



Brain Disorders/Neurological

Hyperbaric Oxygen Therapy In Global Cerebral Ischemia/Anoxia And Coma

Bullet points

Pathophysiology of global ischemia/anoxia and coma

- Ischemic/anoxic encephalopathies
- Rational basis of HBO therapy
- Review of animal experimental studies
- Review of human clinical studies
- Case studies

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1 INTRODUCTION

For a discussion of the effectiveness of hyperbaric oxygen (HBO) therapy in global cerebral ischemia/anoxia and coma, we define HBO as a medical treatment that uses high pressure oxygen as a drug by fully enclosing a person or animal in a pressure vessel and then adjusting the dose of the drug to treat pathophysiologic processes of the diseases. Like all drugs, dose of HBO is crucial and should be customized to each patient's response. It is dictated by the pathological target and is determined by the pressure of oxygen, duration of exposure, frequency, total number of treatments, and timing of the dose in the course of the disease. As diseases and their pathologies evolve, different doses of HBO are required at different times. In addition, patients have individual susceptibility to drugs, manifest side-effects and toxicity. Unfortunately, the ideal dose of HBO in acute or chronic global ischemia/anoxia and coma is unknown. The studies reviewed below suggest higher pressures (2 ATA or higher) and lesser numbers of treatments very early in the disease process whereas lower pressures (2 ATA or lower) and a greater number of treatments have been used as the brain injury matures. While this general trend seems justified, the absolute or effective pressures delivered to the patients in these reports may be slightly less than what is stated since many studies do not specify the HBO delivery system that was employed. For example, an oxygen pressurized chamber has an effective HBO pressure equal to the plateau pressure administered during the treatment, whereas an air pressurized chamber in which oxygen is administered by aviators mask can achieve a far lower effective HBO pressure, depending on the fit of the mask and the amount of its air/oxygen leak. In the later cases, the dose of oxygen is less. This concept is particularly important when analyzing the studies in this chapter performed prior to the late 1980's when the aviator mask dominated delivery systems in multiplace chambers.

In reviewing the data in this chapter, it is surprising that HBO has not enjoyed widespread use for neurological diseases in the United States. This has been partly due to institutional reservations and overt therapeutic nihilism for neurological injuries, both of which are presently waning. To assume that HBO could have efficacy and benefit when liberally applied to various "accepted" indications, yet have none in the great majority of neurological conditions is perplexing. After all, the brain is enclosed within the same body in the same pressure vessel and is exposed to the same elevated oxygen pressure. To justify this distinction, one would have to postulate that an entire set of pathophysiological processes of brain that are insensitive to HBO and distinct from those in the rest of the body's organ systems which are sensitive to HBO and to which we routinely apply HBO. This is illogical and unlikely. Such reasoning is indefensible when one considers the "accepted" neurological indications include carbon monoxide poisoning, brain decompression sickness, cerebral air embolism, brain abscess, and cyanide poisoning. We conclude that HBO should benefit other hypoxic/ischemic conditions of the brain, provided the dose is correct, i.e. target specific.

Other reasons for non-recognition of HBO in neurological conditions concern methodologies. The standard for proof in scientific medicine has been the randomized prospective controlled double-blinded clinical trial. While some of the studies in this chapter meet this rigor (except for double-blinding), many do not. Some are

randomized, prospective, and controlled and thus exceed the quality of studies used to sanction reimbursement for some HBO indications. Other studies are uncontrolled series, case-controlled, or individual cases. All of this clinical data, in conjunction with the animal data, makes a strong case for at least attempting HBO in what are otherwise untreatable conditions with debilitating, tragic, and expensive outcomes, especially when the visual medium is used to prove single-case causality (Kiene 1998; Harch 1996A). In addition, case-controlled series with chronic neurological maladies make powerful statements of efficacy from the statistical (Glantz 1992) and logical perspectives where the counterargument of placebo effect is minimized (Kienle 1996). If these considerations are kept in mind when analyzing this chapter, it appears that the bulk of data is solidly in favor of a beneficial effect of HBO in global ischemia/anoxia and coma.

2 PATHOPHYSIOLOGY

Effect of global ischemia/hypoxia on the brain has been discussed in Chapter 5. Oxidation of glucose is the primary energy source for the brain. Deprivation of oxygen deep psychological unresponsiveness in 8 seconds while glucose and energy stores take a few minutes to exhaust (Plum and Pulsinelli 1992). Global deprivation of oxygen delivery can be achieved by reduction in blood flow (ischemia), oxygen (hypoxia/anoxia), or both (hypoxic or anoxic ischemia). Unfortunately, clinical syndromes and animal models are rarely pure and often result from combinations or sequences and varying degrees and durations of hypoxia/anoxia and ischemia. Since the insult, oxygen deprivation, is similar whether by lowered blood flow or oxygen content the two are often considered as a single type of insult and this concept will be followed in this chapter.

Global ischemia/anoxia is a severe transient insult to the brain that causes a stereotypic pathophysiology characterized by reperfusion hyperemia followed by progressive ischemia which is often heterogeneous (Safar 1986; Dirnagl 1993). The extent of injury is governed by complex interplay and patterns of systemic and local respiratory and circulatory function and selective vulnerability of cells (Meyers 1979) with both immediate and delayed cell death (Cormio 1997). The deterioration of blood flow and late cell death occur in the absence of microvascular disruption by formed blood elements unless the global ischemia is prolonged (Dirnagl 1993) in which case both cellular and non-cellular mechanisms may be responsible. The mechanisms of eventual neuronal energy failure are poorly understood (Siesjo and Katsura 1995).

