Chapter 3

The Future of TBI: Hyperbaric Oxygen as a Primary Therapeutic Approach

B. Miskin, L.A. Fox
Jupiter Medical Center, Jupiter, FL, United States

INTRODUCTION

The human body breathes in and out an average of 10–16 times per minute. The air we breathe contains 21% oxygen, 78% nitrogen, and 1% carbon dioxide and other gases. For an average adult body, the volume of each breath is between 400 and 600 mL. This equals roughly 6–8 L of air per minute. Taking 21% of 6 L equals about 1.3 L of oxygen every sixty seconds. The standard pressure of that air is 1 atm equivalent, or 1 ata, which is equal to roughly 14.5 psi, or 760.00 mm Hg on a barometer. The density of air at sea level under standard atmospheric conditions is roughly 1.2 kg/m^3. At this pressure and density, breathing 21% oxygen provides the average healthy human body with enough oxygen molecules to support normal cellular functions. In other words, our bodies function well when we are breathing in 400–600 mL of 21% oxygen at a pressure of 14.5 psi and a density of 1.2 kg/m^3.

Under a variety of medical situations, supplemental oxygen is used as an adjunct to general atmospheric oxygen. This can occur in both acute and chronic situations where the body is unable to maintain normal cellular function by breathing air alone. Whether in an emergency room, on an operating table, or even at home, people use supplemental oxygen therapy in a variety of situations to assist the distressed human body. However, this is all done at a standard atmospheric pressure and density. What happens when that supplemental oxygen is delivered at a higher pressure? What effects would this have on the body? This is precisely what scientists have been exploring for many years with hyperbaric oxygen therapy, or HBOT. Hyperbaric oxygen tanks are enclosed capsules in which patients lie flat and receive 100% oxygen at anywhere between 1 and 3 ata, or one to three times normal atmospheric pressure. The purpose of this tank is to provide the body with an ultrahigh concentration of supersaturating oxygen that would be unavailable using standard supplemental

New Therapeutics for Traumatic Brain Injury. http://dx.doi.org/10.1016/B978-0-12-802686-1.00003-1

oxygen equipment. HBOT is currently used for a variety of ailments including decompression sickness, cyanide poisoning, and necrotizing infections (Singh and Gambert, 2008). Only within the past decade has HBOT gained a reputation as being a possible treatment for trauma to the brain. This chapter will explore the use of HBOT for traumatic brain injury (TBI), as a review of what is already known and what additional information we must gather in recommending its standard use of therapy.

A BRIEF HISTORY OF HBOT

At 100 ft beneath the surface, the pressure surrounding a scuba diver is about 43 pounds per square inch. With a standard sea level pressure of 14.7 psi, the pressure at that depth is equal to roughly 3 atm of pressure. While being submerged at 100 ft may not pose any inherent danger to the human body, a rapid fall in pressure could be potentially life-threatening. Inert gases, most notably nitrogen, exist in physical solution in the body at high pressure. A sudden decrease in pressure causes the gas molecules to come out of solution and form gas bubbles in the blood stream and other parts of the body. This is exactly what happens when divers surface too quickly and do not allow their bodies to adjust for these dramatic changes in pressure. Professionally called nitrogen sickness, or decompression sickness, popular culture refers to it as "the bends." The bends can be a potentially fatal condition depending on where the gas bubbles form in the body and must be treated immediately. The signs of decompression sickness include a wide array of neurological, cutaneous, musculoskeletal, audiovestibular, and pulmonic symptoms such as fatigue, loss of balance, seizures, confusion, itching, and joint pain. HBOT is the most effective means of dealing with the bends and requires placing the body in an environment that recreates the condition in which inert gases exist in solution. The pressure is then slowly lowered in a way to simulate a slow return to surface that prevents the gas bubbles from forming.

The hyperbaric tank has existed for close to 350 years. Though attempts to conjure its design were previously attempted with no success, a British physician named Nathaniel Henshaw achieved the first documented closed "hyperbaric" environment in the 17th century. Stemming from his work in 1662, Dr. Henshaw reportedly filled a small capsule called a *domicilium* with highly compressed air to create a hyperbaric environment. Henshaw based his work off the principles of the Irish physicist and chemist Robert Boyle, who famously identified the inverse relationship between pressure and volume of air in a closed space. Several 100 years of medical experimentation and development passed before the technology was adopted into mainstream medicine. By the 1870s, hyperbaric tank air therapy was commonly used to treat a variety of ailments with various successes. Due to concerns of oxygen toxicity and limited knowledge of treating such ailments, the original hyperbaric tanks used compressed air instead of oxygen. It was not until 1917 that two German brothers Bernhard and Heinrich Dräger began applying pure oxygen to the tanks, resulting in the

first successful treatment for decompression sickness caused by diving accidents (Singh and Gambert, 2008).

Hyperbaric therapy did not make its way to the United States until 1861, when neurologist James Leonard Corning saw its potential as a unique therapeutic option. Corning was interested in the technique after witnessing severe decompression sickness among site workers in building the Hudson tunnel. He employed the method to treat their collection of symptoms, which was essentially decompression sickness. In 1921, Kansas City-based physician Orval Cunningham built the first hyperbaric tank in the United States with pure oxygen, in treating patients with the flu. Cunningham thought that because there appeared to be a greater incidence of the flu in states with higher altitudes, he could potentially treat the illness with increased pressure. Stunned by his success, Cunningham went on to build the largest known hyperbaric tank in Cleveland, Ohio. The chamber, referred to as the Cunningham Sanitarium, was five stories tall, and contained twelve beds per story. It was considered the "first attempt in history to house people in such a unique structure" (Singh and Gambert, 2008). Due to numerous failures in treating infectious diseases, the chamber was dismantled in 1937.

The use of hyperbaric therapy was widely discontinued for nondecompression-related conditions until 1956, when Dutch cardiac surgeon Ite Boerema used the device to aid in cardiopulmonary surgery. In 1961, Boerema's colleague, Willem Brummelkamp, reported that infections caused by anaerobic bacteria could not survive in a hyperbaric environment, as was postulated by Cunningham and that hyperbaric therapy could provide adequate amounts of oxygen to kill the bacteria. In 1969, the US Navy reported using HBOT to treat patients 3 months following ischemic stroke (Stoller, 2011a). When the neurocognitive tests showed significant improvement, the therapy gained interest as a possible option for treatment of acute stroke. Since its renewal into modern medicine, hyperbaric therapy has been used to treat a variety of conditions including carbon monoxide poisoning, wound healing, various types of bacterial infections, and trauma. Even today, some physicians use HBOT in treating medical conditions including gas gangrene, acute traumatic peripheral ischemia, necrotizing infections, osteoradionecrosis, acute peripheral artery insufficiency, and gas embolism. HBOT is unique in that it is the only nonhormonal therapy used for tissue repair and regeneration (Stoller, 2011b), including such disorders as diabetic wounds, chronic refractory osteomyelitis, and actinomycosis. It is noninvasive which makes it very desirable for patients in their treatment of disease (Singh and Gambert, 2008).

WHAT IS TRAUMATIC BRAIN INJURY?

Brief History

Perhaps the most notable and infamous incident in the history of traumatic brain injury, or TBI, is that of Phineas Gage. Born in 1823, Gage was a railroad

construction worker who experienced severe trauma to the head while assisting in the construction of the Rutland and Burlington Railroad in Cavendish, Vermont. The accident occurred in 1848, when at the age of 25 an unexpected explosion sent an iron rod through Phineas' head and cranium. The rod was three and half feet long, weighed 13 and a half pounds, and had a diameter of one and a fourth inches. The rod entered just under the left cheekbone and flew vertically through his left hemisphere out the top of his head. It landed roughly 30 yards behind him. Even with the substantial head injury, Gage most likely never lost consciousness, as he shortly thereafter walked himself to the office of the physician of Cavendish, Dr. John Martyn Harlow. Gage even explained to Harlow in great detail what had occurred (Macmillan, 2012).

Dr. Harlow treated Phineas' wounds and allowed him to return home 10 weeks after the accident. In 1849, Phineas felt strong enough to return to his work on the railroad. However, the contractor would not rehire Phineas, due to substantial changes in his personality and disposition. Before the accident, Phineas had been a balanced, hard-working, honest individual with a strong intellect and grounded personality. After the accident, Phineas Gage exhibited profanity, would break down in fitful rage, and paraded around like a clown. He became impatient, crude, and obstinate, resorting to immaturity and inappropriate childlike behaviors. These characteristics prevented him from holding any type of intellectual or professional job. Though little is known about the rest of his life, most historians believe that Phineas went on to work remedial jobs as a carriage driver and doorman. His behavior continued to exacerbate throughout his life, causing him to go from one job to another. In 1860, Gage began experiencing epileptic fits, ultimately killing himself that same year (Macmillan, 2012).

