Evidence Report

Chapter 1. Introduction

Purpose

This evidence report describes the methods, results, and conclusions of a literature review on the use of hyperbaric oxygen therapy (HBOT) to treat manifestations of brain injury, cerebral palsy, and stroke in humans. Hyperbaric oxygen therapy is the administration of high concentrations of oxygen within a pressurized chamber. HBOT has become the definitive therapy for patients with decompression illness, gas embolism, and severe, acute carbon monoxide poisoning and is a widely accepted treatment for osteoradionecrosis, soft tissue radionecrosis, wound healing, and several other conditions. However, the role of HBOT in the treatment of patients with brain injuries is controversial.

Brain injury can be caused by an external physical force (this is also known as traumatic brain injury, or TBI); rapid acceleration or deceleration of the head; bleeding within or around the brain; lack of sufficient oxygen to the brain; or toxic substances passing through the blood-brain barrier. A brain injury results in a temporary or permanent impairment of cognitive, emotional, and/or physical functioning. *Cerebral palsy* refers to a motor deficit that usually manifests itself by 2 years of age and is secondary to an abnormality of at least the part of the brain that relates to motor function. *Stroke* refers to a sudden interruption of the blood supply to the brain, usually caused by a blocked artery or a ruptured blood vessel, leading to an interruption of homeostasis of cells, and symptoms such as loss of speech and loss of motor function.

While these conditions have different etiologies, prognostic factors, and outcomes, they also have important similarities. Each condition represents a broad spectrum, from barely perceptible or mild disabilities to devastating ones. All three are characterized by acute and chronic phases and by changes over time in the type and degree of disability. Another similarity is that, for all three conditions, the outcome of conventional treatment is often unsatisfactory. For brain injury in particular there is a strong sense that conventional treatment has had little impact on outcomes.[1] The use of various diagnostic and therapeutic interventions including pre-hospital intubation, intracranial pressure monitoring, intracranial pressure-directed therapy, and head computed tomography scan utilization vary considerably among different centers.[2] Such variation often signifies a lack of consensus on clinical effectiveness.

In early 2000, the Agency for Healthcare Research and Quality asked the Oregon Evidence-based Practice Center to assess the feasibility of conducting a full evidence report on the use of HBOT for treatment of brain injury and stroke. In response, in March 2001, the Oregon EPC conducted a literature search to identify clinical studies of the use of HBOT for chronic stroke and other brain injury. The EPC found that there are controlled studies of at least fair internal and external validity that measured at least some relevant outcomes of HBOT for each type of brain injury. The EPC recommended that a full evidence report be done to provide insight into what is currently known and not known about the efficacy of HBOT in these conditions and shed light on what is missing from the current evidence base. The EPC also recommended that the evidence report should include an assessment of what outcomes are important to patients, caregivers, and clinicians.

After reviewing the results of the feasibility study, AHRQ asked the Oregon EPC to prepare a full evidence report. The purpose of this evidence report is to assess the strength of the evidence about the benefits and risks of HBOT for brain injury, cerebral palsy, and stroke.

Background

Traumatic Brain Injury

Each year, approximately 1.5 million Americans sustain traumatic brain injuries, ranging in severity from mild to fatal.[3, 4] The leading causes of traumatic brain injury are motor vehicle crashes, falls, firearm use, and sports and recreational activities. Adolescents and young adults (aged 15 to 24) as well as adults aged 65 years and older have the highest risk. The annual costs of traumatic brain injuries are estimated to be $56 billion.[5] This figure reflects the costs of medical care and rehabilitation as well as the loss of productivity and income among individuals who have long-term disability due to their injuries.