Coma, on the other hand, is a neurological state resulting from a wide variety of cerebral insults that is caused by diffuse disruption (functional or anatomical) of the bilateral cerebral cortices, proximal brainstem (reticular activating system), or both (Rossor 1993). Coma is characterized by an alteration in the level of awareness, ranges from mild somnolence to deep coma, and is graded on a number of scales, the best known of which is the Glasgow Coma Scale (Teasdale and Jennett 1974). In the studies reviewed below, coma usually refers to the more severe end of the continuum: unresponsiveness, posturing, neurovegetative signs, however, a number of studies are unclear about the exact level of coma.

3 ISCHEMIC/ANOXIC ENCEPHALOPATHIES

4 RATIONAL BASIS OF HBO THERAPY

HBO in acute global ischemia/anoxia is complicated by a lack of knowledge of the exact pathological targets and their oxygen sensitivity. It has been postulated that post-ischemic hypoperfusion may be a neurogenic reflex (Dirnagl 1993) and/or characterized by a block in the transduction of physiologic stimuli and hence protein synthesis (Siesjo 1981). Assuming short-lived (minutes) global ischemia/anoxia and cell death independent of the microcirculation (Dirnagl 1993), positive effects of HBO under these conditions must be due to effects on hypoxia, cellular energy metabolism, ion homeostasis, membrane integrity, gene induction, and/or a plethora of as yet unidentified targets. The dramatic effect of even one HBO exposure on recovery of brain function, as indicated in many of the studies below, implies a powerful on/off drug effect that simultaneously quenches a degradatory process and energizes the cell. It is easy to envision HBO acting at some or multiple points of blockade in the above mentioned reflex or at a physiologic impasse. In the chronic state, a similar action of a single HBO on some of these targets may be responsible for the awakening of

idling neurons (Neubauer 1990), and when delivered repetitively considered a signal transducer (Siddiqui 1995). The signal transduction mechanism is inferred in multiple other non-cerebral HBO wound models where trophic tissue changes result from repetitive HBO (HBO Committee Report 1996), suggested in a preliminary experiment of HBO in a rat model of chronic traumatic brain injury (Harch 1996B), and reaffirmed in a controlled human trial of HBO in chronic traumatic brain injury directed by Harch in Texas (Barrett et al 1998). Future studies should be focused on elucidating the molecular effects of HBO in global cerebral ischemia/anoxia.

With prolongation of global ischemia/anoxia the microcirculation is disturbed (Dirnagl 1993) and the pathophysiology begins to resemble that in acute traumatic brain injury (Cormio 1997): lipid peroxidation, edema, arterial spasm, cellular reperfusion injury, and anaerobic metabolism in the setting of penumbral lesions (Cormio 1997). HBO has been shown to have positive effects on all of these: ischemic penumbra (Neubauer 1990; Neubauer 1998; Barrett et al 1998), cerebral edema (Sukoff et al 1982), arterial spasm (Kohshi 1993), anaerobic metabolism (Holbach 1977 D), and peroxidation/cellular reperfusion injury (Thom 1993A). This last HBO sensitive pathophysiological target is most exciting since it seems to be a generic tissue-independent HBO effect. In a carbon monoxide rat model Thom (1993 B) showed a powerful inhibitory action of HBO on white blood cell mediated brain lipid peroxidation when delivered 24 hours before the poisoning or 45 minutes after removal from carbon monoxide. Zamboni (1993) demonstrated a similar finding in a four hour global ischemic rat gracilis muscle model, using intravital microscopy. This HBO inhibition of WBC=s is inferred in brain decompression sickness and cerebral air embolism (Harch 1996 C) when one combines the Dutka (1989) and Helps (1991) data, which implicates WBC=s in the pathogenesis of these disorders, with Thalmann=s (1990) review which shows a 90% single treatment cure rate in decompression sickness when hyperbaric recompression is delivered within the first 1-2 hours of injury. Similarly, the data of Bulkley (1977) and Engler (1986) that document a WBC-mediated pathogenesis in cardiac reperfusion injury, in conjunction with the Thomas (1990) tissue plasminogen activator/HBO/acute myocardial infarction dog model and the congruent human study of Shandling (1997) strongly suggest an HBO directed action on cellular reperfusion injury, among other effects. All of the above actions of HBO on the pathophysiology in acute traumatic brain injury should sum to provide a beneficial effect. In fact, such is the case as a review of the studies in Table 18-2 shows a convincing argument for the use of HBO in acute severe traumatic brain injury. Similarly, If global ischemia/anoxia is prolonged or incomplete, e.g. unsuccessful hanging, microcirculatory disturbances are incomplete. Under these circumstances, HBO-induced inhibition of cellular reperfusion injury may partly explain the very positive results of the studies listed in Tables 18-1 and 18-2.

For HBO to be effective in coma it must be directed at diffuse targets in the bilateral hemispheric gray and white matter, the brainstem, or both. Acutely, regardless of the nature of the targets, e.g. microcirculatory, non-vascular, cellular, or other, HBO can conceivably act equally effectively on the hemispheres, brainstem, or both. As the pathology progresses to anatomic damage and eventually to penumbral lesions, a significant HBO effect on hemispheric coma is very unlikely because of the large tissue volumes and low ratios of umbra to penumbra. Smaller tissue volumes are favored such that brainstem coma would be expected to have better results. This is suggested by the positive HBO data in the large traumatic mid-brain report of Holbach (1974 B), the brainstem contusion subgroup of Artru (1976 B), and the coma patients of Heyman (1966) and Neubauer (1985 A) In all of these clinical trials, a recovery of just a few millimeters of reticular activating system can translate into far-reaching effects in the hemispheres, e.g. awakening. Additional work will be necessary to confirm this hypothesis.