The importance of Phineas Gage's story allows us to understand not merely the physical injury that occurred at the time of the accident, but the psychological and personality changes that developed as a result of the trauma. The long-term effects of trauma can be much more hidden and show up slowly over time as a change in behavior and affect. A favorite in the world of neuroscience, Phineas Gage's story is the seed that grew into modern day TBI and how to treat this complex increasing disorder throughout the world.

Traumatic Brain Injury

TBI is widely considered to be one of the most damaging and misunderstood conditions to the human body. In fact, many believe it to be the leading undiagnosed brain disorder in the United States (Boussi-Gross et al., 2013; Raji et al., 2014). Every year, roughly 2 million people suffer from a traumatic brain experience in the United States. More than 500,000 are hospitalized and 50,000 die due to the severity of the injury and lack of adequate treatment. The cost of hyperbaric therapy in the United States is ~56 billion dollars per year (Rockswold, Rockswold, & Defillo, 2007). People, who play contact sports

such as football, engage in potentially dangerous hobbies like motorcycling, and members of the military are more likely to experience TBI. While 70–90% of TBI incidents are considered mild, roughly 25% of people do not recover and develop chronic symptoms such as postconcussive syndrome (Boussi-Gross et al., 2013).

Shortly after a TBI, victims can experience symptoms such as confusion, loss of memory, slurred speech, and even seizures (Hoge & Jonas, 2014). Those living with TBI can struggle with its devastating effects for days, months, years, or potentially the rest of their lives (Boussi-Gross et al., 2013). The actual trauma occurs due to a sudden physical assault on the head that causes damage to the brain. The damage can be focal, confined to one area, or diffuse, involving multiple areas of the brain. The injury itself can be closed-head or penetrating. A closed-head injury occurs when the head suddenly and violently hits an object, but the object does not penetrate through tissue or the skull. A penetrating head injury occurs when an object pierces the skull and enters the brain, destroying tissue and brain matter (Jordan, 2013). While ischemia can also cause significant damage to the brain, it is not usually caused by blunt external force, and thus will not be examined in this chapter.

The Centers for Disease Control and Prevention estimates (Rockswold et al., 2007) that there were 2.5 million cases of TBI in 2010; that same year, TBIs contributed to the deaths of more than 50,000 people; TBI-related emergency department visits increased by 70% from 2001 to 2010; and 249,000 children were treated for TBI that resulted from recreational or sporting activities in 2009. It is important to identify TBI as quickly as possible in part due to the "second-impact syndrome." When a patient sustains a second head injury before fully recovering from the first, "It leads to an exaggerated response and carries a 50% mortality rate" (Ling & Marshall, 2008). While some drugs have shown neuroprotection in animals after a TBI, none have proven very useful in humans. In fact, the standard of care for TBI today consists of allowing the brain to rest and providing symptom relief, primarily for pain (Ling & Ecklund, 2011). Improved treatment will come through understanding the physical changes in the brain that occur at the microscopic and molecular levels when the brain is subject to trauma. That understanding is only beginning to emerge (McKee et al., 2009).

SYMPTOMS OF TRAUMATIC BRAIN INJURY

Acute Symptoms

Symptomatology of TBI can be extensive, encompassing a wide variety of both neurological and neuropsychiatric symptoms occurring from the moment of impact. While many symptoms occur shortly after the injury, most long-term effects do not show up until weeks or even months after the incident (Rice et al., 2003; Rink et al., 1995). Acute and chronic symptoms alike can be mild,

moderate, or severe, depending on the extent of damage to the brain (Algattas & Huang, 2013). While it is not uncommon to experience a loss of consciousness, many who experience TBI remain conscious during the event (Siesjo, 1993). The most immediate symptoms are feeling dazed and not quite normal. Other more immediate symptoms include headache, confusion, lightheadedness, dizziness, blurred vision or tired eyes, ringing in the ears, bad taste in the mouth, fatigue, or lethargy. Within a week, an individual may develop a change in sleep patterns, behavior or mood, and trouble with memory, concentration, attention, and thinking (Boussi-Gross et al., 2013).

A person with a moderate to severe TBI may also experience more significant symptoms, including intractable headache, repeated vomiting or nausea, convulsions or seizures, inability to awaken from sleep, dilation of one or both pupils of the eyes, slurred speech, weakness or numbness in the extremities, loss of coordination, and/or increased confusion, restlessness, or agitation (Liu, Fawcett, Hanson, & Frey, 2004; Jordan, 2013). Small children with moderate to severe TBI may display the same symptoms in addition to persistent crying, inability to be consoled, and/or refusal to nurse or eat (Jordan, 2013).

Within days to weeks of the head injury, ~40% of TBI patients develop a host of troubling symptoms collectively referred to as postconcussion syndrome (PCS) (Boussi-Gross et al., 2013). While this typically occurs after the loss of consciousness, a patient need not have had a loss of consciousness to develop PCS. Symptoms of PCS often include headache, dizziness, vertigo, memory problems, trouble concentrating, sleep problems, restlessness, irritability, apathy, depression, and anxiety and can last for weeks or even months. The syndrome is more prevalent in patients who have had previous psychiatric symptoms, such as depression or anxiety, before the injury. Treatment for PCS is often limited to alleviating the pain, inability to sleep, and psychiatric conditions. People with PCS often engage in psychotherapy and occupational therapy as well as a variety of different coping mechanisms (Boussi-Gross et al., 2013).

Another ailment that affects roughly 15–33% of individuals with severe TBI is called paroxysmal sympathetic hyperactivity (PSH), or cerebral storming. PSH takes place in the deep structures of the brain and causes a series of episodic dysfunctions in the nervous system. It can cause dramatic changes in blood pressure, heart rate, body temperature, and muscle tone. Because these symptoms are also present in a variety of other conditions, such as seizure disorders, neuroleptic malignant syndrome, and expanding cerebral lesions, it is often difficult to diagnose them as associated with TBI (Masel, 2011).

Chronic Ailments

Long-term disabilities resulting from a TBI depend upon the location and severity of the injury, as well as the age and general health of the patient (DeKosky, Ikonomovic, & Gandy, 2010). While almost any postinjury neurological abnormality can qualify as a symptom of TBI, common disabilities include problems

with cognition, sensory processing, communication, and behavior or mental health (mood problems, personality changes, and aggression) (Jordan, 2013).

The most common cognitive impairment among severely head-injured patients is memory loss (Siesjo, 1993). This is also referred to as posttraumatic amnesia (PTA), either anterograde or retrograde (Boussi-Gross et al., 2013). Anterograde PTA is impaired memory of events that occurred after TBI, while retrograde PTA is impaired memory before the incident (Jordan, 2013). Many patients with mild to moderate head injuries who experience cognitive deficits become easily confused or distracted and have problems with concentration and attention. They may also have problems with higher level, so-called executive functions, such as planning, organizing, abstract reasoning, problem solving, and making judgments, making it difficult to resume preinjury work-related activities. Unfortunately, recovery from cognitive deficits is greatest within the first 6 months postinjury, becoming slower and more gradual thereafter (Algattas & Huang, 2013). Patients with moderate to severe TBI tend have more problems with cognitive deficits than patients with mild TBI, but a history of several mild TBIs may have an additive effect, causing cognitive deficits equal to a moderate or severe injury (Jordan, 2013).

Some TBI patients can develop quite significant sensory and motor changes (DeKosky et al., 2010). Depending on the severity of the injury, patients who develop severe sensory issues may not be able to register what they are seeing or may be slow to recognize objects. This can also be the case in developing problems with hand–eye coordination (Jordan, 2013). These individuals may be prone to bumping into or dropping objects, or may seem generally unsteady (Boussi-Gross et al., 2013). This can affect activities such as driving a car, working complex machinery, or even playing sports (Jordan, 2013). Other sensory deficits may include problems with hearing, smell, taste, or touch (DeKosky et al., 2010). It is not unusual for TBI patients to develop tinnitus, a ringing or roaring in the ears. Damage to that part of the brain that processes taste or smell may result in a persistent bitter taste in the mouth or perceive a persistent noxious smell (DeKosky et al., 2010). Damage to the part of the brain that controls the sense of touch may cause a TBI patient to develop persistent skin tingling, itching, or pain (Jordan, 2013). While these sensory conditions are not extremely common, they are difficult to treat when they occur.