Of the 1.5 million who are injured each year, 50,000 die, and from 80,000 to 90,000 experience the onset of long-term disability.[3] The Centers for Disease Control has estimated that 5.3 million Americans are living with disability as a result of brain injury. The types of disability range across the entire spectrum of human physical, social, and emotional function. No single instrument can measure all of the consequences of TBI. The two most commonly used measures of outcome were developed for use with severe brain injury. The oldest formal scale, the Glasgow Outcome Scale (GOS), categorizes patients into five broad categories: good recovery, moderate disability, severe disability, persistent vegetative state, and death.[6] This measure is convenient and very widely used, but it is insensitive to many of the cognitive and emotional deficits that, while subtle, have a strong effect on quality of life.

Another commonly used instrument is the Disability Rating Scale (DRS), a 30-point scale based on ratings of the level of consciousness or arousal, cognitive ability for self-care, physical dependence on others, and ability to work.[7] Other measurement instruments have been designed to assess subtler degrees of disability in memory, cognition, attention, social function, or emotional function in chronic brain injury patients. These measures include the Community Integration Questionnaire, the Neurobehavioral Functioning Inventory (NFI), the Patient Competency Rating Scale (PCRS), the Level of Cognitive Functioning Scale (LCFS), and the Revised Craig Handicap Assessment and Reporting Technique (R-CHART).

The prognosis of TBI is related to the severity of the initial injury. Since the 1970s, the Glasgow Coma Scale (GCS) (Table 1) has been the most widely used measure of the severity of an acute brain injury.[8, 9] The scores range from 3 to 15. Three to five is the most serious, and 13 to15 is the mildest, with the best prognosis. "Severe" injury is often defined as a GCS score of 8 or less. For patients with TBI, a score in this range indicates a mortality rate of 50 percent and a high likelihood of suffering from severe long-term disabilities.[10-13]

GCS has several limitations as a predictor for an individual's outcome. Data about the ability of GCS scores to predict functional outcomes come from patients who undergo inpatient rehabilitation, rather than from all patients who are seen for trauma.[14] Patients excluded from inpatient rehabilitation because they are not as severely impaired, are too impaired to benefit, or lack financial resources, have not been well studied. In trauma patients, mortality rates differ between different groups of patients who have similar average GCS scores. For a given GCS score, survival also varies considerably among published studies.[15] The inter-observer reliability of the GCS is only fair, and the differences between observers are large enough to alter the predicted prognosis substantially.[16] Patients who have the same total GCS score, but different scores on the components of the GCS, have different mortality rates.[17]

Table 1. Glasgow Coma Scale

Eye Opening Response

- Spontaneous--open with blinking at baseline **4 points**
- To verbal stimuli, command, speech **3 points**
- To pain only (not applied to face) **2 points**
- No response **1 point**

Verbal Response

- Oriented **5 points**
- Confused conversation, but able to answer questions **4 points**
- Inappropriate words **3 points**
- Incomprehensible speech **2 points**
- No response **1 point**

Motor Response

- Obeys commands for movement **6 points**
- Purposeful movement to painful stimulus **5 points**
- Withdraws in response to pain **4 points**
- Flexion in response to pain (decorticate posturing) **3 points**
- Extension response in response to pain (decerebrate posturing) **2 points**
- No response **1 point**

In addition to GCS, factors such as age,[15, 18, 19] associated injuries,[20] intracranial hypertension,[21, 22] and the presence of a mass effect[23] are also predictors of mortality and severe disability. Preinjury productivity and education also help predict functional outcome in survivors.[24, 25] Hypoxia (defined as PaO2 less than 60 mm Hg, or apnea or cyanosis in the field) and hypotension (defined as a measure of systolic blood pressure less than 90 mm Hg at any time) are also strong predictors of death and severe disability.[22, 26-28]

Some features of the patient's course and management in the hospital are also predictors of mortality and morbidity. For example, the extent of post-traumatic amnesia (PTA) is correlated with the prognosis. The longer the amnesia occurs following the injury, the worse the prognosis for recovery. If the loss of consciousness lasts more than 4 weeks, a high prevalence of impairment, inattention, and memory loss is predicted.[29]

