17 The Use of HBO in Treating Neurological Disorders

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HBO appears to have a number of interesting effects regarding neurological problems. Many such applications remain in their infancy. This chapter reviews evidence concerning the following implications:

Introduction

Since hypoxia and ischemia are involved in the pathophysiology of many disorders of the nervous system, hyperbaric oxygen (HBO) therapy has an important role in their management. To understand the role of HBO in neurological disorders, a basic knowledge of cerebral metabolism, cerebral blood flow, and the neurophysiology of the brain is essential.

Effect of HBO on Cerebral Metabolism

The effect of HBO on cerebral metabolism in the healthy state has been described in Chapter 2. The response of the injured brain to HBO is quite different.

There is evidence for a Pasteur effect (inhibition of glycolysis by oxygen) with hyperoxia in the case of carbohydrate metabolism in cerebrovascular disease. Inhalation of 100% oxygen significantly decreased cerebral metabolic rate (CMR) for lactate and pyruvate. Since cerebral blood flow (CBF) decreased and cerebral pO_2 increased slightly, total glycolysis was decreased. Cerebral pO_2 plotted against CMR lactate showed evidence of the Pasteur effect.

Holbach *et al* (1977) studied the effect of HBO on cerebral metabolism in cases of brain injury. They noted that normally there is aerobic glycolysis with phosphofructokinase as the regulating enzyme. The activity of this enzyme and the glycolysis are inhibited when, through the oxidation of glucose, citrate concentration and adenosine triphosphate rises (the Pasteur effect). Conversely, glycolysis is stimulated when ATP and citrate levels fall from high energy use, as in hypoxia (reverse Pasteur effect).

Since 1 ml of oxygen oxidizes 1.34 mg of glucose, the glucose oxidation quotient (GOQ) is:

AVD of glucose – AVD of lactate = 1.34 AVD of oxygen,

where AVD is the arteriovenous difference.

The normal GOQ is 1.34 because the brain consumes oxygen almost exclusively from the oxidative metabolism of glucose. GOQ increases in anaerobic glycolysis as there is too high an amount of glucose still available for oxidation, even after subtracting the considerably increased AVD lactate.

In patients treated with 100% oxygen at 1.5 ATA (measurements made 10–15 min after the exposure) there was a moderate increase in AVD glucose and AVD lactate. The AVD oxygen remained constant. This resulted in a balancing of the cerebral glucose metabolism as reflected in the normal or near normal GOQ values.

When Holbach *et al* (1977) tried HBO at 2 ATA in similar situations, there was an increase of AVD glucose and a decrease of AVD oxygen compared with the values measured prior to the treatment. The GOQ increased. Th concluded that in the injured brain, HBO at 1.5 ATA h beneficial effects, whereas raising the pressure to 2 ATA h deleterious effects.

Contreras *et al* (1988) measured cerebral glucose uti zation using the autoradiographic 2-deoxyglucose tec nique in rats injured by focal cortical freeze lesions. The treated these animals with HBO at 2 ATA (90-min session for 4 consecutive days. There was an overall increase of ce rebral glucose utilization measured 5 days after injur when compared with the lesioned control animals expose only to air (Figure 17.1). The data indicate that the change in cerebral glucose metabolism persisted beyond the perio of exposure to HBO. This observation is important as i explains the persistence of clinical improvement in patient after exposure to HBO.

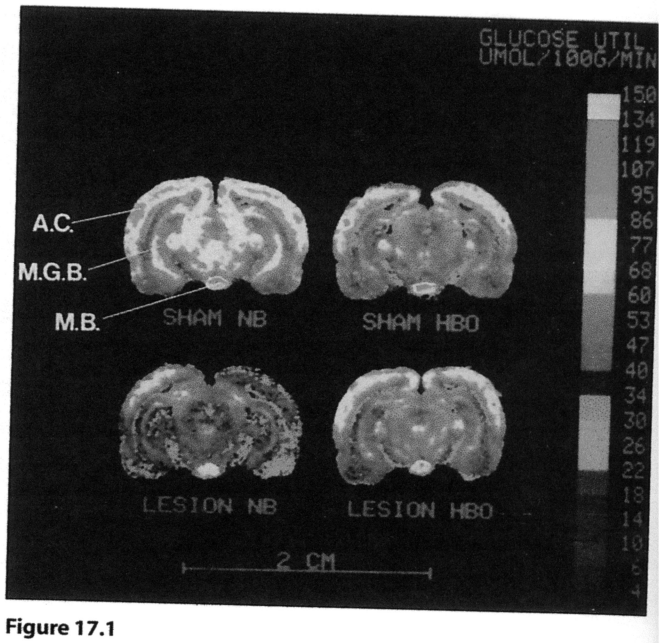

Figure 17.1
Color-coded transformation of autoradiographs of brain sections at the level of the auditory cortex into a quantitative map of glucose utilization. Three of these areas that demonstrate a statistically significant interaction between the lesion and the HBO therapy are the auditory cortex (A.C.), the medial geniculate body (M.G.B.), and the mammillary body (M.B.). The lesion was performed on the right side of the brain and is shown on the right side of these photographs (From Contreras *et al* 1988).

Effect of HBO on Cerebral Blood Flow

Various studies of the effect of HBO on cerebral blood flow (CBF) are shown in Table 17.1 It is generally recognized that oxygen has a vasoconstrictive action and reduces CBF, though the mechanism is unknown. Extracellular superoxide dismutase plays a critical role in the physiological response to oxygen in the brain by regulating nitric oxide (NO) availability. Cerebral blood flow responses in geneti-

Table 17.1
Summary of Cerebral Blood Flow under HBO as Reported by Various Authors

Authors and year	Method	Material	Inhalant	Pressure	Change
Kety and Smith (1948)	Nitrous oxide	Man	O_2 85%–100%	1 ATA	Decrease 13%
Lambertson *et al* (1973)	Nitrous oxide	Man	O_2 100%	3.5 ATA	Decrease 25%
Jacobson and Lawson (1963)	Krypton-85 clearance	Dog	O_2 100%	1 ATA 2 ATA	Decrease 12% Decrease 21%
Tindall *et al* (1965)	Electromagnetic flowmeter	Baboon, internal carotid (5 min.)	O_2 90%	1 ATA 3 ATA 3 ATA	Decrease 9% Decrease 13% Decrease 18% (10 min.)
Harper *et al* (1965)	Krypton-85 clearance	Dogs made hypotensive by bleeding	O_2 100%	2 ATA	No change
Di Pretoro *et al* (1968)	Rheography	Man	O_2 100% Air	2 ATA 2 ATA	Reduced No change
Wuellenweber *et al* (1969)	Thermal probes	Patients with brain injuries	O_2 100%	2.5 ATA	Increase
Miler *et al* (1970)	rCBF		Dogs, cryogenic sprobe lesions	O_2 100%	2 ATA
Hayakawa (1974)	Ultrasonic rheography	Man, internal carotid	O_2 100%	1 ATA 2 ATA	Decrease 1% Decrease 8%
Artru *et al* (1987)	133 Xe clearance	Patients with brain injury	O_2 100%	2.5 ATA	Increase (in patients with cerebral edema)
Ohta *et al* (1987a)	133 Xe	Healthy volunteers	O_2 100%	1 ATA 1.5 ATA 2 ATA 3 ATA	Decrease 9% Decrease 23% Decrease 29% Decrease 14%
Omae *et al* (1998)	Transcranial Doppler to	Human volunteers	O_2 100%	HBO 2 ATA, control with hyperbaric air	Velocity of blood flow in the middle cerebral artery decreased with HBO as compared to hyperbaric air
Demchenko *et al* (1998)	Hydrogen (H_2) clearance method	Rats	O_2 100%	HBO 3 ATA	Decrease 26–39%
Di Piero *et al* (2002)	SPECT	Divers Healthy non-diver controls	O_2 100%	HBO 2.8 ATA	Normobaric O_2 (NBO) No difference in CBF distribution between controls and divers in both NBO and HBO
Demchenko *et al* (2005)	Platinum electrodes in globus pallidum Rats	Air	100% O_2	2 to 6 ATA	Doubling of CBF with HBO led to 13-64 fold increase in pallidum in a linear manner.
Meirovithz *et al* (2007)	Fiber optic probe	Awake restrained rats	100% O_2	1.75 to 6 ATA	The maximal level of microcirculatory Hb O_2 at 2.5 ATA is double the normoxic level

cally altered mice to changes in PO_2 demonstrate that SOD3 regulates equilibrium between superoxide (O_{2-}) and NO, thereby controlling vascular tone and reactivity in the brain. That SOD3 opposes inactivation of NO is shown by absence of vasoconstriction in response to PO_2 in the hyperbaric range in SOD3+/+mice, whereas NO-dependent relaxation is attenuated in SOD3–/–mutants (Demchenko *et al* 2002). Thus, extracellular SOD promotes NO vasodilation by scavenging O_{2-}, while hyperoxia opposes NO and promotes constriction by enhancing endogenous O_{2-} generation and decreasing basal vasodilator effects of NO. The explanation of increase of CBF in some reports is as follows:

- If the probe was measuring flow in the area of the damaged brain, the increase in flow could be an "inverse steal phenomenon" (Lassen & Palvöigyi 1986) due to vasoconstriction elsewhere.
- The area of brain under the probe might have lost its

power of autoregulation, and the increase of blood flow could be due to an increase of perfusion pressure owing to a decrease of intracranial pressure (ICP) consequent upon vasoconstriction elsewhere in the brain.