Language and communication problems can also be common disabilities in TBI patients (DeKosky et al., 2010). The most common is called aphasia, defined as difficulty with understanding and producing spoken and written language. Others may have difficulty with the more subtle aspects of communication, such as body language and emotional, nonverbal signals. In nonfluent aphasia, also called Broca's aphasia or motor aphasia, TBI patients often have trouble recalling words and speaking in complete sentences, in addition to frequent pausing (Vas, Chapman, & Cook, 2015). Patients with fluent aphasia, also called Wernicke's aphasia or sensory aphasia, display little meaning in their speech, even though they speak in complete sentences and use correct

grammar. They often speak in flowing gibberish, drawing out their sentences with nonessential and often invented words. Patients with global aphasia, where damage affects both areas of communication often suffer severe communication disabilities.

Some TBI patients have difficulty with the physical process of speaking, due in part to damage of the brain region that controls speech muscles. In this disorder, called dysarthria, the patient can think of the appropriate language but cannot easily speak the words because he or she is unable to use the muscles needed to form the words and produce the sounds (DeKosky et al., 2010). Speech is often slow, slurred, and garbled. Some may have problems with intonation or inflection, called prosodic dysfunction (Vas et al., 2015). These language deficits can lead to miscommunication, confusion, and frustration for the patient as well as those interacting with him or her.

Due to the nature of the injury, some TBI patients develop significant emotional and behavioral problems that are recognized as psychiatric conditions (Jordan, 2013). Family members of TBI patients often find that personality changes and behavioral problems are the most difficult symptoms to handle. Psychiatric problems include depression, apathy, anxiety, irritability, anger, paranoia, confusion, frustration, agitation, insomnia or other sleep problems, and mood swings. Problem behaviors often include aggression and violence, impulsivity, disinhibition, acting out, noncompliance, social inappropriateness, emotional outbursts, childish behavior, impaired self-control, impaired self-awareness, inability to take responsibility or accept criticism, egocentrism, inappropriate sexual activity, and alcohol or drug abuse/addiction (Amen et al., 2011). Some patients' personality problems may be so severe that their symptoms resemble borderline personality disorders, characterized by a combination of several unusual personality traits (Jordan, 2013).

Patients with severe TBI and extensive neural death often suffer from developmental stagnation, meaning that they fail to mature emotionally, socially, or psychologically, after the trauma. This can be a serious problem for both children and young adults, as attitudes and behaviors that are appropriate for a child or teenager become inappropriate in adulthood. It is fortunate that many TBI patients who display psychiatric or behavioral problems can be helped with medication and psychotherapy/support.

THE MILITARY AND TRAUMATIC BRAIN INJURY

TBI is currently a significant problem in the military, especially among troops returning from the Middle East. It is no surprise that blast injury is the most common cause of war injuries and death (Okie, 2005). However, due to better equipment and protection, closed-head TBI is occurring at very high rates. Blasts or explosions that would have been fatal in the past are now simply injuries. Because nothing actually penetrates the brain in most explosions, blast-induced TBI can be much more difficult to spot and accurately diagnose.

The contribution of the primary blast wave to brain injury is an area of active research. In combat, sources of blast injury include artillery, rocket and mortar shells, mines, booby traps, aerial bombs, improvised explosive devices (IEDs), and rocket-propelled grenades (RPGs) (Coupland & Meddings, 1999; Gondusky & Reiter, 2005; Murray et al., 2005). The severity and pattern of blast injuries depends on the explosive composition and amount of material involved, surrounding environment, delivery method, distance between the victim and the blast, and presence of intervening protective barriers or environmental hazards.

The four basic mechanisms of blast injury are termed primary, secondary, tertiary, and quaternary (DePalma, Burris, Champion, & Hodgson, 2005). Primary injuries occur secondary to a high-order over pressurization shock wave moving through the body. This wave affects gas-filled organs such as the lungs, gastrointestinal tract, and middle ear. These injuries are not necessarily obvious and make diagnosis of any problem rather difficult. Secondary injuries can occur due to flying bomb fragments and other objects propelled by the explosion, resulting in penetration into the body. Tertiary injuries result from the blast wind (in contrast to the high-pressurized shock wave) throwing the victim and can include bone fractures and traumatic amputation. Quaternary injuries are those not included in the first three classes, such as burns, crushing injuries, and respiratory injuries. Blast injuries are often polytraumatic, meaning that they impact more than one body system or organ. It has been estimated that over 60% of blast injuries result in traumatic TBI, and, for this reason, TBI is often referred to as the "signature injury" (Sayer et al., 2008).

One report published in 2012 in the *Journal of Neurotrauma* showed substantial improvements on several neuropsychiatric planes in 16 military personnel treated for TBI with 1.5 ata HBOT, using SPECT as a their primary diagnostic tool (Harch et al., 2012). A case report in *Undersea Hyperbaric Medicine* discussed the treatment of two airmen with significant TBI symptoms including irritability, sleep disturbances, memory issues, and headaches. Preinjury neuropsychiatric testing had been completed on both Airmen, who were each treated with 1.5 ata for 3 months. The treatment not only resulted in complete resolution of their symptoms, but neuropsychiatric test scores were almost identical to scores taken preinjury (Wright, Zant, Groom, Schlegel, & Gilliland, 2009). Because this suggests such positive outcomes, several initiatives have been put in place that would bring HBO tanks to US military bases in the Middle East. A group of scientists from the University of Minnesota have designed a study that would involve troops in Iraq and Afghanistan with the following hypothetical scenario:

> *A Level III Air Force Theater Hospital located in Balad, Iraq, and Bagram, Afghanistan could support the infrastructure and personnel for an HBO facility. We envision a monoplace tank being installed at these Level III facilities. The tanks would be pressurized with air with the patient breathing 100% oxygen. Hyperbaric technicians would be required to maintain the chambers and*

technically deliver the HBO treatments. Critical care nurses and respiratory therapists would need training in the management of these patients in the HBO tanks. Treatments would be delivered to TBI victims immediately after appropriate resuscitation/stabilization had occurred. If craniotomy were to be required, including decompressive craniectomy, HBO treatment would be initiated in the recovery ICU setting as soon as the patient was stable. Although early HBO treatments are important, when ischemia is most severe, our research suggests that treatment given at any time during the 5-day post injury period results in positive response. Whenever transport and transfer of the patient to Landstuhl, a Level IV Army Regional Medical Center in Germany, was deemed appropriate, this would be carried out. The Critical Care Air Transport Team would perform transfer in the usual way. Transport time from Balad to Landstuhl is approximately 7 hours and approximately 9 hours from Bagram to Landstuhl. A second HBO facility as described above would be instituted in Landstuhl. HBO treatments would continue every 12 hours for up to 5 days depending upon response. Since the total average time spent in Iraq/Landstuhl is 4–5 days prior to transport to a continental United States (CONUS) hospital, initial HBO treatment would be completed in most cases. If not, treatment could continue at a CONUS hospital.

The goal of this initiative is to gain additional knowledge on the impact of HBOT on blast-induced TBI, while providing immediate care to injured military personnel. This would hopefully improve their outcome before returning to the United States. Because PTSD is also common in returning soldiers, airmen, sailors, and marines, it adds to the complication of how TBI should be treated. The general consensus is that each ailment be treated individually. By reducing the neuropsychiatric effects of TBI, HBOT may assist in decreasing or even eliminating symptoms of PTSD.

SPORTS AND THE NATIONAL FOOTBALL LEAGUE

Though head injuries are hardly a new discovery in sports, for decades they were a blind spot. While a broken arm or torn ligament would force you from the game, until recently, a warrior who sustained a concussion—who'd had his bell rung—would shake it off and then return quickly to the playing field. Today, there is a growing alarm about the dangers of TBI in sports, especially in regards to how those injuries affect athletes in the long term. In a discussion at the American Association for the Advancement of Science (AAAS), researchers described how injuries that show little abnormality on an MRI or CT scan can, years later, have debilitating effects ranging from irritability to rage and dementia (Roehr & Lempinen, 2012). This seems to especially be the case for a growing number of professional football players.

While TBI has always been associated with contact sports like football, it has only recently gained spotlight in the arena due to a large number of ex-National Football League (NFL) players reporting chronic symptoms of moderate to severe injury. Unfortunately, this is also happening to active players as

well. In 2010, there were reports of 154 concussions just eight weeks into the season. This is an increase of 21% from 2009 and a 34% increase from 2008 (Stoller, 2011a). Not surprisingly, the NFL is facing lawsuits from nearly 4000 ex-players. In addition to reports of severe TBI symptoms, several current or former players have also committed suicide in recent years. Safety concerns are not only on the rise for professional league but have now extended to community peewee and high school football programs. Reports of concussions and moderate TBI in both community and high school football have risen in the last several years. Taken together, this stream of data seems to represent a TBI epidemic (Roehr & Lempinen, 2012) that may also spread to other sports including soccer, rugby, hockey, and even basketball.