In chronic global ischemia/anoxia and coma the pathological targets become more speculative. The ischemic penumbra (Astrup 1981) argument of Neubauer (1990) and sympathetic hibernating myocardium concept of Swift (1992) remain, but given the numbers of treatments reported below the element of time enters the equation and implies a trophic effect. This effect, which could include stimulation of axon sprouting, or possibly an alteration or redirection of blood flow as suggested above (Harch 1996 B), or both, may be indiscriminantly effective on the final common pathway of a variety of brain injuries, given the diversity of reports (Neubauer 1998; Harch 1994 A,B,C; Harch 1996; Keim 1997; Myers 1995 a) in addition to the studies listed below. While the net HBO result appears uniform, the biochemical, molecular, cellular, and anatomic complexities of this phenomenon will need to be developed in the future.

5 REVIEW OF ANIMAL EXPERIMENTAL STUDIES

A review of the studies listed in Table 12-1 leads to the conclusion that HBO is beneficial in acute global ischemia/anoxia regardless of treating pressure, frequency, duration, number of treatments, or time to onset of HBO post insult. Twelve of the fourteen studies are positive, one study did not evidence a benefit, and the last study was a normobaric study, yet no clear consensus emerges as to ideal HBO parameters in either complete or incomplete global ischemia/anoxia. In the complete models, Moody (1970) showed a nearly 50% reduction in mortality without the benefit of artificial ventilation using a prolonged 2 ATA exposure (four hours). Kapp (1982) measured EEG recovery time and CSF lactate change, demonstrating significant improvement with a lower pressure, 1.5 ATA, for a prolonged 2.5 hours. Ruiz (1986) was the sole insignificant result with a 2 ATA/1 hour exposure, but this lack of efficacy may be partially explained by hemodilution with hetastarch prior to HBO. Yatsuzuka (1990) generated a significant decrease in ICP and oxidative stress metabolites with a 2 ATA/170 minute staged protocol. At higher pressures, Takahashi (1992) and Iwatsuki (1994) who used 3 ATA each and Mink (1995 A, B) who used 2.8 ATA, statistically significant positive results on survival, neurological recovery, and various physiological or metabolic measures were obtained. The study by Mink (1995 B) had conflicting results with a simultaneous decrease in brain vascular permeability and blood flow while somatosensory evoked potentials were unchanged. This implies concomitant beneficial and detrimental effects which may be explained by the prolonged (125 minute) exposure at high pressure (2.8 ATA). In 6 of the 8 studies the benefit of HBO was generated with one treatment, and in the other 2 studies with 3 treatments.

The results are similarly impressive and uniformly positive in the group of incomplete global ischemia/anoxia experiments. As in the complete models no consensus emerges as to best HBO pressure, duration, frequency, number of treatments, or time to intervention. Shiokawa (1986) demonstrated an improvement in survival with 2 ATA HBO for only 30 minutes, with best results at three hours post-insult as opposed to one hour. Weinstein (1986) achieved an 84% reduction in mortality with a 15 minute 1.5 ATA treatment and Grigoryeva (1992) demonstrated a superior effect of 1.2 ATA/30 minutes over 2 ATA/60 minutes on survival and preservation of neuronal transcription. Kondo (1996), meanwhile, proved a beneficial effect with repetitive HBO at 2 ATA/60 with preservation of hippocampal neurons and decrease in heat shock proteins; there was a greater effect when the HBO was started at six hours instead of 24 hours. HBO prevented delayed cell death without oxygen toxicity. Lastly, the study by Mickel (1990) showed that normobaric oxygen (NBO) gave mixed results: increased production of white matter lesions while sparing cortical neurons. Despite the inability to establish clear guidelines regarding HBO parameters in incomplete global ischemia/anoxia, the results of HBO treatment have been uniformly positive.

Importantly, almost all of the above studies initiated HBO within three hours of insult and evidenced positive results were obtained with a maximum of three treatments and in most cases one. The two exceptions to this were the Kondo (1996) experiment which began HBO at either 6 or 24 hours (a 2-hour group was used for a separate histological oxygen toxicity examination) after insult and continued treatment to a total of 14 or 35 treatments, and the Wada (1996) experiment which used pre-ischemia/anoxia HBO a maximum of 5 times. Interestingly, despite the prolonged course of HBO exposure in Kondo's study, no overt oxygen toxicity was delineated. The near uniform success of all of the above experiments suggests that hyperacute (0-3 hours) intervention is the most important factor in positive outcomes with the absolute HBO pressure of less importance. The majority of these studies, however, used pressures greater than or equal to 2 ATA and only one Grigoryeva (1992) compared HBO pressures, 1.2 vs. 2 ATA, and found the lesser pressure to be superior. As a result, no firm conclusion can be drawn regarding an ideal HBO pressure.

6 REVIEW OF HUMAN CLINICAL STUDIES

The human HBO experience in cerebral ischemia/anoxia and coma is extensive, complicated, incomplete at times, and spread across multiple medical conditions. Despite the heterogeneous group of studies, the data shows a beneficial effect of HBO, especially in the large series and particularly in traumatic brain injury (TBI). To facilitate review of the literature all reports have been categorized somewhat arbitrarily by amount of time delay to initiation of HBO. Some reports span multiple categories and are unclear about exact times of HBO intervention. In these a rough estimate was attempted based on the implications and inferences in the study,

and references to companion articles. The four categories are hyperacute (≤ 3 hours post insult), acute (4-48 hours post), subacute (49 hours to 1 month post), and chronic (greater than 1 month after insult).

The studies of Mathieu (1987), Voisin (1973), Hutchison (1963), Kohshi (1993), Shn-Rong (1995), Larcan (1977), Viart (1969), Hayakawa (1971) Saltzman (1966), Ingvar (1965), address the hyperacute period of global ischemia/anoxia and coma. The most clearcut of these are the studies reported by Mathieu (1987) and Hutchison (1963). Mathieu used HBO in 170 cases of unsuccessful hanging, 34 of whom received NBO and 136 HBO, and found statistically significant greater recovery without sequelae if HBO was delivered <3 hours post hanging (85 vs. 56%). Worse coma required more treatment, but even the worst only averaged 3.9 HBO=s. The 34 NBO patients were those with minor neurological problems; only patients with impaired consciousness received HBO. The pressures used in this study was 2.5 ATA/90 minute session. In their paper they cite their previous experience with unsuccessful hanging (Voisin 1973) which compared NBO to HBO with a recovery both quicker and of better quality in the HBO group. The Hutchison (1963) paper reported HBO in neonatal asphyxia with 79% resuscitation; 54% were discharged from the hospital. HBO was used at 1-3 ATA in this study and treatment was initiated 2-38 minutes after birth.

