may be one basis of useful effect of HBO in patients with subarachnoid hemorrhage.

HBO as an Adjunct to Surgery for Intracerebral Hematoma

Holbach and Gött (1969b) reported the use of HBO in a patient with a massive intracerebral hematoma (caused by an angioma) who was comatose and did not regain consciousness after surgery. HBO at 2 ATA was started on the seventh postoperative day, and the patient showed improvement in EEG and in level of consciousness. Sugawa et al. (1988) used HBO therapy on a patient who did not recover from coma after evacuation of an intracerebellar hematoma. The patient regained consciousness but motor recovery was incomplete in spite of continuation of HBO treatments.

A favorable response to HBO is useful in deciding on surgery in patients with hypertensive putaminal hemorrhage. These patients are more likely to continue to improve with the use of HBO following surgery. Patients who do not respond to HBO show a poor outcome regardless of subsequent surgery. Kanno and Nonomura (1996) reviewed 81 patients with hypertensive putaminal hemorrhage treated with HBO after an initial CT scan. The surgical technique used was mostly stereotactic aspiration of the clot. Open craniotomy was used only in three cases. The patients were divided into four groups: (1) patients who showed improvement with HBO and underwent surgery ($n=21$); (2) patients who showed improvement with HBO but did not undergo surgery; (3) patients who showed no improvement with HBO but underwent surgery; and (4) patients who showed no improvement with HBO and did not undergo surgery. Of all the groups, patients who had shown clinical improvement with HBO had significantly better outcomes that those who did not respond to HBO. The number of surgical procedures for intracerebral hemorrhage has declined considerably at the authors' institution following the adoption of the policy that only responders to HBO are operated on. The authors have not tried to maintain the patients only on HBO stating that the effects of HBO are not durable. It is conceivable that HBO alone may be able to sustain clinical improvement in these patients in the acute phase and it may not be necessary to operate on these patients at all. This approach has not been tested in any clinical study.

Role of HBO in Extracranial/Intracranial Bypass Surgery

The EC/IC bypass operation was devised to bypass the obstruction in a major cranial artery by anastomosis of an extracranial branch with an intracranial branch, using microsurgical techniques. The most common type of operation was an anastomosis between the superficial temporal and the middle artery branches. The usual indications for this procedure in the past were:

- TIA or RIND (reversible ischemic neurological deficit) or a slowly evolving stroke

- Bilateral carotid occlusion
- Unilateral carotid occlusion with contralateral carotid stenosis (prior to endarterectomy of the stenosed artery)
- Occlusive disease of the intracranial arteries: internal carotid, middle cerebral, or basilar
- Generalized cerebrovascular insufficiency
- Moyamoya disease
- Generalized (primary orthostatic) cerebral insufficiency usually associated with multiple occlusions of intracranial vessels
- As a preoperative adjunctive measure for the treatment of giant intracranial aneurysms requiring carotid occlusion, or vertebral artery aneurysms requiring vertebral artery occlusion.

The Cooperative Study of IC/EC bypass (1985) conducted a multicenter review of more than 1400 patients, and compared the medical versus the surgical treatment. The study concluded that the operation had no advantage over medical management, and that it was useless in preventing TIA and stroke. The 30-day mortality of the surgically treated patients was 0.6 % and the morbidity 2.5 %. A decrease of TIA was noted in 77 % of the surgically treated patients, as compared with a decrease in 80 % of the medically treated patients.

The shortcomings of the EC/IC bypass operation are as follows:

- The operation aims at increasing blood flow to the brain, but this alone may not be effective in preventing stroke and limiting the size of the infarct. Large vessel occlusion is not the only cause of stroke, and the problem may lie at the EC/IC bypass may not prevent strokes due to atherosclerosis.
  - EC/IC bypass does not prevent embolization from the stump of the occluded extracranial carotid artery, which may be the cause of the TIA. A patent bypass may even increase the possibility of passage of emboli through it.
  - Many studies have reported the short-term benefits of EC/IC bypass on rCBF, neurological, and psychological function, but the long-term effects are debatable. Di Piero et al. (1987) monitored the rCBF using SPECT in 14 patients before and after EC/IC bypass operation performed because of carotid occlusion. Preoperatively, all patients showed hypoperfusion in the affected cerebral hemisphere. Shortly after surgery rCBF was shown to improve in six of the patients, but studies repeated at the 6- and 12-month postoperative follow-ups did not show any difference from the preoperative status.

The health technology assessment report of the United States Department of Health and Human Services (Holohan 1990) admits the shortcomings of the cooperative study of 1985, but maintains that no objective evidence has come up since this study to alter its conclusions. The burden of the proof rests on those who advocate the prophylactic value of this surgery for stroke.

Selection of Patients for EC/IC Bypass Operation

Most of the bypass operations reviewed in the cooperative study were carried out on the basis of angiographic studies. CT scan was not available in some of the centers during the earlier part of the study. Many methods of investigation have evolved during the past decade. They are shown in Table 21.3. Of all the methods used for evaluation of patients who are considered for an EC/IC bypass operation, EEG analysis and the SPECT scan are the most practical and most useful when combined with response to HBO.