During the course of intensive care, episodes of hypotension, elevated intracranial pressure, decreased cerebral perfusion, and hypoxia are also predictors of a poor outcome.[30] Such episodes are very common. In a series of 184 patients receiving intensive care for acute, severe TBI,[30] all but seven patients had at least one episode of hypotension. In 157 of these patients, jugular venous oxygen saturation was monitored continuously. Ninety-seven (62 percent) of these patients experienced one or more episodes of hypoxia (jugular venous oxygen saturation <50 percent), and patients spent an average of 1.88 hours in a hypoxic state during the intensive care unit stay. These figures probably represent better-than-typical results because they were obtained in an intensive care unit that used invasive monitoring to minimize the frequency and duration of hypoxic episodes.

GCS and other prognostic factors are of little value in predicting the speed of recovery from coma. In before-after comparison studies, a presumption is often made that a patient who was discharged from the acute care hospital in a vegetative state has a very low chance of recovering consciousness spontaneously. However, several cases of recovery have been documented in

patients who have had stable coma for longer than 6 months.[31] In case series of patients with severe or catastrophic traumatic brain injuries, three of four patients who survived 6 months regained consciousness.[18]

Similarly, data from recent followup studies contradict the widely held view that improvements in neurocognitive function are unlikely to occur if more than a year has passed since the injury.[32, 33] In one of these cohort studies, patients with TBI were administered a battery of 12 neuropsychological tests 1 year and 5 years after injury.[33] On one of the tests (Trails B, a test of complex attention), 22.2 percent of patients improved and 14.1 percent deteriorated between 1 and 5 years post-injury. For the other 11 tests, 0 to 22.7 percent (median 13 percent) improved and 1.2 percent to 18 percent (median 6.2 percent) deteriorated. The authors concluded that clinically significant improvements can occur long after apparently "stable" deficits have been diagnosed.

Nearly 90 percent of TBIs that are reported annually in the United States are classified as mild TBI (MTBI) or concussion. MTBI can cause immediate neurocognitive abnormalities[34] as well as long-term problems such as persistent headaches, confusion, memory problems, mood changes, and changes in vision or hearing.[35] The incidence of MTBI may be under-reported because a large percentage of patients never seek medical evaluation or treatment. Moreover, the subtle long-term consequences of MTBI, although often apparent to patients and family members, may go unrecognized by physicians. It is difficult to predict which patients with MTBI will suffer long-term disability.

Many components of acute and rehabilitative care for patients with brain injuries are not supported by good-quality evidence from clinical trials.[27, 36, 37] A recent consensus conference on clinical trials in head injury summarized the disappointing results of over a dozen treatments which despite promising results in observational studies, proved to be ineffective when tested in randomized trials.[38] Most of these treatments appeared to be effective in animal studies, case reports, and other before-after studies.

Cerebral perfusion pressure (CPP) management provides the best example. Following several case reports and small series, Rosner and colleagues published a series of 158 patients admitted with a Glasgow Coma Scale score less than 7 who underwent cerebral perfusion pressure (CPP) management rather than the conventional approach, control of intracranial pressure (ICP).[39] Mortality was only 29 percent, and 59 percent achieved a good recovery or moderate disability by 6 months post-injury. The authors stated that these mortality and recovery rates were much better than would be expected from other series of patients who had similar GCS scores. These results led to wide use of the CPP management strategy. However, in a subsequent randomized controlled trial that recruited patients with a GCS score less than 5, mortality was under 30 percent in both the cerebral blood flow-targeted and conventionally managed groups, and there was no difference in neurologic outcomes.[40] In this trial, the cerebral blood-flow-targeted strategy significantly reduced the frequency of cerebral ischemia and of jugular desaturation, but these physiologic improvements did not translate into clinical benefits.