The other papers in this group imply hyperacute and acute treatment or do not state the time of HBO intervention. Kohshi (1993) initiated HBO as soon after onset of symptomatic vasospasm in subarachnoid hemorrhage post-neurosurgical comatose patients using 2.5 ATA and an average 10 treatments which decreased subsequent progression to infarcts. Shn-Rong (1995) applied HBO in 336 cases of cardiac arrest, near-drowning, unsuccessful hanging, electrocution, carbon monoxide, TBI, and other toxic and asphyxial coma patients, implying at least some treatment hyperacutely, with 75-100% recovery rates at 2-2.5 ATA. Best results were with earlier treatment; delays to treatment required greater numbers of HBO=s. In the Larcan (1977) paper it appears that only one patient was treated in the hyperacute period with both urokinase and HBO. The result was excellent and the best in their study, but the effect can't be necessarily attributed to HBO alone. The Viart (1969) paper does not mention time to HBO in the three cases of infant hepatic coma, but the profile of HBO seemed extreme since one patient died of pulmonary oxygen toxicity with 36 hours of HBO and the other two experienced cardiac conduction abnormalities during HBO, an extremely rare complication of HBO. Despite the apparent complications, all three patients had normalization of consciousness, EEG, and neurological exam with HBO, two permanently and one transiently. Hayakawa (1971) performed a single 2ATA/1 hour HBO immediately after surgery on four comatose brain tumor patients and nine acute traumatic brain injury (TBI) patients. The time to initiation of HBO was not stated but was probably <3 hours in the post-operative patients. The authors found three patterns of CSF pressure and clinical response that corresponded to differential effects on normal and injured brain; HBO decreases edema in injured brain and produces edema in normal brain. Most patients had an initial decrease of CSF pressure with HBO and then return to pre-HBO level at the end of HBO. The patients with a major decrease in CSF pressure during HBO had remarkable clinical improvement and a mild neurological deficit. If there was no change in CSF pressure the reverse was true. The duration of the HBO neurological improvement was not mentioned.

The coma case reported by Ingvar (1965) showed a transient rapid awakening of a patient with failing circulation but died at the conclusion of a 2-2.5 ATA/1.5-2.5 hour HBO. This could be the natural history of the patient's disease and/or an oxygen toxicity effect. The other single case report was a dramatic near-complete cure of a suspected air embolism patient treated with a 2.36 ATA/5 hour session of HBO (Saltzman 1966). This treatment is similar to the United States Navy Treatment Table VI for air embolism and serious decompression sickness and may explain the near-complete cure without oxygen toxicity after a higher pressure very prolonged oxygen exposure. The preponderance of data in these nine HBO studies (plus the Voisin reference) and 659 global ischemia/anoxia and coma patients is strongly positive with pressures greater than or equal to 2 ATA and a minimum of 1-7 treatments. The effect of lower pressures of HBO can't be stated since no studies were performed at <2 ATA.

Twenty-nine studies fall into the second or acute category. Once again the preponderance of data is positive either transiently or permanently, regardless of the etiology of coma. Kohshi (1993), Mathieu (1987), Voisin (1973), Shn-rong (1995), and Viart (1969) papers span this and the hyperacute period and were already reviewed. The Larcan (1977) study had one patient in the hyperacute period mentioned above and 35 coma

patients in the acute period. HBO appeared to have no effect and, in fact, was no different from the medical treatment group, but the data is incomplete, lacking a pure urokinase group and exact times to initiation of treatment. All ten severe coma patients died with lesser coma grades I-III showing the best response to combined urokinase plus HBO, and minimization of time to treatment the best predictor of success. The Saltzman (1966) report also had one patient in both the hyperacute and acute periods. The acute patient had an embolic clot CVA and was treated 5 hours post CVA at 2.02 ATA/>1 hour with near total permanent improvement. Lastly, nine TBI patients of Hayakawa=s (1971) 13 patients were most likely in the acute period, but the results have already been summed above.

Of the remaining 21 studies, 13 were at pressures greater than or equal to 2 ATA: Heyman (1966), Mogami (1969), Sukoff (1982), Thomson (1992), Dean (1993), Snyder (1995), Dordain (1969), Illingworth (1961), Koch (1952), Hsu (1987), Smilkstein (1985), Van Meter (1998), Sheffield (1976); 6 used 1.5 ATA (Holbach A, B, D, E, F), Rockswold (1992); and two used 1.6-2 ATA Belokurov (1988), Isakov(1982) with near uniform transient or permanent positive results. Four of the six 1.5 ATA reports (Holbach 1974A, 1977 D, E, F) compared 1.5 ATA to either 2, 2.5, or 2-3 ATA and demonstrated better results at 1.5 ATA, using a variety of clinical, biochemical, and physiological outcome measures. Three of the six studies (Holbach 1974B, 1977D; Rockswold 1992) initiated treatment >24 hours after injury and the fourth (Holbach 1974A) does not mention time to treatment, but implies treatment in the acute period since the patients are neurosurgical cases and they are reported incidentally in a paper on cerebral glucose metabolism in acute brain-injured patients which is a preliminary version of patients who were a few days@ post injury (Holbach 1977D). The fifth and sixth 1.5 ATA papers (Holbach 1977E, 1977F) span the acute and subacute periods and are similar patients to those in the other Holbach papers. In (Holbach 1974A) 1.5 ATA had significantly better clinical results than 2-3 ATA. This is confirmed with CBF measurements (Holbach 1977E), EEG (Holbach 1977F), and cerebral glucose metabolism (Holbach 19077D) where 15-30 minute excursions to 2 and 2.5 ATA caused deterioration in the measured parameters. While the Holbach (1977D) experiment did not explore pressures between 1.5 and 2 ATA, the Belokurov study affirmed the efficacy of 1.7-2 ATA pressures in 23 comatose children with 100% recovery of consciousness. Their results were maximal in TBI and if initiated < 24 hours post coma. Similarly, Isakov (1982) experienced good results between 1.6 and 2 ATA in patients with cerebrovascular accidents. 481 of the 640 patients reviewed in this category (excluding Kohshi, Mathieu, Voisin, Shn-rong, and Viart) had TBI; the data strongly argues for the routine use of HBO in TBI at 1.5 ATA. Overall, treatment courses tended to be longer in the acute category than the hyperacute, using higher HBO pressures earlier (less than or equal to 24 hours) and lower pressures later, with overall positive effects regardless of coma etiology: chemical/toxic gas, trauma, CVA, surgery, etc.