Holbach et al. (1977) treated 35 patients in the chronic poststroke stage with HBO. These patients had had internal carotid occlusion for an average of 10 weeks, and their neurological deficits were fixed. The treatments were given at 1.5 ATA for 40 min daily and continued for 10–15 days. Fifteen of these patients improved neurologically; when subsequent EC/IC arterial bypass was carried out, the improvement was maintained. Fifteen patients who did not improve were not operated on. A small group of five patients who did not improve with HBO nevertheless underwent EC/IC bypass, but still did not improve. The authors therefore suggested that the response to HBO be used as a guideline to selection of patients for EC/IC bypass. Response of the patients to HBO was considered a sign of reversibility of the brain lesion, and hence an indicator of a good chance of continuing improvement after a cerebral revascularization procedure. Therefore, EC/IC bypass is useful not only for transient ischemic attacks but also for completed strokes if there is a response to HBO and thus neuronal viability in the penumbra zone. Kapp (1979) reported two cases to illustrate the use of HBO as an adjunct to revascularization of the brain. In both these patients—one with embolism of the middle cerebral artery and the other with occlusion of the left internal carotid artery—circulation was restored to the ischemic areas by surgical means. Both of these patients recovered. In the first case, HBO was used to reverse the patient's neurological deficits while the operating room was being prepared for surgery. A successful embolectomy then restored the patency of the middle cerebral artery. In the second case, HBO treatment stabilized the patient during occlusion of the blood supply to the left hemisphere while the operation was developing enough flow to nourish this hemisphere.

Ohta et al. (1985) elaborated on Holbach's technique and described a method of choosing EC/IC bypass candidates by topographic evaluation of EEG and SSEP with concomitant rCBF studies under HBO.

Table 21.3 Investigation of patients for EC/IC bypass operation

Preoperative
1. Methods for detection of cerebral infarction CT scan and MRI
2. Assessment of vasodilatory capacity of the intracranial arteries
– Acetazolamide response with rCBF
– CO_2 response by transcranial Doppler
3. rCBF measurement
– Xenon 133
– PET
– Xenon and CT blood flow mapping
– SPECT (single photon emission computerized tomography
4. Cerebral blood volume
– C11 carboxyhemoglobin and PET
5. Cerebral metabolism
– Radioactive markers for glucose and oxygen
– PET
6. Electrophysiological
– SSEP
– EEG analysis
– Power spectrum
7. Neuropsychological testing
8. Methods to show reversibility of the cerebral ischemic effects
– HBO therapy
– HBO and EEG analysis
– HBO + EEG + rCBF
– SPECT
Intraoperative
1. Measurement of blood flow through bypass using Doppler and electromagnetic flowmeter
2. Fluorescein angiography
3. pO_2 measurement over the cerebral cortex
Postoperative
1. Angiography
2. rCBF
3. EEG analysis
4. Psychometric tests
5. PET response to HBO may be of use in selecting patients with neurological deficits who could benefit from surgical revascularization

Kapp (1980) reported on the treatment by HBO at 1.5 ATA of 22 patients with cerebral infarction secondary to occlusion of the carotid or the middle cerebral arteries. Ten patients demonstrated motor improvement during HBO. Seven of these had successful surgical revascularization and no recurrence of neurological deficits. In three patients who were not successfully revascularized, the neurological deficits recurred. It was concluded that the response to HBO may be of use in selecting patients with neurological deficits who could benefit from surgical revascularization. The author confirmed the views of Holbach, and agreed that HBO is useful in about 40 % of patients in the chronic stroke stage. Sukoff (1984) also found the response to HBO and improvement of EEG to be good selection criteria for EC/IC bypass operation. Rossi et al. (1987) performed the EC/IC bypass operation on 50 patients using the response to HBO and EEG analysis. Neurological improvement was observed in 43 patients, and in 40 of these the improvement persisted.

The EC/IC bypass study failed to take into consideration any subgroups such as those patients selected by response to HBO. The lack of a favorable response to HBO in a stroke patient can help to exclude those who are unlikely to benefit from surgery, who are then spared the expense and risk of unnecessary surgery. This operation should now be reevaluated critically. It is known that the clinical improvement of the patient may be independent of the improvement of CBF. An increase in CBF is not necessarily accompanied by improved oxygenation of the brain tissue. A response to HBO means that the "idling" cerebral neurons show improved function when their hypoxic environments are corrected by raising the tissue

oxygen tension. This does not mean that restoring the blood flow to the infarcted area will provide an equivalent effect by carrying only normal amounts of oxygen dissolved in the blood. Although the HBO response test can show the viability of the neurons affected by stroke, its effects cannot be compared quantitatively with those of cerebral revascularization.