The high rate of cerebral concussion, or mild TBI, in football affords a unique opportunity to examine the immediate and long-term effects of this injury in athletes. Kevin M. Guskiewicz and colleagues have been researching this epidemic to better understand the long-term consequences of recurrent mild TBI in retired professional football players. They investigated the relationship between sport-related concussion and lifetime clinical depression (Guskiewicz et al., 2007). One of their studies, published in *Neurosurgery*, involved surveying 2552 retired players. Each player filled out a general health questionnaire, including information about prior injuries and other markers for depression. The average age was 54 years old and average career lasted 7 years. A second questionnaire focusing on mild cognitive impairment issues was completed by a subset of 758 retired professional football players (50 years and older). Only 269 (11.1%) of all respondents reported having prior or current diagnosis of clinical depression. The results showed a proportional association between recurrent concussion and diagnosis of lifetime depression, suggesting that the prevalence increases with increasing concussion history. Compared to retired players with no history of concussion, those reporting three or more previous concussions (24.4%) were three times more likely to develop clinical depression, while those with a history of one or two previous concussions (36.3%) were 1.5 times more likely to receive a diagnosis (Guskiewicz et al., 2007).

Guskiewicz's findings were alarming and have significant implications for understanding the relationship of TBI to lifetime history of depression. TBI can result in diffuse lesions in the brain, depending on the mechanism of injury (Rice et al., 2003). These lesions result in biochemical changes, including an increase in excitatory neurotransmitters, which has been implicated in neuronal loss and cell death (Rink et al., 1995). A potential mechanism for lifelong depression could be this initial loss of neurons, which could be compounded by additional concussions, eventually leading to the structural changes seen with major depression. The structural changes could put the individuals at greater risk of depressive episodes, creating a positive-feedback cycle predicated on the original injury (Guskiewicz et al., 2005).

Another condition that is common in players with repeated TBI is chronic traumatic encephalopathy, or CTE (Fig. 3.1). This disease is characterized by

the deposit of excess tau proteins in numerous parts of the deep brain (Amen et al., 2011). Omalu and McKee completed a premier study using multiple brain-imaging methods and neuropsychological testing to demonstrate significant brain abnormalities in a large group of living active and retired professional football players. On SPECT scan, significant decreases in regional cerebral blood flow appeared across the whole brain, especially in the prefrontal poles, temporal poles, occipital lobes, anterior cingulate gyrus, and cerebellum (Fig. 3.2). This pattern is

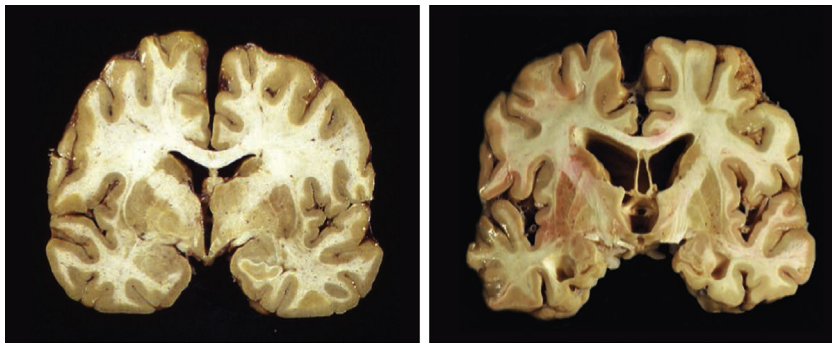

FIGURE 3.1 **Visible damage**. Mild but repetitive brain injury can transform healthy brain tissue (left) into the atrophied and deteriorated tissue associated with chronic traumatic encephalopathy (right). *Reprinted from Roehr, B., & Lempinen, E. (2012). Traumatic brain injury: new insight, but treatment remains elusive.* Science Magazine*, 338.* www.sciencemag.org.

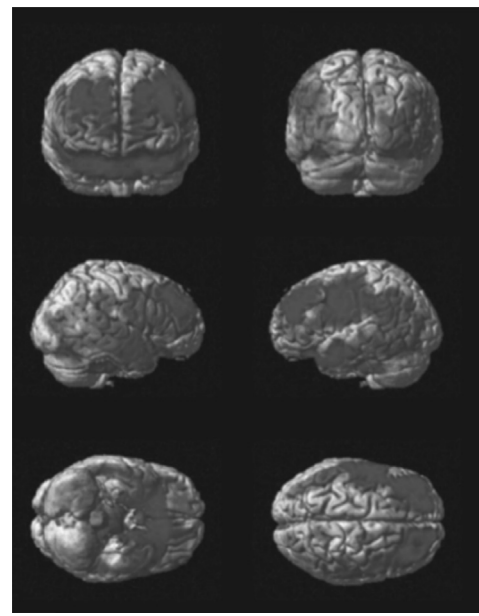

FIGURE 3.2 Darker areas indicate decreased perfusion in the NFL players versus healthy-brain subjects at $p<.0001$, family-wise error. No increases were seen. *Reprinted from Amen, D. G., Newberg, A., Thatcher, R., Jin, Y., Wu, J., Keator, D., et al. (2011). Impact of playing American professional football on long-term brain function.* Journal of Neuropsychiatry and Clinical Neurosciences*,* 23*(1), 98–106.*

consistent with the lasting effects of TBI. They also found significant decreases in the posterior cingulate gyrus and hippocampus, areas implicated in dementia.

The Mild Cognitive Impairment Screen has been found to be a reliable tool in distinguishing mild cognitive impairment and dementia from normal function (Pellman & Viano, 2006). In the general population, the prevalence of mild cognitive impairment or dementia under age 50 is typically 0.1%. In Omalu and McKee's sample, 4.5% of subjects in this age range scored in the abnormal range on the Screen. The general incidence of dementia between age 50 and 65 ranges from 0.3% to 2.2%; in their sample 12% in this age group had abnormal Screen studies. The normal incidence of dementia at 65 is 2.2%, increasing to 6.5% at age 75. In their sample, 36% of players in this age range had an abnormal Screen study. Over age 74, 100% of players had abnormal Screen scores (Amen et al., 2011).

THE SCIENCE BEHIND HBOT FOR TRAUMATIC BRAIN INJURY

How Does It Work?

Although scientists have yet to discover all the intricacies by which HBOT affects the brain both short and long term, some foundational understandings about the nature of HBOT provides us with the basis for how treatment works. Simply stated, HBOT is highly pressurized oxygen that is supplied to the human body in a closed container. Because oxygen is needed for basic cellular function, injury or disease, resulting for example from TBI, can affect the way cells within the body receive oxygen. Because the molecule hemoglobin is responsible for carrying most blood in the body, very little is actually free in the plasma at a given time. Henry's law states that the volume of gas dissolved in a liquid or tissue and the partial pressure of that gas is proportional. As a result, increasing pressure causes more oxygen to dissolve in the plasma, which maximizes oxygenation of the tissues.

Because plasma carries an increased concentration of oxygen in an HBOT environment, the pressure of oxygen in the plasma is higher (Singh and Gambert, 2008). In accordance with Fick's law, which states that the partial pressure of a substance is proportional to its driving diffusion force and distance, this results in the ability for oxygen molecules to go deeper and more readily into tissues than oxygen carried on hemoglobin. For a person breathing normal air at a pressure of 2.0–2.5 ata, the oxygen concentration in the plasma increases by threefold. If that person was to breathe 100% oxygen at 2.5 ata, as per a hyperbaric oxygen chamber, the result is a 17-fold increase in oxygen carried freely in the plasma. Consequently, a healthy person who breathes in 100% oxygen at 2.5 ata would theoretically not require any hemoglobin at all, though this has not been tested. In addition to raising oxygen bioavailability, HBOT also affects the immune system. Not only can oxygen free radical molecules kill certain bacteria, HBOT has been shown to stimulate fibroblast activity and angiogenesis, increase the effectiveness of leukocytes, and stimulate the genesis of granulocytes (Singh and Gambert, 2008). Because of the ischemic affects of

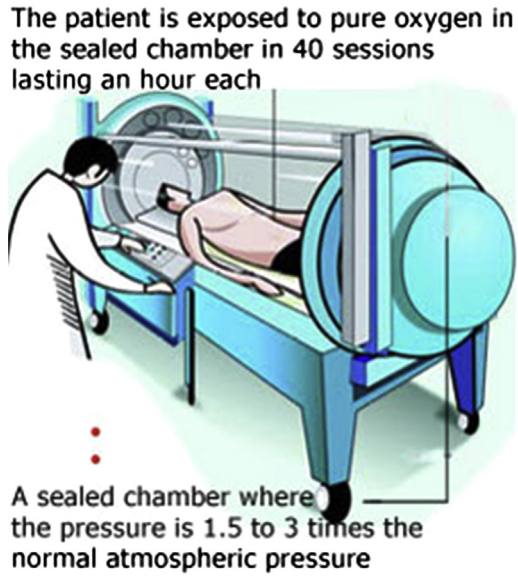

FIGURE 3.3 Cartoon depiction of modern hyperbaric therapy session.