In the third category, subacute (49 hours-1 month) fifteen studies are presented. The papers of Holbach (1974A, B, 1977E, F), Larcen (1977), Shn-Rong (1995), Isakov (1982), and Belokurov (1988) were discussed above, but to reiterate, many of the TBI cases of (Holbach) started HBO 2-10 days post injury. Results were positive and favored treatment at 1.5 ATA for 1-7 times. Lareng (1973) reported two additional late TBI coma cases and had excellent outcomes with prolonged treatment at 2.0 ATA. In the Shn-Rong series a number of carbon monoxide cases presented with >6 days of coma. In general they required more treatment and one case of 90 day coma was Acured finally with normal EEG@ after 150 treatments in three stages. Three patients with TBI coma of 10, 20, and 30 days regained consciousness after 7-20 treatments. Almost all except the initial few treatments were at 2 ATA. Two additional TBI studies by Artru (1976 A), (1976 B) had mixed results. The first involved 60 TBI patients 4.5 days post injury, HBO at 2.5 ATA, and an average 10 treatments with multiple breaks in protocol, and few receiving much treatment in the first week. Only one of nine sub-groups (brainstem contusion) achieved significant improvement with HBO (see above discussion on penumbra/umbra size considerations in brainstem vs. cortical coma). The second study with 6 patients, 5-47 days post insult, examined blood flow, metabolism, and CSF biochemistry before and after 2.5 ATA HBO. Results were inconclusive, but arterial partial pressure of oxygen declined in 8 of 9 patients, CSF oxygen remained elevated above baseline for 2 hours after HBO, and the authors concluded that HBO has different effects on normal and injured brain circulation.. Both of these studies featured high pressure, 2.5 ATA, later in the course of illness and are consistent with an oxygen toxicity effect as Holbach demonstrated in multiple reports above. The final four studies deal with subacute CVA (Holbach 1976C), (Heyman 1966), post-hanging (Satoh 1989), and status epilepticus/hypoglycemia (Neubauer 1998). Holbach reported excellent results at 1.5 ATA, Heyman did not mention immediate effects at 2.02 ATA, Satoh noted "Agradual progress" of his

unsuccessful hanging patient and Neubauer found significant progress at 1.5 ATA. In summary, with delay to treatment of 2-30 days generally positive results are achieved with HBO with a tendency to lower pressures and longer treatment courses.

In the final category, chronic (> 1 month) 8 studies are presented, seven of which are case reports. All feature single cases except the Harch (1994) study of 4 patients, with delay to HBO of 45 days to 12 years. Six of the eight reports used 1.5 ATA and treatment courses of 21-154 treatments. Neubauer and Harch both employed SPECT brain blood flow imaging to register improved neurocognitive outcomes. The general result of HBO in these limited series of chronic patients is positive.

7 CASE STUDIES

To illustrate the effect of HBO in both acute and chronic global cerebral ischemia/anoxia and coma several cases treated by these authors are presented below. In each case the visual medium of SPECT brain blood flow imaging on a high resolution scanner (7 mm ; Picker Prism 3000) registers in a global fashion the neurocognitive clinical improvement experienced by the patients and witnessed by the authors. The SPECT brain scans presented below are CT technology with the patient=s left brain on the reader=s right and vice versa with the 30 frame images registering transverse slices from the top of the brain in the left upper corner to the base of the brain in the lower right corner. Images are approximately 4 mm thick. Brain blood flow is color coded from white-yellow to yellow to orange to purple, blue and black from highest brain blood flow to lowest. Normal human brain shows predominantly yellows and oranges and, most importantly, has a fairly smooth, homogeneous appearance. The companion image (B) to the 30 slice transverse set of images is a three-dimensional surface reconstruction of the transverse images. Abnormalities in perfusion are registered as defects and as coarseness of the brain=s surface.