Hypothermia provides a similar example. In the 1990s, several groups of investigators published dramatic case studies and series of cases that appeared to show that inducing hypothermia in brain-injured patients improved outcomes.[41-43] The goal of this treatment was to reduce hypoxia in the injured brain tissue. In one series, the investigators used hypothermia in 148 patients who had initial GCS scores less than 6.[41] Mortality was 30 percent, and, as measured by the Glasgow Outcome Scale, 40 percent of patients had a good recovery, 13 percent had mild disability, and 10 percent were in a persistent vegetative state. Subsequently, in a

randomized trial of 392 patients, mortality was 28 percent in the hypothermia group and 27 percent in the normothermia group. An additional 30 percent of patients in each group had severe disability or a vegetative state. The hypothermia group had fewer episodes of high intracranial pressure but also had more hospital days because of complications.

These examples show that improvements in physiologic measures do not always translate into tangible clinical results. They also show that relying on assumptions about the expected prognosis of a group of brain-injured patients, rather than on results in a control group, can be misleading.[1] Even over a short time there can be significant changes in the prognosis of TBI. In one trauma center, for example, mortality among patients with a GCS ≥ 4 fell from 40 percent in the period 1980-1981 to 27 percent in 1987-1988 and 2.8 percent in 1996-1997.[44]

Anoxic-ischemic Brain Injury

It is estimated that, in the U.S., more than 1,000 useful lives are lost each day as a result of poor cardiopulmonary and trauma resuscitation outcomes.[45] Among those who survive, permanent brain injury is a common, devastating complication. In addition to cardiopulmonary arrest, toxic substances, congenital disorders, and birth trauma can cause brain injury by means of anoxia and ischemia.

Prediction of the outcome of coma due to anoxic-ischemic coma is poor. In a meta-analysis of studies of patients with anoxic-ischemic coma, the sensitivity of a GCS score of 3 to 5 ranged from 63 percent to 95 percent for a poor outcome, defined as death or persistent vegetative state.[46] The specificity of a GCS in this range was 54 percent to 100 percent. The meta-analysis found that clinical variables are less accurate in predicting outcome after 24-hour coma duration than after 72 hours of coma. The most specific predictors of outcome were the lack of pupillary light reflexes after 72 hours, lack of motor response to pain after 72 hours, and certain somatosensory evoked potential findings. A subsequent meta-analysis by the same authors found there was insufficient evidence to determine whether markers of central nervous system metabolism added substantially to the predictive value of these variables.[47]

Cerebral Palsy

Each year, about 10,000 babies born in the U.S. develop cerebral palsy. More than 500,000 Americans have cerebral palsy. A study in California showed that the lifetime costs per new case of cerebral palsy was $503,000 (in 1992 dollars).[48] Half of these costs are borne by families, who often find it difficult to obtain all the services they need to help their children.

Cerebral palsy results from injury to the brain. About 20 percent of children who have cerebral palsy acquire the disorder after birth, while 80 percent of cases are congenital. Meningitis, encephalitis, and trauma cause most of the acquired cases. According to the National Institute of Neurological Disorders and Stroke, the mechanism of injury in the majority of cases of congenital cerebral palsy is not known. Until recently, the belief that birth complications cause most cases of cerebral palsy was widespread. Then, in the 1980s, a careful study of 35,000 births showed that fewer than 10 percent of children with cerebral palsy had a history of birth complications such as rubella or other infections during pregnancy, jaundice, Rh incompatibility, asphyxia (oxygen shortage), or head trauma during labor and delivery. Most children with congenital cerebral palsy do not have a history of any of these conditions.

Premature birth and low birthweight predispose to cerebral palsy, but the reason for this association is not clear.

Cerebral palsy represents a very broad range of motor disorders, varying in the part of the body they affect (e.g., diplegia, hemiplegia, quadriplegia); the type of motor disorder (spastic, athetoid, or ataxic) and their severity. The most familiar pattern is spastic diplegia, meaning that the patient has stiff, contracted muscles in the legs. By definition, the muscle disorder in cerebral palsy is not progressive. However, muscle spasticity, even if stable, can cause new problems as a child grows. For example, pain and contractures may increase as the bones of the child's legs lengthen.