TBI, the primary contribution of HBOT would be to drastically increase oxygen availability to oxygen-deprived cells in the brain (Fig. 3.3).

On the Cellular and Molecular Level

TBI at the time of insult results in varying amounts of direct cell injury and death. In the first 24 h after injury, there is relatively good evidence of ischemia resulting in decreased oxygen delivery that is inadequate to maintain efficient oxidative cerebral metabolism (Bouma et al., 1992; Vigue et al., 1999). This metabolic state appears to trigger a marked increase in the glycolytic metabolism of glucose (Bergsneider et al., 2001; Hovda, Yoshino, Kawamata, Katayama, & Becker, 1991). This relatively inefficient anaerobic metabolism results in a depletion of cellular energy. As the demands for energy production are no longer met, brain cells lose their ability to maintain ionic homeostasis and this can result in abnormally high intracellular concentrations of calcium (Siesjo, 1993; Waxman, Ransom, & Stys, 1991; Young, 1992). A combination of cellular acidosis and excessive concentrations of calcium activate various important intracellular proteins. This abnormal cellular environment results in the release of excitatory amino acids and the formation of highly reactive free radicals that are extremely damaging to cell membranes (Krause, Kumar, White, Aust, & Wiegenstein, 1986). The high levels of intracellular calcium can also lead to excessive levels absorbed onto neuronal mitochondria membranes, leading to the impairment

of mitochondrial respiratory chain-linked oxidative phosphorylation and further disruption of aerobic metabolism (Menzel et al.,1999; Verweij et al., 1997). Mitochondrial dysfunction can persist for days after the initial insult (Lifshitz, Sullivan, Hovda, Wieloch, & McIntosh, 2004; Signoretti et al., 2001; Verweij et al., 2000) leading to neuronal cell death via apoptosis.

Postmortem studies have consistently shown a high incidence of global and/or focal ischemia following severe TBI (Bouma et al., 1992). This is related to the fact that cerebral blood flow (CBF) studies in severe TBI done early after injury have demonstrated a marked reduction in blood flow to the brain. In addition, oxygen delivery to brain tissue is impaired by diffusion barriers to oxygen reaching the cells (Menon et al., 2004). As a consequence of reduced blood flow and diffusion barriers, and at the precise time that energy demands are increased following TBI, oxygen delivery to the brain is reduced. This process has aptly been termed a "metabolic/flow" mismatch.

Oxygen delivery depends on a pressure gradient from the alveolar spaces to blood and finally to the brain itself. HBO greatly increases this vital oxygen delivery pressure gradient. Brain tissue oxygen monitoring, both experimentally and clinically, routinely demonstrates levels of 200–300 mm Hg compared to a baseline of 20–30 mm Hg with HBO at 1.5 ata, which is standard setting in clinical studies for treating TBI (Daugherty, Levasseur, Sun, Rockswold, & Bullock, 2004; Rockswold et al., 2007). Global oxygen consumption has been shown to significantly increase following HBO treatment in clinical studies of severe TBI patients as well as experimental animals (Daugherty, et al., 2004; Rockswold et al., 2001). Since there is little if any oxygen storage in the brain and mitochondria consume 90% of the oxygen, this suggests improved oxidative mitochondrial metabolism. In a series of experimental studies of TBI, HBO-treated animals compared to control-injured animals showed restored mitochondrial function, significantly improved production of adenosine triphosphate (ATP), decreased hippocampal neuronal cell loss, and improved cognitive recovery (Daugherty et al., 2004; Zhou et al., 2007). These experimental data strongly suggest that mitochondrial function is significantly reduced by TBI, but have the potential for recovery, and that HBO treatment promotes recovery in mitochondria and allows them to use baseline oxygen more efficiently after HBO treatment. This improves cerebral metabolism as manifested by improved neurocognitive function in the animal model as well as preservation of brain cells in the hippocampus. Other areas that are significantly impacted by HBOT include the sensory-motor and visual cortices. Micarelli and colleagues showed that after 40 min of HBOT, regional cerebral blood flow (rCBF) had increased in these areas using SPECT. They also showed higher perfusion distribution in areas involved with dorsal attention and in default mode network (Micarelli, Jacobsson, Larsson, Jonsson, & Pagani, 2013).

Maintaining the balance between hyperoxia and hypoxia is critical for effective HBOT management (Algattas & Huang, 2013). One study found that hyperoxia at a normobaric pressure actually increased cerebral excitotoxicity

due to increased CMD glutamate levels (Quintard, Patet, Suys, Marques-Vidal, & Oddo, 2015). As a result, monitoring brain tissue oxygenation plays a critical role in the proper administration of HBOT. It is possible that more consistent, accurate measurement methods would align the HBOT literature and support the case for its use. Monitoring technologies, specifically for critically injured patients in an ICU setting, involve either the placement of a catheter into the brain parenchyma or the use of optical sensory and wavelength analysis to quantify oxygen concentrations via a photochemical reaction visualized by indicator compounds (Algattas & Huang, 2013). Along with oxygen saturation, it is valuable to monitor intracranial pressure or ICP. Technologies to do this include external ventricular drains, intraparenchymal (or "Bolt"), subdural, and extradural monitors. ICP spectral waveform analysis, which measures heart rate, slow vasogenic waves, and respiratory waves has also been used. Bioengineers are currently improving the computational analysis involved to allow more sophisticated use of the spectral software (Algattas & Huang, 2013).

CLINICAL TRIALS OF HBOT FOR TRAUMATIC BRAIN INJURY

Animal modeling has been very important in demonstrating preliminary effectiveness of HBOT. Previous animal studies of HBO therapy for TBI have shown that increases in PO_2 immediately after injury can enhance mitochondrial redox potential and increase brain tissue O_2 consumption (Daugherty et al., 2004). Investigators at the University of Minnesota recently completed a preliminary animal study, using a cognitive water maze test 11–15 days after the animals had experienced TBI. Rats were given TBI by lateral fluid percussion impact and then exposed to normobaric 30% or 100% O_2 alone for 4 h, or 1 h of HBO followed by 3 h of normobaric 100% O_2. The HBO therapy consisted of 100% O_2 pressurized to 1.5 ata. They found that injured animals receiving only 30% O_2 took a significantly longer time to reach the goal platform (90.5 s) compared with rats in the other groups (100% normobaric O_2 treatment, mean time 77.4 s; HBOT treatment, mean time 65.5 s; and sham-injured group treated with 30% O_2, mean time 42.2 s). The ANOVA analysis of goal latencies revealed a significant main effect of the group. These results demonstrate that HBO therapy can extensively reduce cognitive deficits associated with TBI in rats (Personal communication, 2014).

Another animal study demonstrated that HBOT suppressed microglial activation, TNF-α expression, and neuronal apoptosis in rats in both groups treated either 1 or 8 h after fluid-percussion-induced TBI (Lim et al., 2013). A study completed by Chen and colleagues demonstrated that interleukin-10 (IL-10) plays a role in the neuroprotection of mouse brain affected by TBI. Their study showed that after only 1 h at 2.0 ata HBOT, the brains showed reductions in lesion volume, cerebral edema, apoptosis (decreased ratio of caspase-3 to pro-C3 and decreased Bax expression), inflammation, and improved neurological

status. They also noticed an improvement in the blood–brain barrier and unregulated expression of tight junction proteins. From these results, they concluded that IL-10 had a significant role in the protection of tissue (Chen et al., 2014). Vlodavsky and colleagues demonstrated a reduction in neuroinflammation and expression of matrix metalloproteinase-9 in 10 rats that underwent two sessions of 2.8 ata 45-min HBOT treatments. They discovered that animals treated with HBOT had a significant decrease of apoptotic cells as determined by TUNEL analysis and had a substantial reduction of neutrophilic inflammatory infiltration. Animals in the control group (normobaric oxygen) showed no significant changes (Vlodavsky, Palzur, & Soustiel, 2006).