The conflict among the reports in the literature on this subject arises from the variable effect of HBO on the normal versus the injured brain. If CBF is impaired by cerebral edema or raised ICP it can be improved by HBO. Leniger-Follert and Hossman (1977) made observations on the microcirculation and cortical oxygen pressure, during and after prolonged cerebral ischemia, that are relevant to the effect of HBO. According to these authors, complete cerebral ischemia of 1 h in cats followed by reactive hyperemia, and recirculation as well as reoxygenation of the brain can occur. However, there is a critical phase of a few hours after the recommencement of circulation as soon as reactive hyperemia ceases. If brain swelling occurs during this period, cerebral hypoxia may develop. If brain swelling can be prevented, however, the distribution of oxygen pressure in the cortex can be restored to normal. HBO has a beneficial effect on cerebral edema.

Bean *et al* (1971) suggested that HBO had a dual influence on the central vasculature initial vasoconstriction followed by vasodilatation – and that prolonged exposure to HBO – results in the loss of oxygen vascular constrictive controls. Based on the evidence available, it may be concluded that HBO generally causes vasoconstriction and results in a reduction of CBF. The detailed response of cerebral vessels to HBO, however, varies according to the degree of compression, exposure time, region of the brain, and pathological process in the brain and blood vessels. Ohta *et al* (1987a) believe that too much oxygen disturbs the regulatory oxygen response of CBF and may explain the pathogenesis of oxygen toxicity. These investigators state that reduced CBF under HBO is a protective response against oxygen toxicity.

Bergö *et al* (1993) measured the changes in CBF distribution during HBO (5 ATA for 5 and 35 min) exposure in rats with unilateral frontal decortication lesions. CBF was reduced in most cerebral regions on the lesioned side. Brainstem showed reduction of CBF below the increased oxygen content after 35 min of HBO. The hypoxia as well as the disturbed balance between glutaminergic and GABAergic neurotransmitter systems was considered to have contributed to the increased frequency of convulsions in these animals. Cerebral blood flow decreases during HBO treatment at a constant $PaCO_2$. Hypercapnia prevents this decline and elevated $PaCO_2$ augmented oxygen delivery to the brain, but increases the susceptibility to oxygen toxicity (Bergö & Tyssebotn 1999).

Omae *et al* (1998) have conducted a study to clarify the relationship between HBO and CBF in humans. Middle cerebral arterial blood flow velocity (MCV) was measured using transcranial Doppler (TCD) technique in a multiplace hyperbaric chamber. The Doppler probe was fixed on the temporal region by a head belt, and the transcutaneous gas measurement apparatus ($tcPO_2$ and $tcPCO_2$) was fixed on the chest wall. MCV and transcutaneous gas were measured continuously in eight healthy volunteers under four various conditions: 1 ATA air, 1 ATA O_2, 2 ATA air, and 2 ATA O_2. Next, the effect of environmental pressure was studied in another eight healthy volunteers, in whom the $tcPO_2$ was kept at almost the same level under conditions of both 1 ATA and 4 ATA by inhaling oxygen at 1 ATA. MCV of 1 ATA O_2, 2 ATA air, and 2 ATA O_2 decreased, and $tcPO_2$ increased significantly in comparison with that of 1 ATA air. A significant difference in MCV was observed between the O_2 group and the air group under the same pressure circumstance. On the other hand, there were no differences in MCV or $tcPO_2$ between 4 ATA air and 1 ATA plus O_2, and the influence for the MCV of the environmental pressure was not observed. The authors concluded that hyperoxemia caused by HBO reduces the CBF, but the high atmospheric pressure per se does not influence the CBF in humans.

A decrease in nitric oxide (NO)availability in the brain tissue due to the inhibition of nitric oxide synthase (NOS) activity during the early phases of HBO exposure is involved in hyperoxic vasoconstriction leading to reduced rCBF. Increased levels of asymmetric dimethylarginine , an endogenous inhibitor of NOS, have been demonstrated in rat brains exposed to HBO (Akgül *et al* 2007).

Effect of HBO on the Blood-Brain Barrier

Some earlier animal experimental studies indicated that HBO increases the permeability of the cerebral vessel walls in normal animals. These findings were not substantiated in later studies. Blood brain barrier (BBB) is disturbed in certain disorders such as cerebrovascular ischemia, and HBO may serve to decrease the permeability of BBB. Intraischemic HBO therapy reduces early and delayed postischemic BBB damage and edema after focal ischemia in rats and mice (Veltkamp *et al* 2005).

Effect of HBO on Oxygen Tension in the Cerebrospinal Fluid

Hollin *et al* (1968) studied the effect of HBO on the oxygen tension of cerebrospinal fluid (CSF). They found that CSF levels usually reflect the arterial pO_2 tensions. Katsurada *et al* (1973) studied ventricular fluid oxygen tension in head injury patients and concluded that in severe brain injury, intracranial arteriovenous shunts or capillary blocks may prevent the rise of CSF oxygen tension with a rise of respi-

ratory oxygen, and that this difference may be an index of the degree of injury to the brain. This may also mean that in a brain with multiple injuries, HBO may not affect the damaged part.

Rationale for the Use of HBO in Neurological Disorders

The following are the main mechanisms of the effectiveness of HBO in neurological disorders:

- Relief of hypoxia
- Improvement of microcirculation
- Relief of cerebral edema by vasoconstrictive effect
- Preservation of partially damaged tissue and prevention of further progression of secondary effects of cerebral lesions
- Improvement of cerebral metabolism

Relief of hypoxia is the most significant effect of HBO. Hypoxia has been described in Chapter 5. Hypoxemia can be corrected by normobaric 100% oxygen inhalation, but hypoxia of some lesions of the CNS requires HBO for correction.

The beneficial effect of HBO on cerebral hypoxia has been shown by biochemical studies. It is well known that there is an increase of lactate in brain and CSF in cerebral injury and anoxia. Mogami *et al* (1969) showed that there was a decrease in the CSF lactate:pyruvate ratio under HBO, suggesting reduction of anaerobic in favor of aerobic metabolism.

The rational basis of the use of HBO in some neurological disorders is understandable in view of one concept of the pathogenesis of multiple sclerosis. According to James (1982, 1987), the following phenomena may occur in multiple sclerosis:

- Failure of pulmonary filtration of fat microemboli.
- Blood-brain barrier dysfunction that allows access of fat emboli to the brain parenchyma.
- Focal areas of perivenous edema preceding demyelination.

Vascular disturbances in the pathogenesis of multiple sclerosis may provide the rational basis for HBO therapy in this disease.

Cerebral Hypoxia

Oxygen is vital for the brain, and oxygen deficiency, regardless of the cause, starts a vicious circle of pathological changes in brain tissue:

Primary brain damage → hypoxia → edema → aggravation of hypoxia → secondary brain damage

The object of HBO therapy in brain injuries is to supply the brain tissue with adequate oxygen and to interrupt this process.