Patient 1: HBO treatment for coma due to traumatic brain injury

A 19 year old. male was inadvertently ejected from a motor vehicle at 65 mph with impact on the left frontal/parietal region of the skull. Within one-half hour Glasgow coma scale was 6-7 and the patient was ventilator dependent. CT of the brain revealed diffuse edema, midline shift, petechial hemorrhages, subarachnoid hemorrhage, small subdural hematoma, and basilar skull fracture. HBO was given 19 hours post injury at 1.75 ATA/90 bid. On the first treatment the patient began to fight the ventilator. Initial SPECT brain imaging obtained five days post injury on a single-head low-resolution scanner was Anormal@. Repeat SPECT imaging on a triple-head high -resolution scanner occurred 30 days post injury (Figure 18-1, A and B) and now clearly demonstrated the significant injury to the left frontal area as well as the contra coup injury to the right parietal/occipital area characterized by luxury perfusion. Nine days later and two hours after a fifth additional HBO, SPECT was repeated, (Figure 18-2, A and B) and showed a dramatic Afilling in@ of the injured areas thus giving functional neurophysiological support to the clinical decision to continue HBO. The patient, meanwhile, progressed rapidly on twice daily HBO for four weeks with often new neurological or cognitive findings occurring in the chamber and then continued on HBO 4 times a day for seven weeks, at which time he was conversant and independently ambulatory with slight spasticity. At 11 weeks the patient was transferred to a rehabilitation center and his HBO discontinued by the new medical team. SPECT imaging at this time (Figure 18-3, A, B, and C) registers the patient=s clinical progress with a persistent increase in flow to the left frontal region while some deterioration occurs to the area of previous luxury perfusion on the posterior right. The patient made transient limited initial progress at the rehabilitation center then quickly leveled off cognitively while his spasticity and balance worsened. Three months after discontinuance of HBO the patient=s father requested further HBO and repeat SPECT brain scan (Figure 18-4, A and B), psychometric, and motor testing were obtained. SPECT now demonstrates a significant deterioration in the right frontal and posterior areas, while the left frontal normalization persists. The right posterior area has infarcted on simultaneous MRI. To assess recoverable brain tissue the patient underwent a single 1.75 ATA/90 min HBO followed by SPECT imaging (Figure 5, A and B); SPECT showed improvement in the right frontal and parietal/occipital lesions along the ischemic penumbral margins. HBO was resumed for an additional 80 treatments, once/day at 1.75 ATA/90 min. The patient made a noticeable improvement in cognition (40 percentile gain in written computational mathematics), insight (the patient now verbalized for the first time the understanding that he had sustained a brain injury and could no longer aspire to be a surgeon),

and balance (improvement in gait and progression from a 3-wheel tricycle to a 2-wheel bicycle). HBO (188 treatments total) was discontinued when the patient desired enrollment in remedial courses at a community college. SPECT imaging at this time (Figure 6, A and B) shows improvement in perfusion in the ischemic penumbral areas of the right-sided lesions. The left hemisphere remains intact. In summary, HBO, when reinstated following SPECT and relapse after discontinuation of HBO, prevented further deterioration and improved SPECT image as well as neurocognitive function in TBI, demonstrating the benefit of HBO in chronic stage of TBI

Figure 18-1 A

HMPAO SPECT brain imaging, Transverse slices, one month post injury>

Note severe reduction in left frontal, parietal, and temporal brain blood flow with luxury perfusion in the right occipital parietal region.

Figure 18-1 B

Frontal projection three-dimensional surface reconstruction of Figure 1 A.

Non cerebral uptake is shown in scalp and neck soft tissues.

Figure 18-2 A

HMPAO SPECT brain imaging, transverse slices, 9 days after Figures 1 A and 1 B and 2 hours post 5th additional hyperbaric treatment. Note improvement in flow to the left frontal, parietal, and temporal regions while defects begin to appear in the right frontal and parietal area. Luxury perfusion is no longer evident.

Figure 18-2 B

Frontal projection three-dimensional surface reconstruction of Figure 2 A.

Figure 18-3 A

HMPAO SPECT brain imaging, transverse slices, 11 weeks and 108 hyperbaric treatments post injury. Note maintenance of perfusion in the left frontal, parietal, and temporal regions with further progression of defects in the right frontal-parietal and posterior parietal-occipital areas

Figure 18-3 B

Frontal projection three-dimensional surface reconstruction of Figure 3 A.

Figure 18-3 C

Right lateral projection three-dimensional surface reconstruction of Figure 3 A.

Figure 18-4 A

HMPAO SPECT brain imaging, transverse slices, 3 months after Figures 3 A, B, and C. Left frontal, parietal, and temporal perfusion is maintained with further deterioration of the right frontal and posterior defects.

Figure 18-4 B

Right lateral projection three-dimensional surface reconstruction of Figure 4 A.

Figure 18-5 A

HMPAO SPECT brain imaging, transverse slices, 2 hours following single HBO at 1.75 ATA/90 minutes. Note improvement in the right frontal and posterior defects.

Figure 18-5 B

Right lateral projection three dimensional surface reconstruction of 5 A

Figure 18-6 A
HMPAO SPECT brain imaging, transverse slices, 5 months and 80 HBO=s after Figure 4 A. Note improvement in flow to the ischemic margins of the right frontal and posterior defects.

Figure 18-6 B
Right lateral projection three dimensional surface reconstruction of Figure 6 A.

Patient 2: Near drowning, chronic phase

The patient is a 4 year old male who was found at the bottom of a swimming pool after an estimated 5 minutes of submersion. Resuscitation measures were instituted and a pulse was regained 45 minutes after removal from the pool. Two years after the injury, the patient was wheelchair bound with significant motor disabilities, inability to speak and communicate, and problems with drooling, attention span, and swallowing. SPECT brain imaging was performed on a high resolution scanner before (Figures 1, A and B) and two hours after (Figures 2, A and B) a 1.5 ATA/60 minute HBO. The baseline scan in Figure 1A shows a severe reduction in blood flow to the frontal lobes, while Figure 2A shows a generalized improvement in brain blood flow, particularly to the frontal lobes, and denotes recoverable brain tissue after the single hyperbaric treatment. The patient embarked on a course of 80 hyperbaric treatments at 1.5 ATA/60 minutes four times a day, 5 days per week with a 3 week break at the 40 treatment point. At the end of 80 treatments, he returned for evaluation and was noted to have a generalized improvement in spasticity, movement of all 4 extremities, increase in trunk and head control as well as improvements in swallowing, awareness, non-verbal communication, and attention span. There was a global increase in blood flow on SPECT brain imaging performed at that time. (Figures 3, A and B).