Standardized scales, such as gait analysis, and functional scales, such as the Gross Motor Function Measure (GMFM), are used to assess and monitor progress. The GMFM is a validated and reliable scale used for measuring function in patients with cerebral palsy. It consists of five domains with a possible total score of 88. Various prognostic criteria for the patient's function have been developed over the years. For example, if a patient is not sitting independently when placed by age 2, then one can predict with approximately 95 percent confidence that he/she never will be able to walk.[49] On occasion, such a child will walk, but usually aids are necessary, such as a walker. Most children with cerebral palsy will improve in their function over time, [50] but many have deficits that continue into adulthood.

Stroke

Mortality and morbidity from a stroke are related to older age, history of myocardial infarction, cardiac arrhythmias, diabetes mellitus, and the number of stroke deficits.[51] Evaluation by magnetic resonance imaging (MRI) of the brain obtained during the first few days of the stroke will predict a favorable outcome if less than 80 cc of the brain is infarcted.[52] The 30-day survival after a first stroke has been estimated to be less than 80 percent.[53] For those who survive, it has been estimated that 95 percent of patients reach maximal recovery within 3 to 5 months of the stroke.[54] Functional recovery is dependent on numerous variables, including age, neurologic deficit, comorbidities, psychosocial factors, educational level, vocational status, and characteristics of the stroke survivor's environment.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy is the inhalation of 100 percent oxygen inside a hyperbaric chamber pressurized to greater than 1 atmosphere (atm). HBOT causes both mechanical and physiologic effects by inducing a state of increased pressure and hyperoxia. Hyperbaric oxygen pressure is expressed in multiples of atmospheric pressure at sea level, where 1 atm is about 760 mm Hg or 1 kilogram per square centimeter.[55, 56] The oxygen dissolved in blood at 1 atm (sea level) breathing room air is 0.3 ml/dL, and this is in addition to hemoglobin-bound oxygen. Breathing 100 percent oxygen at 1 atm results in an increase in blood oxygenation to 1.5 ml/dL. Increasing the pressure to 3 atm increases the blood oxygen (dissolved oxygen, not carried by hemoglobin) to 6 ml/dL.[57, 58] At rest and with good perfusion, tissues require 5-6 ml/dL of oxygen, whether from dissolved or hemoglobin-bound oxygen. Hence, in situations where hemoglobin-bound oxygen is limited (e.g., carbon monoxide poisoning), tissue oxygen needs can be met without hemoglobin-carried oxygen.

In addition to this hyperoxic effect, the increased pressure reduces the volume of gases in the blood by virtue of Boyle's law (in an enclosed space, the volume of a gas is inversely

proportionate to the pressure exerted upon it). This is the mechanism relied upon in decompression illness and arterial gas embolism to reduce the size of the gas bubbles and allow replacement of inert gas in the bubbles with oxygen, which can be metabolized by tissues.

HBOT can be administered in two primary ways, using a monoplace chamber or a multiplace chamber.[59, 60] The monoplace chamber serves one patient at a time. It is the less-costly option for initial setup and operation but provides less opportunity for patient intervention while in the chamber. Monoplace chambers are generally constructed of clear acrylic or with acrylic view ports that allow for patient observation. Monoplace chambers are generally pressurized with 100 percent oxygen.

Multiplace chambers allow medical personnel to work in the chamber and care for acute patients to some extent. Each patient is given 100 percent oxygen through a facemask, tight-fitting hood, or endotracheal tube. The entire multiplace chamber is pressurized with air, so medical personnel may require a controlled decompression, depending on how long they are exposed to the hyperbaric air environment.