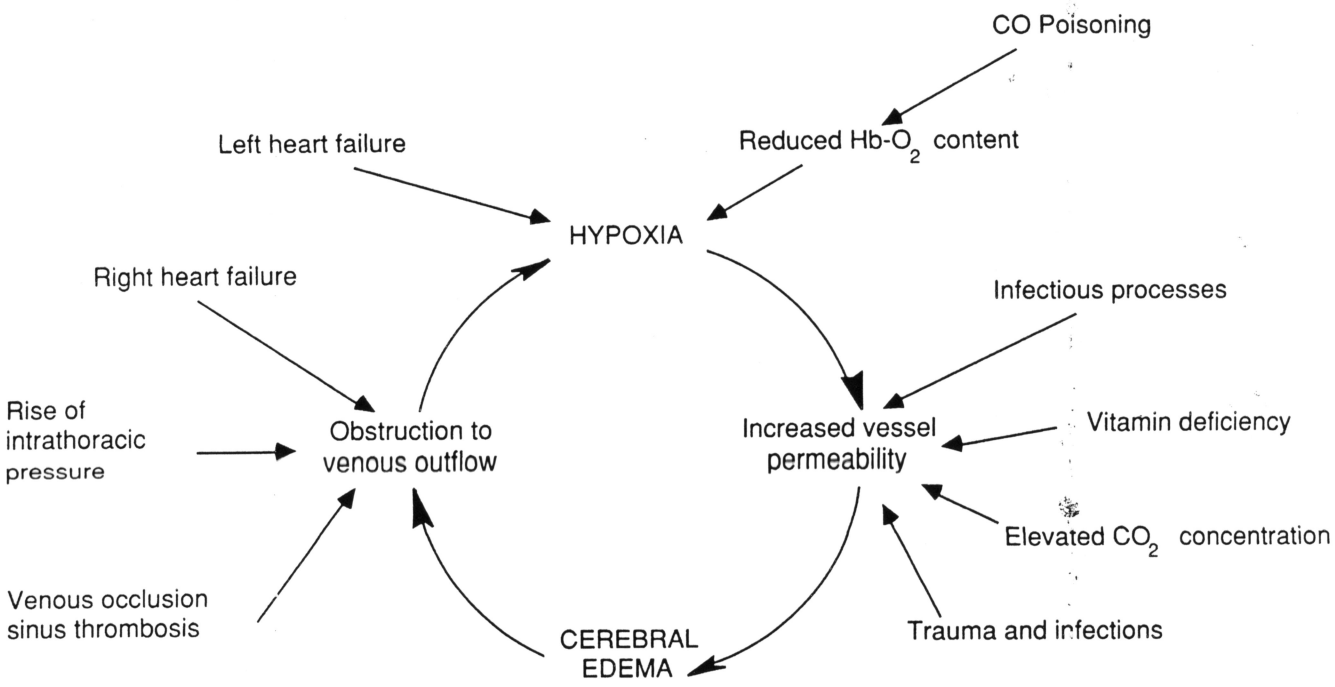

Figure 17.2
Pathophysiology of cerebral edema.

Cerebral Edema

Brain edema is divided into three types:

- *Vasogenic.* There is cerebral vasomotor paresis with transudation of plasma proteins into the extracellular space of the brain, e.g., brain injury, abscess, tumor, or infarction.
- *Cytotoxic.* Swelling in the intracellular space, e.g., CO poisoning, hypoosmolarity.
- *Interstitial.* Fluid escapes from the ventricle to enter the extracellular space of the periventricular white matter. This is unique to hydrocephalus.

Cerebral edema is a frequent finding in many disorders of the CNS. Its pathogenesis is depicted in Figure 17.2.

Generalized edema is a life-threatening process due to the rise of intracranial pressure (ICP) associated with it. The role of localized edema in aggravating the neurological deficits resulting from focal vascular and demyelinating le-

Table 17.2
Experimental Studies of the Effect of HBO on Cerebral Edema

Authors and year	Experimental animals and methods	Results and comments
Jamieson and Van Den Brenk (1963)	Rats. Oxygen tension measured in the brain under HBO (2 ATA).	Decrease of edema. Increase of brain oxygen tension in spite of vasoconstriction.
Coe and Hayes (1966a,b)	Rats. 2 groups with brain injury by liquid nitrogen. One group treated by HBO at 3 ATA.	Treated group survived longer and had less cerebral edema and less neuronal damage than the untreated group.
Dunn and Connolly (1966)	Dogs. One group treated by HBO, the other by normobaric 100%. Single 2 h treatment.	Reduction in mortality in both groups equal. Authors concluded that any any additional benefits from HBO was not manifest because of vasoconstriction.
Jinnai *et al* (1967)	Cats and rabbits.	Extradural balloons and intracarotid injections. Group tested by HBO at 3 ATA for 1 h.
Sukoff *et al* (1967)	Dogs. Psyllium seed injections in brain.	HBO at 3 ATA given at every 8 h starting 25 h after injury. Decreased mortality and morbidity in treated animals as compared with untreated ones.
Moody *et al* (1970)	Dogs. Injuries simulating extradural hematomal. Assisted respiration with 100% oxygen (1 ATA) in one group and 100% oxygen at 1 ATA or 2 ATA in other groups with spontaneous respiration.	Best reduction in mortality was in animals breathing spontaneously with 100% oxygen at 2ATA for 4 h.,
Hayakawa *et al* (1971)	Dogs with and without brain injury at HBO 3 ATA. CSF pressure measurements.	In dogs without brain damage CSF pressure decreased initially but rose later due to CBF disturbances. There was more consistent decrease in brain injured animals.
Dunn (1974)	Freeze lesions to produce cerebral edema. Four groups 1. control 2. ventilated for 2–3 h with air 3. 3 h of 97% oxygen + 3% CO_2 hyperventilation 4. 3 h of HBO at 3 ATA (97% oxygen + 3% CO) + hyperventilation	The lowest mortality (29%) was in group 4 (mean survival 5.3d). The highest mortality was in group 3 (mean survival 2d). HBO with hyperventilation was shown to reduce ICP definitely.
Nagao *et al* (1975)	25 dogs. Anesthetized and ventilated.	ICP raised by extradural balloons. HBO reduced ICP only when cerebral circulation was responsive to CO_2. In animals treated by HBO, CO_2 reactivity was maintained until high levels of ICP.
Miller (1979)	Dogs. Cerebral edema by liquid nitrogen. Effect of HBO on CBF and ICP.	HBO caused a 30% reduction of ICP and 19% reduction of CBF so long as the cerebral vessels remained responsive to CO_2.
Gu (1985)	Rabbits. Experimental edema. Treated by various mixtures of nitrogen and oxygen as well as 100% O2 at 1 and 4 ATA.	No effect of mixtures of oxygen and nitrogen 100% caused a drop of ICP at both 1 and 4 ATA.
Isakov *et al* (1985)	30 rabbits. Head injury 15 treated by HBO. The rest were controls.	Ten sessions of HBO led to significant reduction of tissue water in the brain of animals treated by HBO.
Nida *et al* (1995)	Fluid percussion (FP) injury or cortical injury (CI) in rats. Treated with HBO (1.5 ATA for 60 min), starting 4 h after head trauma.	HBO reduced edema produced by FP but not by CI although both were equally severe.

sions is generally not well recognized. With modern neuroimaging techniques, it has become possible to demonstrate focal brain edema *in vivo*.

The ICP represents the sum of three components: the volume of the brain substance, the CSF, and the blood present in the cranial cavity at any time. Reduction of any of these components can lower ICP. The conventional treatments for brain edema and raised ICP include corticosteroids, osmotic diuretics, hyperventilation, barbiturate coma, and ventricular drainage.

Experimental Studies

Most of the research regarding the effect of HBO on cerebral edema and raised ICP has been done on experimental animals. These studies are shown in Table 17.2.

Clinical Studies

Clinical studies of the effect of HBO on cerebral edema are shown in Table 17.3. Pierce and Jacobson (1977) reviewed the role of HBO in cerebral edema. Their classical conclusion, which is still valid is as follows:

"this therapy directly decreases vasogenic brain edema and due to improvement of O_2 delivery to anoxic tissue acts on cytotoxic brain edema as well. The mechanism underlying the potentially beneficial action of HBO appears clear and is well supported by animal and clinical studies. HBO should be considered an adjunct for patients who are not sufficiently responsive to standard methods. Treatment levels should not exceed 2 ATA and an effort should be made to prevent the rebound phenomenon by titrating pO_2 downwards, preferably by varying O_2 concentrations while maintaining hyperbaric pressure levels."