Figure 18-7 A
HMPAO SPECT brain imaging transverse slices, baseline study two years status post near drowning. Note considerable reduction in frontal blood flow.

Figure 18-7B
Frontal projection three dimensional surface reconstruction of Figure 18-7A.

Figure 18-8 A
HMPAO SPECT brain imaging, transverse slices, one day after Figure 18-8 A and two hours following single HBO at 1.5 ATA/60 minutes. Note diffuse increase in perfusion to the frontal lobes and improvement in overall brain blood flow.

Figure 18-8 B
Frontal projection three dimensional surface reconstruction of Figure 18-8A.

Figure 18-9 A
HMPAO SPECT brain imaging, transverse slices, 4 months and 80 HBO=S following Figure 1 A. Note persistent increase in perfusion to the frontal lobes.

Figure 18-9 B
Frontal projection three dimensional surface reconstruction of Figure 18-9 A.

Patient 3: Near drowning, chronic phase

Case 3: The patient is a 4 year old boy who is 2 years status post 30 minute submersion in a pond. Resuscitation regained a pulse 45 minutes after removal from the water. Two years later, the child is severely disabled with almost no cognition, frequent posturing, inconsistent tracking, extreme difficulty swallowing fluids, choking, and 10 petit mal seizures a day. Baseline SPECT brain imaging is shown in Figure 1A with prominent abnormalities in the inferior frontal lobes. The patient underwent a single HBO at 1.5 ATA/60

minutes with repeat SPECT imaging 2 hours after chamber exit (Figure 2A). A generalized improvement in flow is noted, particularly to the frontal lobes, identifying potentially recoverable brain tissue. The patient underwent a course of 80 hyperbaric oxygen treatments at 1.5 ATA/60 minutes QD, 5 days per week with approximately one month break after 40 treatments. On return evaluation, SPECT brain imaging was repeated (Figure 3A). Improvement in frontal lobe blood flow is noted over the baseline scan. The child exhibited greater awareness, control of his head, eye tracking, alertness, non verbal communication, performance of some simple commands, improvement in swallowing and decrease in seizure frequency.

Figure 18-10
HMPAO SPECT brain imaging, transverse slices, baseline study two years post near drowning.

Figure 18-11
HMPAO SPECT brain imaging transverse slices one day after Figure 18-10A and two hours after a single HBO treatment at 1.5 ATA/60 minutes. Note generalized improvement to frontal lobe brain blood flow.

Figure 18-12
HMPAO SPECT brain imaging transverse slices four months and 80 HBO treatments after Figure 18-10 A. Note persistent improvement to blood flow to the frontal lobes over baseline scan of Figure 18-10 A.

Patient 4: Cerebral palsy

The patient is a 5 year old male whose mother had a complicated gestation characterized by diabetes, two weeks post term delivery, prolonged labor (30 hours), and macrosomia at 12 pounds 10 ounces. The patient was born with a grossly misshapen head, low Apgars, and required resuscitation. Meconium aspiration occurred. Maximum Apgar was 4 at 7 minutes. At time of evaluation, the patient's main problems were incoordination, both gross and fine, imbalance, awkward gait, expressive and receptive aphasia, and delayed milestones. Baseline SPECT brain imaging in Figure 18-11A shows diffuse heterogeneity to cortical blood flow. Figure 18-12A, approximately 2 hours after a single HBO at 1.5 ATA/60 minutes shows generalized improvement in brain blood flow. Figure 18-13A was obtained at the conclusion of 80 HBO=s at 1.5 ATA/60 minutes four times a day with a one month break at 40 treatments. At the conclusion of treatment the patient had a significant improvement in his truncal hypotonia, an improvement in gait, communication, expressive and receptive aphasia, development of emotions, and in school performance.

Figure 18-13
ECD SPECT brain imaging, transverse slices, baseline study. Note generalized heterogenous appearance to the scan.

Figure 18-14
ECD SPECT brain imaging transverse slices one day following Figure 18-11 A and two hours after single HBO treatments at 1.5 ATA/60 minutes. Note smoothing of the brain blood flow and improvement in perfusion.

Figure 18-15
ECD SPECT brain imaging transverse slices four months and 80 HBO treatments following Figure 18-11 A. Notice overall smoothing of the brain blood flow pattern and improvement in flow to the basal ganglia and thalami.

8 CONCLUDING REMARKS

Despite multiple causes of coma and global cerebral ischemia/anoxia, HBO has been used in a variety of animal models and in over 1,250 patients in several countries. Although HBO protocols have varied, the results have been remarkably consistently positive with improvement in a variety of physiological and

biochemical measures and outcomes, the most important of which was improvement in overall clinical condition and consciousness. This consistent success rate suggests an effect of HBO on common brain pathophysiological processes at different stages in global ischemia/anoxia and coma. Importantly, this review excluded thousands of cases of acute carbon monoxide (CO) coma in the medical literature treated with HBO because of the confusion over HBO effects on the metabolic poison and COHb dissociation vs. hypoxia and other pathophysiology. No doubt hypoxia is a major contributing insult to the patient's overall condition in CO and reperfusion injury a significant component of the pathophysiology, and both of these are treated definitively by HBO early after extrication, but many patients arrive for HBO hours after extrication (Thom 1992; Goulon 1969; Raphael 1993), adequately oxygenated, with low or normal COHb levels, and outside the 45 minute HBO window identified in Thom's rat model of CO reperfusion injury. Clearly, HBO is effective treatment for CO coma, irrespective of COHb and hypoxia, and it is acting on yet unidentified pathological targets (see Chapter 12). Cerebral arterial gas embolism (CAGE) of diving and non-diving etiology (thousands of cases) similarly was excluded because of the argument that bubbles are the primary pathophysiological target and not ischemia/hypoxia (for discussion see Chapter 11). It has been proposed that most bubbles in CAGE/cerebral decompression sickness have passed the cerebral circulation by the time of HBO and the primary pathological target of treatment is reperfusion injury which is responsive to HBO (Harch 1995). In conclusion, the collective experience of HBO in many of the cases of coma due to CO (especially with delayed treatment >6 hours or so) and CAGE is strongly positive and further bolsters the above conclusion on usefulness of HBO in coma and global ischemia/anoxia.