While the duration of an HBOT session is typically 90 to 120 minutes, the duration, frequency, and cumulative number of sessions has not been standardized. The dose received by the patient may be affected by the type of chamber used. Monoplace chambers using face masks or hoods that do not fit snugly may result in dilution of 100 percent oxygen with room air.[59]

Indications for HBOT

HBOT is used in a wide range of conditions. The following list indicates those uses that are currently recognized by the Food and Drug Administration (FDA):

1. Air or Gas Embolism
2. Carbon Monoxide Poisoning
3. Clostridal Myositis and Myonecrosis (Gas Gangrene)
4. Crush Injury, Compartment Syndrome, and other Acute Traumatic Ischemias
5. Decompression Sickness
6. Enhancement of Healing in Selected Problem Wounds
7. Exceptional Blood Loss (Anemia)
8. Intracranial Abscess
9. Necrotizing Soft Tissue Infections
10. Osteomyelitis (Refractory)
11. Delayed Radiation Injury (Soft Tissue and Bony Necrosis)
12. Skin Grafts & Flaps (Compromised)
13. Thermal Burns
14. Actinomycosis

This list of FDA-approved indications was based on a list of accepted indications produced by the Undersea and Hyperbaric Medical Society (UHMS) in 1978 and updated by the UHMS in 2002.[61] The Centers for Medicare and Medicaid Services (CMS) has a similar list of indications for which it provides coverage. This list is further delineated by the ICD-9 codes used for these indications. These two additional lists appear in Appendix A. Stroke, brain injury, and cerebral palsy are not currently included on these lists of approved indications.

The CMS recently commissioned a systematic review of the evidence for the effectiveness of HBOT in treating hypoxic wounds.[62, 63] The review found that of the 10 types of wounds

currently covered by CMS, "there is sufficient objective evidence that HBOT aids in wound healing for: compromised skin grafts, osteoradionecrosis, gas gangrene, progressive necrotizing infections, and nonhealing wounds. There was evidence from case series suggesting the beneficial effect of HBOT for soft tissue radionecrosis,"[62] but evidence was insufficient to support its use for acute traumatic peripheral ischemia (one case series), crush injuries and suturing of severed limbs (one randomized controlled trial), acute peripheral arterial insufficiency (no study), and chronic refractory osteomyelitis (one non-randomized study, one case series). In a decision memorandum on August 30, 2002, CMS found adequate evidence to continue to provide coverage for the use of HBOT to treat diabetic lower extremity wounds, but did not extend coverage to hypoxic wounds.[64]

Current Policy and Regulation of HBOT

Hyperbaric chambers are classified as class II medical devices by the FDA, and as such require the manufacturers to comply with specific regulations before marketing. The regulatory process requires the manufacturer to specify the intended uses of the device. Manufacturers applying for uses beyond the 14 already acknowledged are required to submit supporting evidence. The evidence would be reviewed by the Center for Drug Evaluation and Research (CDER) in consultation with the Center for Devices and Radiological Health (CDRH). An Investigational New Drug Application (IND) would be required for studies of significant risk, and Investigational Review Board (IRB) approval for any study.[65] Manufacturers cannot advertise or promote uses that are not approved by the FDA.

The FDA has deemed hyperbaric chambers to be prescription devices. This designation requires that a valid prescription is required prior to use. Practitioners authorized to prescribe HBOT vary by state. As is the case with other prescription devices and drugs, a physician who believes that HBOT is the best therapy for a patient with an indication that is not on the list may prescribe HBOT for this "off-label" use.

At present, there are no individual state or nationally mandated standards for hyperbaric facility staffing or training. Other local, state, and federal regulations may apply to the chambers, primarily fire safety and building code regulations. Currently, other types of accreditation or certification of chambers and personnel are not strictly required. Third-party reimbursement typically requires that a physician be present during treatments and is limited to the 13 indications approved by the FDA. Medical center-based chambers also must comply with additional safety and quality-of-care criteria as required by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

Cost of HBOT

In 1996, the cost of an average 90-minute session in the United States was reported to be $300-$400.[56] However, increased demand for HBOT and availability of fee-for-service chambers may have altered the typical cost. A year 2000 report by the Office of the Inspector General[66] reviewed the use of HBOT among Medicare recipients between 1995 and 1998. The average total allowed charge per treatment in 1998 was $405, with an average allowed therapy cost per patient of approximately $12,000.