Table 17.3
Clinical Studies of the Effect of HBO on Cerebral Edema

Authors and year	Diagnosis and no. of patients	Results and comments
Jinnai *et al* (1967)	Head injuries, 7; Post-operative neurosurgery, 8	Neurological and EEC improvement but not long lasting
Hayakawa *et al* (1971)	Brain trauma or neurosurgery, 15 continuous monitoring of ICP and CBF before, during and after HBO at 2 ATA	Three types of responses: I CSF pressure decreased initially and then rose (n = 9) II ICP was lowered and remained so (n = 2) III Little or no response of ICP to HBO (n = 4)
Miller (1973)	Head injury patients 30% reduction of ICP at 2 ATA (PAO2 1227 mmHg)	No further education when pressure raised to 3 ATA
Sukoff and Ragatz (1982)	Head injury patients, 50	Considerable reduction of cerebral edema as shown by CT scan and clinical evaluation

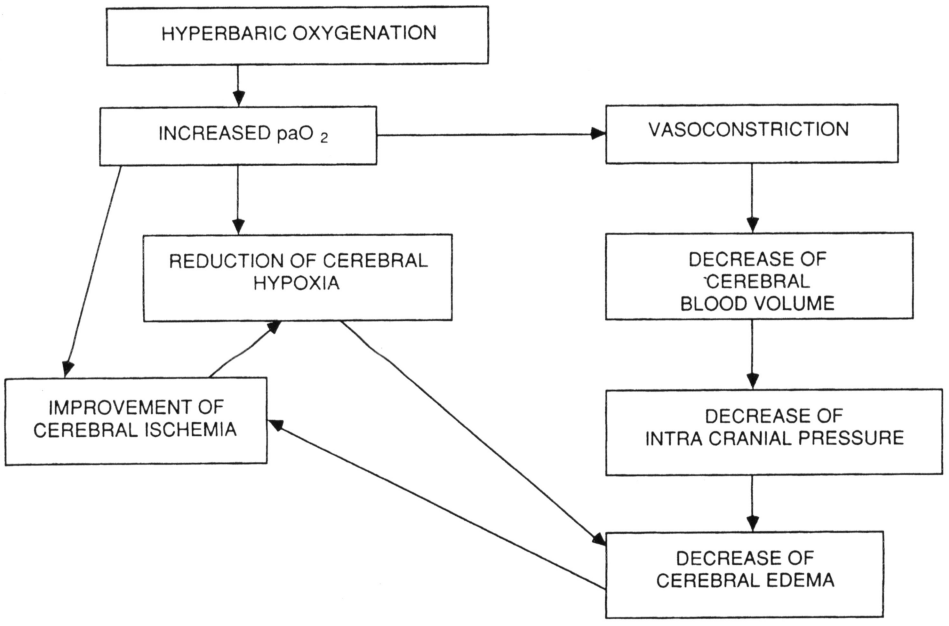

Figure 17.3
Mechanism of effectiveness of HBO in cerebral edema.

The favorable results of HBO on cerebral edema in experimental animals have been confirmed by the clinical use of HBO for the relief of traumatic cerebral edema (Sukoff & Ragatz 1982). HBO (1.5 ATA) treatment of patients with severe brain injury reduces raised intracranial pressure and improves aerobic metabolism (Rockswold *et al* 2001; Sukoff 2001).

Application of HBO during the early phase of severe fluid percussion brain injury in rats significantly diminished ICP elevation rate and decreased mortality level (Rogatsky *et al* 2005). In conclusion, it can be stated that HBO relieves cerebral edema by the following mechanisms (Figure 17.3):

- Reduction of CBF but maintenance of cerebral oxygenation.
- HBO counteracts the effects of ischemia and hypoxia associated with cerebral edema and interrupts the cycle of hypoxia/edema.

HBO lowers raised ICP in traumatic cerebral edema as long as the cerebral arteries are reactive to CO_2. It is ineffective in the presence of vasomotor paralysis and is contraindicated in terminal patients with this condition. The effects of HBO can persist after the conclusion of a session and there is no rebound phenomenon, as is the case with the use of osmotic diuretics. If the ICP is elevated due to obstruction in the CSF pathways, as is the case in intraventricular hemorrhage, HBO and dehydrating agents have only a temporary effect in lowering ICP. Ventricular drainage is important in these patients, not only to lower the ICP but also to improve the CBF that decreases as an effect of raised ICP. Persistence of raised ICP can cause further cerebral damage. Studies of the effect of HBO on raised ICP in patients with brain tumors and cerebrovascular disease indicate that reduced ICP is initially due to direct vasoconstriction caused by hyperoxia but tends to rise again. However, the secondary rise can be prevented by induced hypocapnia.

The injured brain is susceptible to oxygen toxicity if high pressures are used. This is usually not a problem as the pressures seldom exceed 2.5 ATA; 1.5 ATA is used for most neurological indications.

Table 17.4
Neurological Indications for the Use of HBO Therapy

1. Cerebrovascular disease
   - Acute cerebrovascular occlusive disease
   - Chronic poststroke stage
   - Treatment of spasticity
   - Aid to rehabilitation
   - Adjunct to cerebrovascular surgery
   - Selection of patients for IC/EC bypass operation on the basis of response to HBO
   - Postoperative complications of intracranial aneurysm surgery: cerebral edema and ischemia
   - Carotid endarterectomy under HBO as a cerebral protective measure
2. Cerebral air embolism
3. Head injuries: cerebral edema and raised intracranial pressure
4. Spinal cord lesions
   - Acute traumatic paraplegia within 4 h of injury
   - Spinal cord decompression sickness (spinal cord "hit")
   - Ischemic disease of the spinal cord
   - Aid to the rehabilitation of paraplegia and quadriplegia
   - Residual neurological deficits after surgery of compressive spinal lesion
5. Cranial nerve lesions
   - Occlusion of the central artery of the retina
   - Facial palsy
   - Sudden deafness
   - Vestibular disorders
6. Peripheral neuropathies
7. Multiple sclerosis
8. Cerebral insufficiency (decline of mental function): multi-infarct dementia
9. Infections of the CNS and its coverings: brain abscess, meningitis
10. Radiation-induced necrosis of the CNS: radiation myelopathy and encephalopathy
11. CO poisoning
12. Migraine headaches
13. Cerebral palsy

Indications for the Use of HBO in Neurological Disorders

Various neurological conditions where HBO has been reported to be useful are listed in Table 17.4. Most of these are based on a review of the literature. There are few controlled clinical studies. The Undersea and Hyperbaric Medical Society USA does not list any of these conditions (with the exception of cerebral air embolism) as approved for payment by third-party insurance carriers.

There are several good reviews of the use of HBO in neurological disorders (Hayakawa 1974; Kapp 1982; Sukoff 1984). The role of HBO in cerebrovascular disease is described in Chapter 18. HBO for the management of anoxic encephalopathies is dealt with in Chapter 19, neurosurgical disorders in Chapter 20, HBO as an adjunct to the management of multiple sclerosis is discussed in Chapter 21, cerebral palsy in Chapter 22, and migraine headaches in Chapter 23. The rationale for the use of HBO is discussed, along with the indications.

Diagnostic Procedures Used for Assessing the Effect of HBO

Routine neurological procedures are not necessarily useful in assessing the effects of HBO therapy but the following are worthy of consideration.

Clinical Neurological Assessment of Response to HBO

Neurological examination in the hyperbaric chamber is important in determining the effect of hyperbaric oxygen. Some of the effects are transient and may not been seen after removal of the patient from the chamber. It is not necessary to have a specialist provide a simple brief neurological examination, because any physician should be able to carry out such an investigation. Due to constraints of space and time, the examination should be limited to less than 5 min and repeated as often as possible, but at least three times during a hyperbaric session – once during the compression phase, once during the oxygenation phase, and once during decompression. A simple procedure such as measurement of the handgrip by a hand dynamometer can be done more often. The following are some examples as guidelines. Each hyperbaric center should develop its own protocol for the minimum neurological testing acceptable to the attending neurologist.