Another conclusion drawn from this review is that the earlier the HBO intervention the more impressive the results. In particular, if HBO is instituted within about 3 hours of cerebral insult, over 75% of patients will be noticeably improved or cured. This finding very strongly suggests targets that are both inhibited and stimulated by oxygen. A single hyperacute HBO greater than or equal to 2 ATA is possibly quenching an ongoing injurious cascade and re-energizing stunned neurons similar to the hibernating myocardium reactivation by HBO (Swift 1992). HBO simultaneously reverses any hypoxia, anoxia, and, if ischemia is incomplete or prolonged, inhibits reperfusion injury as demonstrated by the animal data of Thom and Zamboni. As treatment is delayed to 6 hours, pressures above 2 ATA are still very effective, but they lose their effectiveness as delays approach 24 hours. At this time lower pressures and more treatment are required and suggests treatment of different pathology. With delays longer than one month, HBO assumes a trophic role stimulating brain repair and possibly manipulating brain blood flow and metabolism (Harch 1997).

HBO in acute cerebral ischemia/anoxia and coma appears to satisfy the cardinal rule of medicine, *primum non nocere*. In the multitude of cases above and those not reviewed (CO and CAGE) the incidence of serious side-effects of HBO is surprisingly small, e.g. In one review of over 1,000 CO poisoned patients (Hampson 1994), the maximum seizure frequency was 3% and only occurred at the highest pressures, 2.8-3 ATA, which is greater than the pressure in 36 of the 43 human studies in Table 18-2. The rate dropped ten-fold to 0.3% with pressures of 2.4 ATA. These facts alone argue overwhelmingly for a reasonable attempt, without endangering patients in transport, to perform HBO in acute cerebral ischemia/anoxia and coma, especially where no other treatment modality exists or has shown clearcut superiority. In essence, HBO is a simple treatment with potentially profound impact after a single hyperacute administration on devastating incurable neurological conditions that generate monumental long-term tolls of material and human capital and suffering.

HBO in acute cerebral ischemia/anoxia and coma satisfies the second cardinal rule of medicine - treat until the patient no longer benefits from treatment. In many of the hyperacute and acute studies HBO benefit was observed on the first or second treatment and was a prelude to further improvement with 1-2 weeks of treatment. The advance in care levels of such patients makes a powerful cost/effectiveness argument from human and financial perspectives. Unfortunately, the tradition in hyperbaric medicine has been to treat once or twice based on the U.S. Navy's miraculous early results with hyperacute treatment of decompression sickness and air embolism, results not attained equally in the sport scuba diving arena. (DAN Report 1993) This stereotyped thinking has subsequently governed the approach to treatment of carbon monoxide poisoning, stroke, and other neurological maladies, ignoring the fact that HBO initiated at different times after a neurological insult is treating different neuropathology as has been discussed in this chapter. Such an approach may explain the limited positive results of Saltzman (11 of 25 patients with temporary improvement after single HBO) and Rockswold (40% reduction in mortality with 21 treatments, but no long term effect on

functional outcome) among others. The greater consideration of the fixed HBO approach to neurologic injury and the finite, predetermined endpoint of the prospective controlled clinical trial is raised by asking the question of why stop HBO when the patient is continuing to benefit from treatment or showing neurological gains in the chamber at depth. (See Patient 1) New neurological activity at depth strongly suggests ischemic neurological tissue, e.g. ischemic penumbra that would benefit from further HBO. This arbitrariness is most evident in DCI and CO poisoning where after 5-10 treatments a treating physician is asked how he knows that the patient would not continue to improve on his own. No one knows for sure with each individual case, but, if the patient is making stepwise improvement with each or a few HBO=s, it is known that it takes one year for a human tissue injury to mature (e.g. wound healing tensile strength, time for neurological injury to be considered chronic). Smoldering inflammatory cascades are the underlying pathology and the analogy of Ajump starting a failed engine with a dead battery@ is grossly inadequate. We ask why this factor is not considered at the outset, or after the 2nd, 4th, 7th, 11th, or any other subsequent HBO treatment. In fact, the deciding factor in determining the number of HBO=s may be the point in the injury process at which HBO is initiated, not financial considerations, a factor increasingly dominating medical decision-making in the United States today.

In our accumulating extensive experience, repetitive HBO appears to be trophic, stimulatory to brain repair, and may not be complete in some cases until 200-300 treatments. (see Patient 1) Perhaps the best and most expedient method to assess the HBO potential and endpoint of treatment at any time after injury for any brain pathology is SPECT brain imaging on a high resolution camera (see Figure 18-1 to 18-6). SPECT before and after any single HBO at any point in the treatment process may help identify the injured brain=s potential for any or further HBO. HBO can then be initiated or continued and combined with multiple other treatment modalities. This approach may help document cost-effectiveness of prolonged HBO by choosing endpoints. Currently, there are about 500 hyperbaric centers in the United States but less than 12 of these routinely treat the neurological conditions addressed in this chapter with the exception of decompression sickness and CO poisoning. As hyperbaric medicine continues to experience a resurgence in use and expansion of applications and research, the proliferation of chambers and increasing ease of access will facilitate use of HBO in acute cerebral ischemia/anoxia and coma and will be driven by ever greater lay public and physician knowledge of the above data through widespread computer-assisted dissemination.

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