Adverse Effects of HBOT

Adverse events can occur during compression, treatment, and decompression and are related to the increased pressure and/or the increased oxygen concentration.[67] Complications such as pulmonary barotrauma or seizures can occur seen immediately, but more subtle adverse effects may emerge after a series of treatments. The findings of a recent study of HBOT for acute carbon monoxide poisoning (which is not covered in this report) raise concerns over worse cognitive outcomes in patients receiving HBOT compared to normobaric oxygen.[68]

Rationale for Use HBOT in Brain Injury

In chronic infected or nonhealing soft tissue wounds, local tissue hypoxia predisposes to infection and prevents effective healing.[56] Hyperbaric oxygen reverses local hypoxia, inhibits postischemic vasoconstriction, and promotes the formation of collagen matrix, which is essential for angiogenesis and restoration of blood flow to the injured tissue.[55-57] Although the biochemical and cellular effects of oxygen deprivation and oxygen therapy are well-accepted for soft tissue injuries, the application of these concepts to brain injuries is controversial. Recent theories of neuronal damage and recovery implicate a complex cascade of events that begin with depletion of intracellular ATP and expression of immediate early genes leading to energy failure, mitochondrial dysfunction, oxidative damage to RNA/DNA, and functional or structural brain damage.[69]

A detailed examination of the theoretical basis for the use of HBOT in brain injury is beyond the scope of this report. The theories of brain pathophysiology and recovery from injury, along with the animal experimental studies and human case studies supporting these theories, have been reviewed in detail elsewhere.[70] The following discussion is not comprehensive, but highlights some of the underpinnings of these theories and how they differ from other theories of brain injury and recovery.

Acute Brain Injury. Inadequate supply of blood and oxygen clearly causes injury and cell death in stroke, in which the artery supplying a region of the brain is blocked, and in anoxic-ischemic encephalopathy, in which perfusion to the entire brain is compromised by shock, hypotension, strangling, or another insult. In acute traumatic brain injury, hypoxia and hypotension are each independently associated with increased mortality and morbidity. Thus secondary ischemia and oxygen deficiency are thought to be important mechanisms of cell death in traumatic brain injury.[40]

Because of the devastating effects of hypoxia and hypotension in brain-injured patients, aggressive efforts to avoid or correct hypovolemic shock and to prevent cerebral hypoperfusion became fundamental principles of the management of trauma care. These principles, however, have recently been challenged by studies suggesting that management of perfusion pressure does not improve, and may worsen, the outcome of resuscitation. However, aggressive management of trauma reduces the frequency of hypoxic and ischemic episodes, but does not come close to eliminating it. For this reason, there is renewed interest in finding more effective strategies for ensuring adequate oxygenation and redistributing cerebral blood flow to injured areas of the brain.

Immediately after a brain injury, brain cells can be inactivated temporarily by local, injury-related sequelae such as ischemia and edema which are thought to compromise local perfusion.[5] This observation forms part of the rationale for the use of HBOT, which increases blood flow to the damaged areas of the brain, as documented by serial Single Photon Emission Computed Tomography (SPECT) scans and other techniques.[71-74]

In some experimental models of acute cerebral ischemia and acute carbon monoxide poisoning, HBOT prevents cell death.[70] The mechanism is unclear. Even if redistribution of cerebral blood flow is a factor, the effects of oxygen on the cellular and inflammatory response to injury may be more important.[70] Recently, for example, in a rat model of focal cerebral ischemia, HBOT reduced brain leukocyte myeloperoxidase (MPO) activity, which is produced by white blood cells (polymorphonuclear neutrophils) and is a marker of the degree of inflammation. Rats randomized to HBOT had reduced infarct size and improved neurological outcomes compared with untreated rats, and the degree of neurologic damage was highly correlated with the level of MPO activity.[75] In a separate model of cardiac arrest and resuscitation, the same investigators found that dogs treated with HBOT had better neurological outcomes and, histologically, fewer dying neurons than dogs treated conventionally.[76] The magnitude of neuronal injury correlated well with the neurological outcomes, but was not related to cerebral oxygen delivery or to the rate of oxygen metabolism.