Comatose Patients

For comatose patients, the following should be included in the testing:

1. Reaction to painful stimuli by movement of limbs
2. Presence or absence of decerebrate rigidity
3. Pupil size and reaction to light
4. Fundoscopic examination – look for any vasoconstriction
5. Glasgow coma scale in case of patients with head injury

Paraplegics

1. Mark the level below which the sensory loss begins and chart the sensory loss, if partial
2. Grading of the major muscle group power if incomplete lesion
3. In subacute or chronic cases with spasticity, clinical grading of spasticity by passive range of motion

Hemiplegics (Stroke Patients)

1. Fundoscopic examination, visual acuity and visual fields by confrontation
2. Motor power testing, proximal muscles of the arm and the leg; test the time it takes for the stretched out (in sitting position) and the raised leg (in supine position) to drift; measurement of the hand grip by a hand-held dynamometer
3. Testing for spasticity; clinical grading of spasticity (see Chapter 18); measurement of spasticity of fingers by a handy muscle tonometer

A patient's response to a single HBO treatment is sometimes used for determining the response to HBO therapy and to make a decision regarding continuation of the therapy but this may not be adequate. In some patients, the

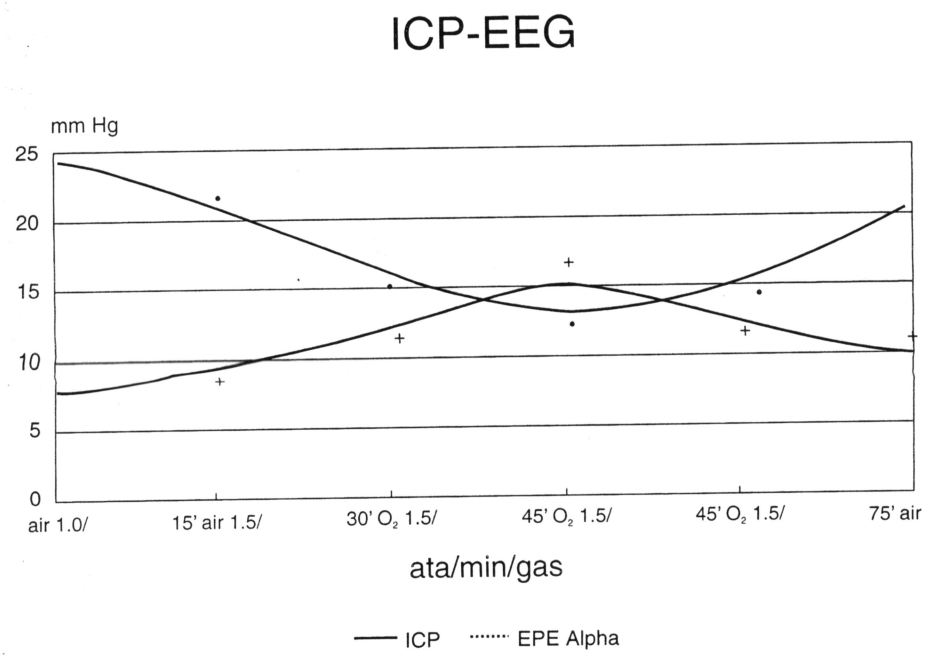

Figure 17.4
HBO therapy of a patient with severe cerebral edema and raised intracranial pressure (ICP). Continuous recording of arterial pO_2, pCO_2, ICP, and electrical power equivalents (EPEs) of alpha EEG activity. (From Wassman and Holbach 1988).

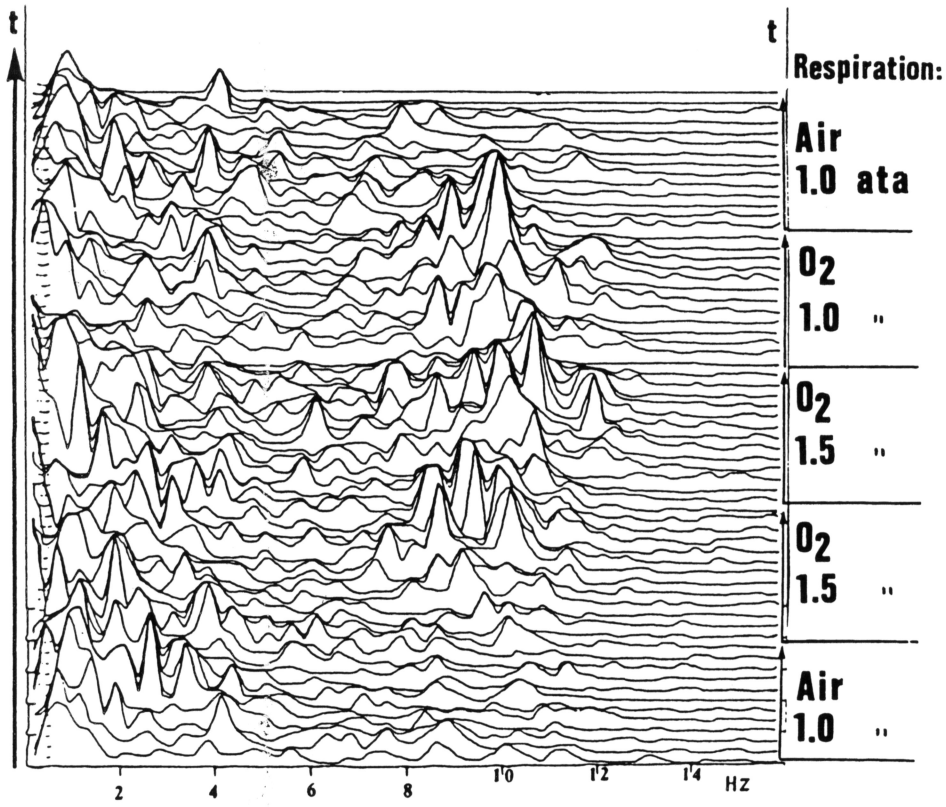

Figure 17.5
Illustration of EEG power spectrum during HBO treatment of a patient suffering from cerebral hypoxia. A definite increase of alpha activity is seen during the rise of oxygen partial pressure. (From Wassmann and Holbach 1988).

improvement resulting from HBO therapy is noticeable only after several treatments.

Electrophysiological Studies

The EEG has been found to be useful in assessing the response of patients to HBO treatment. Wassmann (1980) described the technique of interval amplitude EEG analysis (power spectrum) of patients during HBO therapy sessions. Two examples of the use of EEG in evaluating the response to HBO are shown in Figures 17.4 and 17.5. Matsuoka and Tokuda (1983) observed that slow waves tended to decrease and alpha activity tended to increase on the side of the lesion in patients undergoing HBO at 2 ATA. Topographic EEG mapping is an acceptable objective parameter of the effect of HBO on the brain (Tsuru *et al* 1983). In normal subjects somatosensory evoked potentials (SSEP) are reproducible under hyperbaric conditions and can be used to assess the response of spinal cord injury patients to HBO therapy. EEG is used little now for the evaluation of HBO treatment effects. The emphasis is now on brain imaging methods.

Cerebral Blood Flow (CBF)

This is most relevant to stroke and its management using HBO. Brain dysfunction after stroke closely relates to the site and extension of lesions and thus correlates with the degree of reduction of CBF and metabolism. The most commonly used method in the past few years has been the ^{133}Xenon (Xe) inhalation method. The technique is based on gamma scintillation counting on NaI crystals after inhalation of ^{133}Xenon. This gives the values for regional CBF (rCBF). More recently positron emission tomography (PET) has been used for measuring rCBF. Relations between rCBF, Glucose metabolism, oxygen consumption and the structural lesions have been studied in the acute stroke to assess the impact of various treatments on the evolution of stroke during the first few hours after the onset. rCBF is also useful in the subacute and chronic phases of stroke. The severity of hemiparesis correlates with degree of asymmetry of CBF. Bilateral reductions of CBF are more likely to be associated with cognitive impairment. Quantitative CBF in acute ischemic stroke can be determined by XeCT and these measurements correlate with early CT findings (Firlik *et al* 1997). This system is commercially available as the XeCT System + (Diversified Diagnostic Products, Houston, Tx) and the advantages of this method are that CBF can be determined by the CT-staff along with routine CT without waiting for the CBF-staff. Results are available within 20 minutes.

Computerized Tomography (CT)

Principles. Computerized tomography (CT) permits the examination of tissue by the same principle as conventional

x-ray imaging, except that the radiation passes successively through tissue from multiple different directions, detectors measure the degree of attenuation of the exiting radiation relative to the incident radiation, computers integrate the information and construct the image in cross section. Administration of a contrast agent increases x-ray attenuation owing to the high atomic number and electron density of the iodinated compounds used. Use of intravenous contrast agent enables the assessment of the integrity of the BBB. CT angiography (CTA) can also be performed after intravenous infusion of a nonionic contrast agent. Recent experimental studies indicate that contrast CT can detect cytotoxic edema (Von Kummer & Weber 1997).