In an effort to better define the indications for cerebral revascularization in patients with carotid artery occlusion or middle cerebral artery stenosis, a group of 29 patients was examined. Exposure to HBO (1.5 and 2 ATA) for 30 min each with computer analysis of the EEG was utilized. It proved to be confirmatory for denying surgery in patients with large infarctions or diffused intracranial vascular disease. In clinically stable or transient ischemic episode patients, an improved EEG (increase in alpha activity) supported the indications for EC/IC bypass. The EC/IC bypass operation is contraindicated in the following situations:

1. Stroke patients who show no response to HBO therapy: They are unlikely to benefit from EC/IC bypass.
2. Patients with completed cerebral infarcts who have shown no neurological recovery and have no further ischemic episodes.
3. Patients with single TIA and recovery: Even though these patients may have carotid occlusion, the risk of stroke is not high enough to justify an operation.
4. TIA with marginal circulation and no fixed neurological deficit (EC/IC Bypass Study 1985).
5. Stroke due to thromboembolism.
6. In the acute phase of a stroke in the presence of edema and hemorrhagic infarct: The operation should not be performed within 3 weeks of the onset of infarction.
7. Patients with infarcts located in a strategic location, such as internal capsule with dense hemiplegia are not candidates for EC/IC bypass.
8. Elderly patients with cerebral atrophy and mental impairment associated with chronic cerebrovascular ischemia are not candidates for this operation.

Redefinition of the Indications for EC/IC Bypass Operation in Cerebral Ischemia

The EC/IC bypass is a useful and safe operation. It has been technically refined using sutureless laser microvascular anastomosis (Jain 1984). Its use as a planned supplement to permanent occlusion of the internal carotid artery for the treatment of a giant intracranial aneurysm is justified in some circumstances. HBO may be useful for identifying patients with viable yet nonfunctional ischemic brain, who may benefit from cerebral revascularization. There is need for a controlled study to compare the effect of the EC/IC bypass operation in responders to HBO, where the control group would be maintained on long-term HBO treatments. The objective of such a study would be to determine if long-term HBO treatment may make the use of an EC/IC bypass operations unnecessary. Redefinition of the indications of the EC/IC bypass operation would involve further separation of the HBO responders into those who should be maintained on long-term HBO therapy and those who should have the operation. Stroke patients who do not respond to HBO therapy are unlikely to benefit from an EC/IC bypass operation.

Neuroprotection During Neurosurgery

Neurosurgical procedures that carry a risk of stroke are most those on the cerebrovascular system and most of these are carried out to prevent a stroke. These complications have been reduced to extremely low figures with the introduction of modern monitoring during surgery and refinement of surgical techniques such as microsurgery. Several methods for neuroprotection have been described (Jain 2011; Jain 2016). Refinements of neurosurgical technique have reduced the need for vascular interruption during neurosurgery but cerebral edema as well as cerebral ischemia are still encountered as complications of some neurosurgical procedures.

HBO preconditioning (PC), described in Chap. 19, may be useful for neuroprotection in procedures where ischemia is anticipated. A study has explored the role of osteopontin (OPN) in HBO-PC-induced neuroprotection (Hu et al. 2015). In a randomized comparative study on rat models, neurological outcome in HBO-PC group was better than that of stroke group. After OPN siRNA was administered, neurological function aggravated compared with control siRNA group. Brain morphology and structure seen by light microscopy was diminished in stroke group and OPN siRNA group, while fewer pathological injuries occurred in HBO-PC and control siRNA group. The infarct volume in HBO-PC group was the lowest, followed by OPN siRNA group and stroke group, respectively. OPN reduced the expression of IL-1β/nuclear factor-k-gene binding (NFkB) and augmented protein kinase B. OPN siRNA reversed these changes. OPN plays an important role in the neuroprotection elicited by HBO-PC. Pretreatment with HBO may be beneficial for patients prior to brain surgery.

Conclusion

The most important application of HBO appears to be in the management of acute TBI. The bulk of the evidence available indicates the effectiveness of HBO in reducing cerebral edema and intracranial pressure. Sufficient experimental and clinical studies have demonstrated the effectiveness of HBO as a part of comprehensive multimodality management of survivors of TBI to improve the outcome. HBO is increasingly under clinical investigation in the treatment of sequelae of less severe TBI such as posttraumatic stress syndrome.

Pressures used for treatment of patients with brain injury are usually less than those for other systems of the body. Dosimetry and monitoring are the essence of success with HBO in TBI. In most cases it is safe to start with 1.5 ATA.

Postoperative cerebral edema is still a problem in neurosurgery, and the use of HBO in reducing this is well documented and should be utilized. There is still no satisfactory treatment for acute spinal cord injury. Experimentally and anecdotally HBO has proven more effective in the acute stages than any pharmacological method. Its potential is high.

A decision regarding the removal of intracerebral hematomas can be facilitated by response to HBO. Additionally, it will afford protection to the patient during the period that the decision to operate or not to operate is being deliberated. Parallel to the potential of HBO in redefining the indications for extracranial/intracranial bypass operation based on favorable response to HBO is the usefulness of this therapy in the treatment of acute vascular occlusive disease. TBI had received the most support and investigation and has arrived at a stage, in our opinion, of acceptance.

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