In 2012, Harch and colleagues conducted a preliminary study on the efficacy of only 1.5 ata HBOT on military patients with blast-induced mild to moderate TBI and posttraumatic stress disorder. Sixteen subjects received the entire round of treatment. After just a few weeks of treatment, patients experienced significant improvements in full-scale IQ, working and delayed memory, impulsivity, PCS symptoms, PTSD symptoms, depression, anxiety, and quality of life. In addition, there were extensive improvements in physical exam findings and SPECT scan abnormalities. Fig. 3.4 shows areas of the cortex that experienced increased regional cerebral blood flow (Harch et al., 2012).

A meta-analysis involving seven HBOT studies and over 500 patients found HBOT to be associated with a decrease in unfavorable outcomes 1 month after treatment using the Glasgow Coma Scale (GCS) (Bennett, Trytko, & Jonker, 2012). The same study revealed that the relative risk of death with HBOT was 0.69 (NNT = 7) compared to normal treated controls.

It is not surprising that both location and severity of brain damage can make a significant difference in the level of recovery. As one 2004 study points out, "In young patients with brainstem contusion, significantly more regained

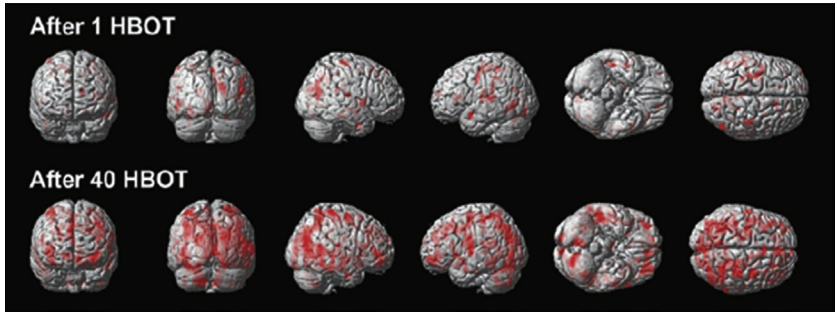

FIGURE 3.4 Cortical views from the front, back, right, left, inferior, and superior aspects show effects of 1 HBOT (top row) and 40 HBOTs (bottom row) at a significance level of $p < .001$. Significant increases in brain blood flow are shown in *red* (HBOT, hyperbaric oxygen therapy). *Reprinted from Harch, P. G., Andrews, S. R., Fogarty, E. F., Amen, D., Pezzullo, J. C., Lucarini, J., et al. (2012). A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder.* Journal of Neurotrauma, 29*(1), 168–185.*

consciousness at 1 month with HBOT (67%) than control (11%)" (McDonagh, Helfand, Carson, & Russman, 2004). The study also pointed out that "patients with an intracranial pressure (ICP) greater than 20 mm Hg or a Glasgow Coma Scale score of 4 to 6 had significantly lower mortality at 1 year with HBOT than with the control group." The researchers noted that HBOT could be used to actually reduce ICP in patients with TBI. With further regards to the GCS, a 2008 study found that out of 44 patients, 22 enrolled in HBOT versus control and improved from 11.1 to 13.5 on average. The control group averaged an increase of 10.4–11.5 (Lin et al., 2008).

A clinical analysis in the United Kingdom showed that patients who have TBI and received 30 sessions of HBOT in addition to standard treatment had a better outcome than those who were only given standard treatment. The research group found that those with a Disability Rating Scale (DRS) score of 22–24 (vegetative state) showed the most improvement. Following the treatment, a larger portion of patients who received HBOT versus those who did not exhibited a stronger recovery in cognitive functions (Sahni, Jain, Prasad, Sogani, & Singh, 2012).

Dr. Shai Efrati of Tel Aviv University's Sackler Faculty of Medicine has demonstrated significant preservation of neurological function in brain tissue thought to be chronically damaged even years after initial injury. Theorizing that high levels of oxygen could reinvigorate dormant neurons, Dr. Efrati and his fellow researchers, including Professor Eshel BenJacob of TAU's School of Physics and Astronomy and the Sagol School of Neuroscience, recruited poststroke patients for HBOT. Analysis of brain imaging showed significantly increased neuronal activity after a 2-month period of HBOT treatment compared to control periods of nontreatment, as reported by Dr. Efrati in *PLoS ONE*. Patients experienced improvements such as a reversal of paralysis, increased sensation, and renewed use of language. Seventy-four participants spanning 6–36 months poststroke were divided into two groups. The first treatment group received HBOT from the beginning of the study, and the second received no treatment for 2 months, then received a 2-month period of HBOT treatment. Treatment consisted of 40 2-h sessions five times weekly in an HBO tank. The results indicated that HBOT treatment can lead to significant improvement in brain function in poststroke patients even at chronically late stages, helping neurons strengthen and build new connections in damaged regions (Efrati et al., 2013). It was also suggested that while there is no agreed-upon effective metabolic intervention for TBI, HBOT appears to be an invaluable tool in repairing and maintaining metabolic function of the brain after TBI (Efrati & Ben-Jacob, 2014).

In 2006, a group of Chinese scientists conducted a study on 310 patients exhibiting neuropsychiatric ailments resulting from mild TBI. After receiving only two treatments of HBOT, 70% of the patients did not show any signs of brain damage on SPECT scan. The patients had also improved significantly on their neuropsychiatric tests (Shi, Tang, Sun, & He, 2006).

Because TBI occurs in children as well due to sport and recreational injuries, it is important to gain a baseline understanding of whether HBOT has the same effect on a child's body. Prakash and colleagues conducted an HBOT study on 56 pediatric patients with head injury, in which 28 received HBOT, all of whom had GCS scores below 8. The results showed significant improvement in patients who received treatment over control patients, for duration of hospitalization, GCS (average increase of 5 points), disability reduction, and social behavior (Prakash et al., 2012).

Wolf and colleagues from the US Air Force School of Aerospace Medicine conducted an HBOT study on 50 military service people who had suffered at least one combat-related mild TBI. After receiving either 30 sham-controlled (room air at ata 1.3) or HBO (ata 2.4) treatments, the investigators concluded that HBO therapy did not make a significant difference on their symptoms measured by the Posttraumatic Disorder Check List-Military Version (PCL-M). The results suggested that HBOT may not have as dramatic effects on milder forms of TBI, whereas the real benefit may come in individuals with more severe injury (Wolf, Cifu, Baugh, Carne, & Profenna, 2012). Paul Harch later stated that the study was not sham-controlled (placebo implied), and thus did not meet the criteria to serve as a valid study. Rather it was mischaracterized as sham-controlled but in fact included a group that received a lower dose of therapy. Moreover, Harch classified Wolf's work as a Phase II comparative dosing study of two composite doses of hyperbaric therapy (Harch, 2013).

POTENTIAL SIDE EFFECTS AND CURRENT USE

As with most medical treatments, there is always the possibility of undesired side effects. These would result from either oxygen toxicity or trauma created by the hyperbaric environment. Patients may experience middle ear barotraumas or traumas to other parts of the vestibular system. They may also experience sinus squeeze or a general feeling of pressure on the face. Other symptoms that have been reported are headache, nausea, numbness, and heartburn (Wolf, Prye, et al., 2012). Due to the closed-environment setting of the tank, there are many who experience claustrophobia. More serious side effects might include progressive myopia, as well as pulmonary barotraumas such pneumothorax or loss of airway. However, these are unlikely to occur if the patient meets the criteria for barotherapy, which includes no conditions affecting the pulmonary-respiratory system such as emphysema and certain infections (Masel, 2011; Singh and Gambert, 2008). Peleg and colleagues also found that blood glucose levels decreased following hyperbaric therapy although there was no evidence that the decrease was a direct result of the hyperbaric environment (Peleg et al., 2013).

Although most hospitals have not yet accepted HBOT as a main-line therapy for head injury, several private organizations, including the US Olympic

Team, have added it to their array of treatment protocols. In addition to TBI, some medical groups are hoping to use the technology as standard care for ischemic stroke. Several nursing homes around the country intend to install HBOT machines in their facilities, making it readily available for elderly patients (Singh and Gambert, 2008). The Amen clinic uses HBOT as a therapeutic option for their patients suffering from a wide variety of physical and psychological ailments. McDonagh and colleagues published a review of HBOT in 2004, stating that "the evidence for HBOT for TBI is insufficient to prove effectiveness or ineffectiveness." They further went on to say that "there is a small chance of a mortality benefit, which may depend on subgroup selection" (McDonagh et al., 2004). One of the current challenges is the fact that a proper dosage and treatment regiment has not been established. Most investigators have pursued 60–90 min treatments for their patients at 1.5–2.5 ata, with a total of 30–40 sessions per treatment course. It is also very unclear how well HBOT will work for people with more mild to moderate TBI, where injury is not necessarily life-threatening. Unfortunately, the cost of HBOT can be relatively high, and it is not recognized by the Centers for Medicare and Medicaid Services as "off-label" use for TBI. In 2000, a US Government Accounting Office reported that an average HBOT session for non-TBI was $405, with a total treatment cost of roughly $12,000 per patient (Masel, 2011).