Advantages and disadvantages. Advantages of CT are the widespread availability, short study time, sensitivity for detection of calcification and acute hemorrhage. It can be used in situations where MRI cannot be used in persons with intracranial metallic clips, pacemakers and other metal prostheses. It is preferred in rapidly evolving neurologic disorders where direct observation of the patient and life support systems is essential during scanning procedure. CT usually costs about half as much the MRI scan. Main disadvantages of CT scan are that it involves radiation and is less sensitive than MRI. More than 90% of the hospitals in the USA with 200 or more beds has this equipment. The distribution of this diagnostic facility is much lower in Europe and rare is confined mostly to large medical centers in developing countries.

Uses. This is the most widely used diagnostic procedure in neurological disorders. CT scan is the method of choice for assessment of ischemic injury to the brain. It is done without contrast to determine whether the stroke is hemorrhagic or ischemic. It is absolutely essential because all subsequent therapeutic decisions depend on the results of this examination. It can detect almost all of intracranial hematomas more than 1 cm in diameter and more than 95% of subarachnoid hemorrhages. Definite changes of infarction are usually not seen for 24 to 48 hours after onset but subtle signs of ischemia may appear before 3 h.

CT scan is used for detecting traumatic hematomas, brain tumors, abscesses and other infectious granulomas such as tuberculomas. Edema surrounding intracranial lesions such as those due to brain tumor and injury can be detected. Changes from cerebral edema include a local mass effect with distortion of the ventricular system.

Magnetic Resonance Imaging (MRI)

Principle of MRI. A tissue, when placed in a strong magnetic field, causes certain naturally occurring isotopes (atoms) within the tissue to line up within the field, orienting the net tissue magnetization in the longitudinal direction. Current MRI uses signals derived from ^{1}H, the most plentiful endogenous isotope. Within a magnetic field, these atoms do not orient precisely with the axis of the field, but wobble a few degrees off center. Application of a radio-frequency pulse perpendicular to the applied magnetic field reorients the net tissue magnetization from the longitudinal to the transverse plane. When the radio-frequency pulse is turned off, the net tissue magnetization returns to its previous orientation, resulting in a magnetic resonance signal that can be detected by receiver coils. Application of different-gradient magnetic fields to the tissue under study permits reconstruction of the signal from individual volume units in space. The result is a clear image of the tissue in space.

Sequences such as T_1 and T_2, proton-density, and spin-echo weighted images enhance the utility of the MRI. Use of intravascular contrast material gandolinium-diethyleneamine pentaacetic acid with MRI enhances the magnetic susceptibility of the adjacent tissue, thereby providing information about the integrity of the BBB. Diffusion-weighted imaging can detect cytotoxic edema and is sensitive to early ischemic changes in the brain. Magnetic resonance angiography (MRA) enables noninvasive visualization of the cerebral and extracerebral vessels. Magnetic resonance spectroscopy provides a noninvasive method of studying brain metabolites, brain pH, and some neurotransmitter without the use of ionizing radiation. Functional MRI is a method of imaging the oxygen status of hemoglobin in order to visualize local changes in cerebral blood flow that reflect changes in neuronal activity in response to a specific sensory stimulus or motor task.

Advantages and disadvantages. The advantages of MRI are the absence of ionizing radiation, sensitivity to blood flow, high soft tissue contrast resolution and capacity to produce images in any plane. MRI is superior to CT for detecting most CNS lesions including cerebral infarction but is not as effective as CT for detecting subarachnoid hemorrhage. MRI may show evidence of ischemic stroke sooner than CT. Drawbacks of MRI include the lack of general availability and difficulty in monitoring seriously ill patients during the examination, and the time needed to perform it which is longer than that for unenhanced CT scan. SAH can be missed by MRI scan.

Uses. With newer MRI techniques such as diffusion-weighted and perfusion-weighted imaging, immediate identification of ischemic injury is possible and reversible ischemia can be estimated (Lutsep *et al* 1997). MRI is superior to CT in detecting cerebral edema and for detecting small lacunar lesions, particularly those located deep within the cerebral hemispheres and in the brain stem.

MRI is also used for evaluating the progression or regression of lesions of multiple sclerosis.

Positron Emission Tomography (PET)

This is a method of radionuclide scanning which requires the intravenous radioligand with a positron-emitting isotope, accumulation of the ligand in the brain and subsequent emission of the positrons from the ligand into the adjacent tissue during radioactive decay. Positrons are the antimatter equivalent of electrons. The collision of an electron and a positron annihilates both particles, converting their masses to energy in the form of two photons (gamma rays) that leave the brain at an angle of 180 degrees to each other and can be decayed. The radioligands that are most frequently used are ^{18}F-fluorodeoxyglucose and ^{15}O-water for determining cerebral blood flow. The use of PET is limited by a high cost, the need for a nearby cyclotron to produce radioisotopes with short half-lives, and its restricted spatial and temporal resolution. Routine use for neurodiagnostics is not currently practical. PET is referred to as functional imaging because, by using appropriate tracers, one can determine CBF and regional cerebral metabolic rate for oxygen (CMR O_2) and CMR for glucose (CMR glu). These techniques are extremely sensitive in the early detection of a cerebrovascular disturbance and can delineate the natural course of an episode that can lead to cerebral infarction. Evidence of ischemia is clearly demonstrated by substantial reduction in CBF and elevated CMR O_2 and CMR glu. The effect of a therapeutic intervention can be assessed by demonstrating the complete or partial reversal of these physiological and biochemical parameters.

Permanently and irreversibly damaged cortex in acute stroke can be detected by flumzenil PET. Evidence of tissue damage might be of relevance in selection of individualized therapeutic strategies. PET can be utilized in pilot trials for selection of patients who might benefit from particular therapeutic strategies and can be used to evaluate therapeutic effects in an experimental setting which then might form the basis for large clinical trials (Heiss *et al* 1998).

Kitani *et al* (1987) presented the use of PET with radioactive ^{15}O to compare CBF and regional cerebral oxygen consumption in a group of patients with CO poisoning and patients with acute cerebral ischemia treated by HBO. The findings proved to be a useful guide to the prognosis of HBO as well as to HBO treatment. The results suggested that HBO confers protection against ischemic brain damage. PET is expensive, not easily available, and its use is limited.

SPECT (Single Photon Emission Computed Tomography)

This is a useful tool for assessing the effect of HBO in neurological disorders. SPECT uses principles similar to those of PET but the radioligands decay to emit only a single photon. Conventional brain scanning uses highly polar radiopharmaceuticals such as ^{99m}Tc-pertechnitate. These tracers do not penetrate the normal brain but can cross a damaged BBB and appear as focal areas of increased activity in the region of the brain pathology. The long half-life of these tracers is a disadvantage. A radiolabeled lipid-soluble amine, Iofetamine (^{123}I-IMP) is an indirectly agonistic amphetamine derivative that readily crosses the BBB, is taken up by the functioning neurons, and its distribution in the brain mirrors that of the CBF. Brain activity is observed 30 s after injection (Holman *et al* 1983) and can be detected for up to 4–5 h. The areas of the brain affected by stroke show a reduced uptake of the tracer material and can be used to document the pathophysiology in stroke patients (Raynaud *et al* 1987). This test has been used in many of the studies to monitor the natural recovery and effect of therapy on stroke patients. The ^{123}I SPECT scan is ideal for evaluating the effect of HBO on stroke patients for the following reasons:

1. It is more widely available and less costly than PET scan. Any nuclear medicine facility with a gamma camera has the capability for this procedure.
2. There is a short waiting period for uptake of the isotope. The procedure can be integrated with HBO sessions and a post-HBO scan can be done with the same injection as for the pre-HBO scan.
3. This scan documents the area of cerebral infarction as diminished uptake, and any improvement is easy to document by noting the increased uptake of the tracer.
4. Improvement in the scan can be correlated with clinical improvement, which is not always the case when CT scan is used.
5. Recent work by Raynaud *et al* (1989) has indicated that two areas, the central area representing the infarct core and the peripheral area or the peri-infarct zone, may be differentiated during the subacute period of the stroke. The pathophysiology and outcome are different in these two areas, and studies of subacute infarction should refer to the area involved. The central area is the site of wide variations of rCBF and IMP uptake during the development of necrosis. The peripheral area, with its slight decrease in rCBF and IMP uptake without morphological changes, appears stable because it is present early after stroke and may persist for years. Knowledge of the spontaneous changes in rCBF and IMP uptake in these two areas during the subacute period will facilitate the evaluation of new treatment for cerebral infarction.
6. SPECT performed within 24 hours may be helpful in predicting outcome in clinical practice and in appropriately categorizing patients into subgroups for clinical trials (Laloux *et al* 1995).