Chronic Brain Injury. Many brain-injured patients progress spontaneously from coma to consciousness to recovery of some cognitive functions. This phenomenon of spontaneous recovery from brain injury implies that some brain cells that have lost function can regain it, sometimes after long periods of time. Several theories of recovery after injury in the central nervous system invoke the concept of temporary, reversible inactivity of brain tissue to explain this phenomenon.

The use of HBOT for chronic brain injury, cerebral palsy, and stroke is based on the theory that, in any brain injury, there are inactive cells that have the potential to recover. According to this theory, these "idling neurons" exist in the ischemic penumbra, a transition area of dormant neurons between areas of dead tissue and the unaffected healthy tissue.[70, 74, 77-79] The theory is that oxygen availability to these cells stimulates the cells to function normally, reactivating them metabolically or electrically.

It is useful to distinguish between this theory and a popular theory in the field of neuropsychology. Both theories invoke the concept of temporary inactivation of neurons, but the neuropsychological theory postulates that the neurons are inactivated by deprivation of innervation that had come from cells now destroyed by TBI.[5] According to this theory, recovery occurs as surviving neurons establish new synaptic connections that can help reactivate cells that are temporarily inactive. Terms such as synaptic reorganization and collateral sprouting are used to describe the process of increasing the number and complexity of these synaptic connections.

This concept arose from observations in animal studies demonstrating growth and reorganization of surviving hippocampal cells after surgical elimination of afferent excitatory input.[80] It was first applied by Russian physicians and psychologists treating soldiers injured in World War II.[81] These early efforts form the basis for "restorative" cognitive rehabilitation and other therapies that aim to restore (rather than compensate for) brain functions that have been lost due to injury.

Recently, a National Institutes of Health Consensus Development Conference conducted an independent, critical assessment of the animal and human evidence regarding this theory and clinical approaches based on it.[5] The panel noted, first, that synaptic reorganization and

"sprouting" observed in the denervated animal brain had not been translated into functional improvements. Second, they noted the lack of evidence that any therapy actually promotes these physiologic processes, either in animal models or in humans. No animal experiments or human case studies have succeeded in linking the clinical observation of improved cognitive function with anatomic or physiologic measures of synaptic enrichment. In fact, human studies have found no relationship between the amount of treatment, frequency of family visits, or other forms of stimulation hypothesized to promote the growth of new synaptic connections. Regarding clinical evidence, the panel found "a notable lack of scientific data concerning the effectiveness of [restorative] interventions. On balance, the limited data available have also been equivocal with respect to the effectiveness of restorative approaches."[5] Subsequently, in a randomized trial in 120 active duty military personnel with moderate to severe TBI, intensive in-hospital cognitive rehabilitation was no more effective than limited home rehabilitation program with weekly telephone support from a psychiatric nurse.[82]

In contrast with the cognitive stimulation theory, the "idling neuron" theory views neuron inactivity denervation as the result of chronic hypoxia, and postulates that restoring oxygen stimulates the growth of blood vessels and of new synaptic connections among previously dormant neurons. Supporters of the use of HBOT in brain injury, argue that this theory has a stronger experimental base than the theory underlying restorative cognitive therapies.[70] In contrast to the theoretical effects of cognitive stimulation, the effects of the proposed treatment—pressurized oxygen—can be observed directly in animal models. As noted above, animal studies have examined HBOT's effects on physiologic and anatomic endpoints, including neuronal death, infarct size, and, in some models, development or preservation of synapses. The physiologic effects of hyperbaric oxygen have also been examined in before-after treatment case studies in humans using SPECT imaging and markers of cerebral metabolism.[72, 74, 83]