CONCLUSIONS

In recent years, there is a growing literature published in highly respected journals to support the use of HBOT for the treatment of TBI. Despite this, HBOT is still considered experimental, in part, based on equivocal data, political and economic issues, and a general lack of not understanding the technology. It is imperative that additional controlled trials be done to ultimately bring this technology forward as standard care of head trauma. At the time of injury, TBI patients develop dormant neural tissues that maintain cellular homeostasis but are unable to maintain effective neurotransmission. The addition of HBOT provides a favorable environment by which neuronal reactivation can take place. It will always be critical to evaluate each patient before referring him/her to hyperbaric HBOT. In general, reports have demonstrated substantial reduction in mortality rates and improvement in favorable neurological outcomes. While conflicting results have been reported on patients with milder TBI, the outcome for those who suffer more extensive damage is often much better than those who are not treated. Both animal and human studies indicate that HBOT preserve mitochondrial function, reduce apoptosis and neuroinflammation, and promote neuronal plasticity. Therefore, conducting methodologically based multicentric clinical trials will be critical to determine proper guidelines for inclusion of HBOT for the treatment of TBI. With the knowledge that even a few exposures to HBOT might

contribute to the recovery of brain injury, we are obligated to establish this age-old technology as an effective treatment for the 21st century.

REFERENCES

Algattas, H., & Huang, J. H. (2013). Neurotrauma and repair research: traumatic brain injury (TBI) and its treatments. *Journal of Biomedical Engineering and Computational Biology*, *5*, 51–56.

Amen, D. G., Newberg, A., Thatcher, R., Jin, Y., Wu, J., Keator, D., et al. (2011). Impact of playing American professional football on long-term brain function. *Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(1), 98–106.

Bennett, M. H., Trytko, B., & Jonker, B. (2012). Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. *Cochrane Database Systematic Reviews*, *12*.

Bergsneider, M., Hovda, D. A., McArthur, D. L., Etchepare, M., Huang, S. C., Sehati, N., et al. (2001). Metabolic recovery following human traumatic brain injury based on FDG-PET: time course and relationship to neurological disability. *Journal of Head Trauma Rehabilitation*, *16*(2), 135–148.

Bouma, G. J., Muizelaar, J. P., Stringer, W. A., Choi, S. C., Fatouros, P., & Young, H. F. (1992). Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. *Journal of Neurosurgery*, *77*, 360–368.

Boussi-Gross, R., Golan, H., Fishlev, G., Bechor, Y., Volkov, O., Bergan, J., et al. (2013). Hyperbaric oxygen therapy can improve post-concussion syndrome years after mild traumatic brain injury-randomized prospective trial. *PLoS One*, *8*(11), e79995.

Chen, X., Duan, X. S., Xu, L. J., Zhao, J. J., She, Z. F., Chen, W. W., et al. (2014). Interleukin-10 mediates the neuroprotection of hyperbaric oxygen therapy against traumatic brain injury in mice. *Neuroscience*, *266*, 235–243.

Coupland, R. M., & Meddings, D. R. (1999). Mortality associated with use of weapons in armed conflicts, wartime atrocities, and civilian mass shootings: literature review. *British Medical Journal*, *319*, 407–410.

Daugherty, W. P., Levasseur, J. E., Sun, D., Rockswold, G. L., & Bullock, M. R. (2004). Effects of hyperbaric oxygen therapy on cerebral oxygenation and mitochondrial function following moderate lateral fluid-percussion injury in rats. *Journal of Neurosurgery*, *101*, 499–504.

DeKosky, S. T., Ikonomovic, M. D., & Gandy, S. (2010). Traumatic brain injury: football, warfare, and long-term effects. *The New England Journal of Medicine*, *363*(14), 1293–1296.

DePalma, R. G., Burris, D. G., Champion, H. R., & Hodgson, M. J. (2005). Blast injuries. *The New England Journal of Medicine*, *352*, 1335–1342.

Efrati, S., & Ben-Jacob, E. (2014). Reflections on the neurotherapeutic effects of hyperbaric oxygen. *Expert Reviews in Neurotherapy*, *3*, 233–236.

Efrati, S., Fishlev, G., Bechor, Y., Volkov, O., Bergan, J., Kliakhandler, K., et al. (2013). Hyperbaric oxygen induces late neuroplasticity in post stroke patients-randomized, prospective trial. *PLoS One*, *8*(1), e53716.

Gondusky, J. S., & Reiter, M. P. (2005). Protecting military convoys in Iraq: an examination of battle injuries sustained by a mechanized battalion during Operation Iraqi Freedom II. *Military Medicine*, *170*, 546–549.

Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Cantu, R. C., Randolph, C., et al. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery*, *57*(4), 719–726.

Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Harding, H. P., Matthews, A., et al. (2007). Recurrent concussion and risk of depression in retired professional football players. *Medicine and Science in Sports and Exercise*, *39*(6), 903.

Harch, P. (2013). Hyperbaric oxygen therapy for post-concussion syndrome: contradictory conclusions from a study mischaracterized as sham-controlled. *Journal of Neurotrauma*, *30*(23), 1995–1999.

Harch, P. G., Andrews, S. R., Fogarty, E. F., Amen, D., Pezzullo, J. C., Lucarini, J., et al. (2012). A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. *Journal of Neurotrauma*, *29*(1), 168–185.

Hoge, C. W., & Jonas, W. B. (2014). The ritual of hyperbaric oxygen and lessons for the treatment of persistent post-concussion symptoms in military personnel. *JAMA Internal Medicine*, *175*(1), 53–54.

Hovda, D. A., Yoshino, A., Kawamata, T., Katayama, Y., & Becker, D. P. (1991). Diffuse prolonged depression of cerebral oxidative metabolism following concussive brain injury in the rat: a cytochrome oxidase histochemistry study. *Brain Resolution*, *567*(1), 1–10.

Jordan, B. D. (2013). The clinical spectrum of sport-related traumatic brain injury. *Nature Reviews Neurology*, *9*(4), 222–230.

Krause, G. S., Kumar, K., White, B. C., Aust, S. D., & Wiegenstein, J. G. (1986). Ischemia, resuscitation, and reperfusion: mechanisms of tissue injury and prospects for protection. *American Heart Journal*, *16*, 1200–1205.

Lifshitz, J., Sullivan, P. G., Hovda, D. A., Wieloch, T., & McIntosh, T. K. (2004). Mitochondrial damage and dysfunction in traumatic brain injury. *Mitochondrion*, 1–9.

Lim, S. W., Wang, C. C., Wang, Y. H., Chio, C. C., Niu, K. C., & Kuo, J. R. (2013). Microglial activation induced by traumatic brain injury is suppressed by post-injury treatment with hyperbaric oxygen therapy. *Journal of Surgical Research*, *184*(2), 1076–1084.

Lin, J. W., Tsai, J. T., Lee, L. M., Lin, C. M., Hung, C. C., Hung, K. S., et al. (2008). Effects of hyperbaric oxygen on patients with traumatic brain injury. *Acta Neurochirurgica Supplement*, *101*, 145–149.

Ling, G. S. F., & Ecklund, J. M. (2011). Traumatic brain injury in modern war. *Current Opinions on Anesthesiology*, *24*(2), 124–130.

Ling, G. S. F., & Marshall, S. A. (2008). Management of traumatic brain injury in the intensive care unit. *Neurologic Clinics*, *26*(2), 409–426.

Liu, X. F. F., Fawcett, J. R., Hanson, L. R., & Frey, W. H. (2004). The window of opportunity for treatment of focal cerebral ischemic damage with noninvasive intranasal insulin-like growth factor-I in rats. Journal of Stroke and Cerebrovascular Diseases, *13*(1), 16–23.

Macmillan, M. (2012). *The Phineas Gage information page. Maintained by The Center for the History of Psychology*. Ohio: University of Akron. Reproduced from the Phineas Gage Information Page at http://www.uakron.edu/gage.

Masel, B. E. (2011). Hyperbaric oxygen therapy for traumatic brain injury: still an enigma. *Archives of Physical Medicine and Rehabilitation*, *92*(9), 1519–1521.