IMP is no longer available commercially and its use has been replaced by ^{99m}Tc in hexamethylpropyleneamine

oxime (HM-PAO). In HM-PAO scans half of the dose of the tracer is given initially and the brain is imaged. The patient is then exposed to HBO for 60 to 90 min and the other half of the dose is given following by brain imaging. Alternatively, the second scan using full dose HM-PAO can be done at a later time, 24 to 48 h after the initial scan (also using full dose) followed by the HBO session. The difference between the two scans helps to determine whether there is potentially recoverable brain tissue present (Neubauer & Gottlieb 1993). Hypometabolic but potentially viable areas in the brain can be identified using HM-PAO SPECT in conjunction with HBO. Data from Neubauer *et al* (1992) supports the hypothesis that idling neurons are capable of reactivation when given sufficient oxygen. Changes in tracer distribution after HBO may be a good prognostic indicator of viable neurons. Recoverable brain tissue can be identified and improved with cerebral oxygenation using HBO and the results can be documented with SPECT (Neubauer & James 1998)..

One study has used archival data to compare 25 older and 25 younger subjects who were investigated with SPECT scans for evaluation of HBO for chronic neurological disorders: pretherapy, midtherapy, and posttherapy (Golden *et al* 2002). ANOVAs using the SPECT scans as a within subjects variable and age as a between subjects variable confirmed the hypothesis that the cerebral measures all changed but that the cerebellar and pons measures did not. Post-hoc *t*-tests confirmed that there was improvement in blood flow from the beginning to the end of the study. An age effect was found on only two of the five measures; however, there were no interactions. Analysis by post-hoc *t*-tests showed that the younger group had higher blood flows, but not more improvement than the older group. The results provided the first statistical research data to show the effectiveness of HBO in improving blood flow in chronic neurological disorders.

Use of HBO in Miscellaneous Neurological Disorders

The use of HBO in significant neurological disorders is described in separate chapters that follow. A few miscellaneous indications, particularly benign intracranial hypertension and peripheral neuropathy, that do not fit into these are described here.

HBO in the Treatment of Benign Intracranial Hypertension (BIH)

This syndrome is characterized by prolonged raised intracranial pressure without ventricular enlargement, focal neurological signs, or disturbances of consciousness and intellect. The most frequent symptoms are headaches, diplopia, and impairment of visual acuity. It occurs most frequently in obese women in the child-bearing period. The cause is not known, but the following explanations have been considered for the pathophysiology of BIH:

1. An increased rate of CSF formation
2. Sustained increase in intracranial venous pressure.
3. A decreased rate of CSF absorption by arachnoid villi apart from venous occlusive disease.
4. Increase in brain volume because of an increase in cerebral blood volume or interstitial fluid. There is histological evidence for cerebral edema

Diagnostic criteria of BIH are as follows:

1. Signs and symptoms of raised intracranial pressure.
2. No localizing neurological signs in an awake and alert patient except for abducent palsy.
3. Documented elevation of intracranial pressure (250 mm H_2O).
4. Normal CSF composition.
5. Normal neuroimaging studies except for small ventricles and empty sella turcica.

Various methods are used for lowering the intracranial pressure, including lumbar punctures, dehydrating agents such as mannitol, diuretics, and corticosteroids. Ventriculo-peritoneal shunts have been performed frequently and afford good relief from headaches, but the small ventricles present a technical difficulty in inserting catheters into this space. The main concern is preservation of vision and the preferred operation is fenestration of the sheath of the optic nerve.

Luongo *et al* (1992) treated various groups among 53 patients with BIH by several methods. Eight of the patients were treated only by HBO at 2 ATA, daily for 15 days. In all patients a gradual disappearance of signs and symptoms of elevated intracranial pressure was observed. However, the intracranial pressure was elevated again after discontinuation of HBO. The mechanism of this effect is not clear, but reduction of CSF production and an anti-edema effect of HBO are possible explanations. Further studies are required to assess this therapy for BIH but to date there have been no further publications on this topic.

Peripheral Neuropathy

Clioquinol-induced damage to the peripheral nerves has been shown to be decreased in animals treated using HBO as compared with controls (Mukoyama *et al* 1975). The authors speculated that oxygenation might prevent the death

of intoxicated neurons in the spinal root ganglia and resuscitate them, as well as accelerate the sprouting and regeneration of nerve fibers in the peripheral part. They indicated that HBO may be useful in the treatment of peripheral nerve lesions.

Peripheral neuropathy in streptozotin-induced diabetic rats has been shown to be partially reversed by HBO treatment (2 ATA, 2 h, 5 days/week) for 4 weeks (Low *et al* 1988). There was enhancement of nerve energy metabolism in the HBO-treated animals as compared with the control animals with similar lesions, not treated by HBO.

Neretin *et al* (1988), after a review of their experience in treating polyradiculoneuritis with HBO have concluded that: "The results of clinico-electromyographic examinations point to a sufficiently high effectiveness of hyperbaric oxygenation in polyradiculoneuritis and permit its inclusion into the multimodality treatment of the latter. Hyperbaric oxygenation (HBO) accelerates regression of neurological disorders, with the predominant effect on the severity of motor and autonomic-trophic disturbances. HBO makes it possible to reduce the doses of glucocorticoids and the period of treatment and hospitalization of patients."

HBO in Susac's Syndrome

The Susac syndrome consists of a clinical triad of encephalopathy, loss of vision, and hearing defects (Jain 2003f). It is caused by microangiopathy of unknown origin affecting the small arteries of the brain, retina, and cochlea. This rare disorder, with 75 cases documented in the literature, affects mainly young women. The course of the illness is self-limiting. The deficit of visual acuity is caused by occlusion of tributaries of the retinal artery. The auditory defect is bilateral and symmetrical, and particularly affects medium and low frequencies. NMR is of great diagnostic value, showing multiple lesions in the gray and white matter. Li *et al* (1996) were the first to report HBO treatment with favorable outcome in a young woman with Susac syndrome who presented on two separate occasions with visual acuity loss from a recurrent branch retinal artery occlusion. Meca-Lallana *et al* (1999) reported the case of a young woman who presented with psychiatric symptoms and migraine followed by clinical encephalopathy and acute/subacute coma. There were also visual and auditory deficits. The patient responded to systemic treatment with cortico-steroids and HBO. The encephalopathy resolved in a few days and 2 months later she had resumed her former daily activities. Treatment with HBO was considered to have definitely reduced visual sequelae in this case. In another similar case, combination of intravenous steroids and HBO reduced the ischemic lesions (Cubillana Herrero *et al* 2002).

Cerebral Malaria

Cerebral malaria (CM) is a syndrome characterized by neurological signs, seizures, and coma. Despite the fact that CM presents similarities with cerebral stroke, few studies have focused on new supportive therapies for the disease. An experimental study has explored the use of HBO for CM. Mice infected with *Plasmodium berghei* ANKA (PbA) were exposed to daily doses of HBO (100% oxygen at 3 ATA for 1–2 h per day) before or after parasite establishment (Blanco *et al* 2008). Cumulative survival analyses demonstrated that HBO therapy protected 50% of PbA-infected mice and delayed CM-specific neurological signs when administrated after patent parasitemia. HBO reduced peripheral parasitemia, expression of TNF-α, IFN-γ and IL-10 mRNA levels and percentage of gammadelta and alphabeta $CD4^+$ and $CD8^+$ T lymphocytes sequestered in mice brains, thus resulting in a reduction of BBB dysfunction and hypothermia. These data indicate that HBO treatment could be used as supportive therapy, perhaps in association with neuroprotective drugs, to prevent CM clinical outcomes, including death.

Neurological Disorders in Which HBO Has Not Been Found to Be Useful

This section presents historical information on several diseases where HBO has been used. Dementia and neuromuscular diseases are two examples. There have been no further studies done to prove the efficacy of HBO in these areas, and at present HBO cannot be recommended for these conditions except in the few cases noted.

Dementia

Dementia is defined as "a global impairment of higher cortical function, including memory, the capacity to solve problems of everyday living, the performance of learned motor skills, the correct use of social skills and the control of emotional reactions, in the absence of gross clouding of consciousness."

The causes of dementia are varied, and no single mode of treatment is applicable uniformly to the varied causes. HBO has been used as a treatment for dementia. Interest in the use of hyperbaric environments for central nervous system pathology has existed since the report by Corning (1891). McFarland (1963) theorized that sensory and mental impairment in the elderly are due to diminished availability or utilization of oxygen in the nervous system.

Various clinical trials of HBO in dementia are shown in Table 17.5.

Table 17.5
Clinical Trials of HBO in Dementia

Authors and year	Indication	Patients (n)	Technique	Results and comments
Jacobs *et al* (1969)	Cognitive deficits of the elderly	80	HBO sessions of 390 min each daily using 100% oxygen at 2.5 ATA 5 patients were used as controls, breathing 10% oxygen + 90% nitrogen so that their pO_2 did not rise above prepressurization levels	Psychological improvement in all patients which persisted beyond the of oxygen tension
Jacobs *et al* (1972)	Cognitive deficits in the elderly	52 incl. the previously reported 8	as above Psychological testing EEG. Cerebral blood flow. Blood and CSF pO_2 pCO_2 and lactate and pyruvate	Patients divided into 4 groups of 13 each. Group I, above study of 1969; Group II, Psychological evaluation performed 72 h after the last HBO treatment; Group III, evaluation performed 1 week after the last treatment; Group IV, evaluation performed 10 days after the last treatment. Improvement in mental function in all groups but was the in Group IV
Ben-Yishai and Diller (1973)	Cognitive deficits in the elderly	?	Same technique as that of Jacobs *et al* (1969) but combined with cognitive training	Cognitive improvement in patients persisted 3 months after treatment
Edwards and Hart (1974)	Decline of mental function	20	HBO at 2 ATA (100% oxygen) 15 daily sessions of 2 h each	Maximum improvement in those patients whose memory quotient was 70–100 before the treatment Little or no improvement above and below those values
Harel *et al* (1974)	Senile dementia	8	?	No significant effect of HBO on CBF or cerebral metabolism which was already reduced
Imai (1974)	Memory disturbance of presenile dementia, chronic alcoholism, cerebrovascular disease and CO poisoning	?	HBO at 1.5 ATA (100% oxygen) 15 daily sessions of 2 h each	Improved performance on psychological testing
Thompson *et al* (1976)	Cerebrovascular disease and cerebral atrophy	21	100% oxygen at 2.5 ATA for 90 min twice daily for 15 days	Double-blind study. No effect of HBO on psychological function, EEG or CFF
Ben-Yishai *et al* (1978)	Cognitive deficits in the elderly	?	Same as in 1973 study by the author except that the control group received only cognitive training	No difference between the combined HBO treatment and the cognitive treatment alone. The latter was considered to be responsible for improvement in 1973 study

Considerable criticism followed publication of the study by Jacobs *et al* (1972), some of which can be summarized as follows:

1. Lack of oxygen supply to the brain was the main reason for using hyperoxygenation therapy. According to Sokoloff (1966), however, the proportional relationship between oxygen supply and oxygen consumption is near normal in patients with chronic brain syndrome.
2. The study failed to sort out the various reversible psychotic states that need to be differentiated from senility.
3. The validity of some of the psychological tests used was questioned by discussants of the paper. There was paucity of measurement..
4. There was no randomization regarding inclusion in the study or division into groups.
5. A wide variety of symptoms and signs were manifested by the patients and they belonged to a large number of diagnostic categories. Such a heterogeneous group would make the interpretation of the most precise and the most concrete results difficult.
6. The treatment is time-consuming and expensive. Elderly patients may dislike it or refuse it. The results are short-lived.
7. The placebo treatment of five patients with 10% O_2 + 90% N_2 is dangerous in elderly patients. Thomas *et al* (1976) studied the interaction of hyperbaric nitrogen and oxygen mixtures on behavior in rats. Raised oxygen

pressure modulated and interacted with the narcotic effect of nitrogen on behavior – an initial increase in response rate was followed by decline.

Raskin *et al* (1978) assigned 82 elderly subjects with significant cognitive impairment to treatment with HBO, hyperbaric air, normobaric air, or normobaric oxygen. Treatment consisted of two 90-min sessions per day for 15 days. Psychological evaluation immediately after treatment and 1, 2, 3, and 8 weeks later did not reveal any enhanced cognitive function in experimental subjects (who received normobaric or hyperbaric oxygen) as compared with controls (who received normobaric or hyperbaric air). Kron *et al* (1981) reviewed the published literature on the application of HBO in senile dementia and their own experience. They made a number of observations about the difficulties encountered in evaluating this therapy's usefulness in treating mental dysfunction, and came to the following conclusions:

1. The definitive study on the efficacy of HBO in the treatment of senile dementia has yet to be performed.
2. The gross discrepancies in the published reports may be attributed to inadequate design of experiments, poor research methodologies, and great variability in the clinical research populations. They noted that many of the psychological test instruments used in these studies lack the precision and reliability necessary to demonstrate small changes in mental capacity in response to therapeutic intervention. Further, because of logistical and safety considerations, the administration of HBO does not lend itself to well-controlled double-blind studies. Also, there is lack of agreement on the etiology and diagnosis of mental dysfunction in the aged, contributing to the difficulty in determining which patients may benefit from HBO therapy.

Schmitz (1977, 1981) evaluated HBO therapy for senility and concluded:

"At the present time, there is no basis for claiming that HBO is beneficial in reversing senility or any other central nervous system deficit that occurs in the aged . . . the only indication for HBO therapy in senility would be as a part of research study . . . Subjecting older people to hyperbaric environments, even if the risks are minimal, is contraindicated."

HBO in the Management of Neuromuscular Disorders

Muscular Dystrophy. The muscular dystrophies are hereditary degenerative disorders of the muscles. Most of the theories of the etiology of muscular dystrophy relate to the neuromuscular system. According to other theories, however, the primary disturbance is in the vascular supply to the skeletal muscles; blood flow is reduced to the exercising muscles. Biochemical abnormalities in the muscles may either be the cause or the effect of muscle degeneration.

Hirotani and Kuyama (1974) treated ten patients with muscular dystrophy using HBO. Five were of the Duchenne type and five of the limb-girdle type; 100% oxygen was used at 2 ATA daily and 19 sessions were completed in 3 weeks. Along with this an intravenous infusion of fructose + adenosine triphosphate (cytidine phosphatase choline), reduced glutathione, and sodium carbazochrome sulfanate was given. As controls, three patients with muscular dystrophy of the Duchenne type were subjected to HBO without the intravenous medications. There was improvement in muscle strength in the group given HBO plus medications but none in the group given HBO alone. The effect, however, was transient, and 5 years later there was no difference in condition between the controls and the treated group. The authors concluded that HBO in combination with ATP and CDP-choline may be effective in the symptomatic relief of muscular dystrophy.

Badalian *et al* (1975) summarized their experience in treating 306 patients with muscular dystrophy during different phases of the disease. The treatment was carried out keeping in mind the disturbance of protein metabolism and decreased permeability of the cell membranes. The treatment consisted of HBO with anabolic hormones, amino acids, vitamins, muscle electrostimulation, and so forth. There was no clinical progression of symptoms in 3 years of follow-up.

There has been no further progress in this area during the past 20 years and there appears to be no rational basis for the use of HBO for this indication. Considerable advances are taking place in molecular genetics and gene therapy for muscular dystrophy is a reasonable possibility.

Myasthenia gravis. Myasthenia gravis is an autoimmune disease. A specific antibody against the acetylcholine receptor is found in 85% of the patients, and the major component of this antibody is IgG.

Li *et al* (1987) carried out a controlled trial of HBO in 40 patients with myasthenia gravis; one group was treated with HBO alone and the other with HBO plus steroids. The rate of improvement with HBO alone was 88.9%, with HBO plus steroids it was 86.5%, and in the control group treated by steroids alone, it was 45%. IgA and IgM were reduced in the HBO group, indicating an immunosuppressive effect.

There has been no further work done in this area during the past decade. The immunosuppressive effect of HBO has not been demonstrated conclusively. There appears to be no justification for using HBO in myasthenia gravis at present.