McDonagh, M., Helfand, M., Carson, S., & Russman, B. S. (2004). Hyperbaric therapy for traumatic brain injury: a system review of the evidence. *Archives of Physical Medicine and Rehabilitation*, *85*(7), 1198–1204.

McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, T., Gavett, B. E., Budson, A. E., et al. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy following repetitive head injury. *Journal of Neuropathology and Experimental Neurology*, *68*(7), 709–735.

Menon, D. K., Coles, J. P., Gupta, A. K., Fryer, T. D., Smielewski, P., Chatfield, D. A., et al. (2004). Diffusion limited oxygen delivery following head injury. *Critical Care Medicine*, *32*(6), 1384–1390.

Menzel, M., Doppenberg, E. M., Zauner, A., Soukup, J., Reinert, M. M., & Bullock, R. (1999). Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury. *Journal of Neurosurgery*, *91*, 1–10.

Micarelli, A., Jacobsson, H., Larsson, S. A., Jonsson, C., & Pagani, M. (2013). Neurobiological insights into hyperbaric hyperoxia. *Acta Physiology (Oxford)*, *209*(1), 69–76.

Murray, C. K., Reynolds, J. C., Schroeder, J. M., Harrison, M. B., Evans, O. M., & Hospenthal, D. R. (2005). Spectrum of care provided at an echelon II medical unit during Operation Iraqi Freedom. *Military Medicine*, *170*, 516–520.

Okie, S. (2005). Traumatic brain injury in the war zone. *The New England Journal of Medicine*, *352*, 2043–2047.

Peleg, R. K., Fishlev, G., Bechor, Y., Bergan, J., Friedman, M., Koren, S., et al. (2013). Effects of hyperbaric oxygen on blood glucose levels in patients with diabetes mellitus, stroke, or traumatic brain injury and healthy volunteers: a prospective, crossover, controlled trial. *Diving Hyperbaric Medicine*, *43*(4), 218–221.

Pellman, E. J., & Viano, D. C. (2006). Concussion in professional football: summary of the research conducted by the National Football League's Committee on mild traumatic brain injury. *Neurosurgical Focus*, *21*(4), E12.

Prakash, A., Parelkar, S. V., Sanjay, N. O., Rahul, K. G., Beejal, V. S., Mitesh, B., et al. (2012). Role of hyperbaric oxygen therapy in severe head injury in children. *Journal of Pediatric Neuroscience*, *7*(1), 4–8.

Quintard, H., Patet, C., Suys, T., Marques-Vidal, P., & Oddo, M. (2015). Normobaric hyperoxia is associated with increased cerebral excitotoxicity after severe TBI. *Neurocritical Care*, *22*(2), 243–250.

Raji, C. A., Tarzwell, R., Pavel, D., Schneider, H., Uszler, M., Thornton, J., et al. (2014). Clinical utility of SPECT neuroimaging in the diagnosis and treatment of traumatic brain injury: a systematic review. *PLoS One*, *9*(3), e91088.

Rice, A. C., Khaldi, A., Harvey, H. B., Salman, N. J., White, F., Fillmore, H., et al. (2003). Proliferation and neuronal differentiation of mitotically active cells following traumatic brain injury. *Experimental Neurology*, *183*, 406–417.

Rink, A., Fung, K. M., Trojanowski, J. Q., Lee, V. M., Neugebauer, E., & McIntosh, T. K. (1995). Evidence of apoptotic cell death after experimental traumatic brain injury in the rat. *American Journal of Pathology*, *147*, 1575–1583.

Rockswold, S. B., Rockswold, G. L., & Defillo, A. (2007). Hyperbaric oxygen in traumatic brain injury. *Neurological Research*, *29*, 162–172.

Rockswold, S. B., Rockswold, G. L., Vargo, J. M., Erickson, C. A., Sutton, R., Bergman, T. A., et al. (2001). The effects of hyperbaric oxygen on cerebral metabolism and intracranial pressure in severely brain-injured patients. *Journal of Neurosurgery*, *94*, 403–411.

Roehr, B., & Lempinen, E. (2012). Traumatic brain injury: new insight, but treatment remains elusive. *Science Magazine*, 338. www.sciencemag.org.

Sahni, T., Jain, M., Prasad, R., Sogani, S. K., & Singh, V. P. (2012). Use of HBO in TBI. *British Journal of Neurosurgery*, *2*, 202–207.

Sayer, N. A., Chiros, C. E., Sigford, B., Scott, S., Clothier, B., Pickett, T., et al. (2008). Characteristics and rehabilitation outcomes among patients with blast and other injuries sustained during the global war on terror. *Archives of Physical Medicine and Rehabilitation*, *89*, 163–170.

Shi, X. Y., Tang, Z. Q., Sun, D., & He, X. J. (2006). Evaluation of hyperbaric oxygen treatment of neuropsychiatric disorders following traumatic brain injury. *Chinese Medical Journal (English)*, *119*(23), 1978–1982.

Siesjo, B. K. (1993). Basic mechanisms of traumatic brain damage. *Annals of Emergency Medicine*, *22*, 959–969.

Signoretti, S., Marmarou, A., Tavazzi, B., Lazzarion, G., Beaumont, A., & Vagnozzi, R. (2001). N-Acetylaspartate reduction as a measure of injury severity and mitochondrial dysfunction following diffuse traumatic brain injury. *Journal of Neurotrauma*, *18*(10), 977–991.

Singh, S., & Gambert, G. (2008). Hyperbaric oxygen therapy: a brief history and review of its benefits and indications for the old adult patient. *Annals of Long Term Care*, *22*, 7–8.

Stoller, K. P. (2011a). Hyperbaric oxygen therapy (1.5 ATA) in treating sports related TBI/CTE: two case reports. *Medical Gas Research*, *1*(1), 1–6.

Stoller, K. P. (2011b). Hyperbaric oxygen therapy for TBI. *Medical Gas Research*, *1*(1), 17.

Vas, A. K., Chapman, S. B., & Cook, L. G. (2015). Language impairments in traumatic brain injury: a window into complex cognitive performance. *Handbook of Clinical Neurology*, *128*, 497–510.

Verweij, B. H., Muizelaar, J. P., Vinas, F. C., Peterson, P. L., Xiong, Y., & Lee, C. P. (1997). Mitochondria dysfunction after experimental and human brain injury and its possible reversal with a selective N-type calcium channel antagonist (SNX-111). *Neurological Research*, *19*, 334–339.

Verweij, B. H., Muizelaar, P., Vinas, F. C., Peterson, P. L., Xiong, Y., & Lee, C. P. (2000). Impaired cerebral mitochondrial function after traumatic brain injury in humans. *Journal of Neurosurgery*, *93*(5), 815–820.

Vigue, B., Ract, C., Benayed, M., Zlotine, N., Leblanc, P. E., Samii, K., et al. (1999). Early SjvO2 monitoring in patients with severe brain trauma. *Intensive Care Medicine*, *25*, 445–451.

Vlodavsky, E., Palzur, E., & Soustiel, J. F. (2006). Hyperbaric oxygen therapy reduces neuroinflammation and expression of matrix metalloproteinase-9 in the rat model of traumatic brain injury. *Neuropathology and Applied Neurobiology*, *32*(1), 40–50.

Waxman, S. G., Ransom, B. R., & Stys, P. K. (1991). Non-synaptic mechanisms of Ca^{2+} mediated injury in CNS white matter. *Trends in Neuroscience*, *14*, 461–468.

Wolf, G., Cifu, D., Baugh, L., Carne, W., & Profenna, L. (2012). The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. *Journal of Neurotrauma*, *29*(17), 2606–2612.

Wolf, G., Prye, J., Michaelson, R., Brower, G., Profenna, L., & Boneta, O. (2012). Hyperbaric side effects in a traumatic brain injury randomized clinical trial. *Undersea Hyperbaric Medicine*, *39*(6), 1075–1082.

Wright, J. K., Zant, E., Groom, K., Schlegel, R. E., & Gilliland, K. (2009). Case report: treatment of mild traumatic brain injury with hyperbaric oxygen. *Undersea Hyperbaric Medicine*, *36*(6), 391–399.

Young, W. (1992). Role of calcium in central nervous system injuries. *Journal of Neurotrauma*, *9*, S9–S25.

Zhou, Z., Daugherty, W. P., Sun, D., Levasseur, J. E., Altememi, N., Hamm, R. J., et al. (2007). Protection of mitochondrial function and improvement in cognitive recovery in rats treated with hyperbaric oxygen following lateral fluid-percussion injury. *Journal of Neurosurgery*, *106*, 687–694.