The Use of Hyperbaric Medicine in Acute Trauma

Department of Defense Brain Injury Rescue & Rehabilitation Project
(DoD-BIRR) SCIENTIFIC BACKGROUND AND OVERVIEW

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Hyperbaric oxygen therapy (HBOT) is the use of greater than atmospheric pressure oxygen as a drug to treat basic disease processes and their diseases (1). In the simplest terms HBOT is a pharmaceutical or prescription medication similar to the thousands of medications routinely prescribed by physicians everyday throughout the world. The key differences with HBOT, however, are that it is a drug that treats basic disease processes that are common to every disease, that it acts as a repair drug in these processes, and that it replaces an essential element of life for which there is no substitute, oxygen. This effectiveness in treating basic common disease processes explains the ability of HBOT to act in a generic beneficial fashion to a multitude of diseases, including and especially traumatic injuries to all areas of the body.

HBOT has both acute and chronic drug effects. HBOT exerts these effects by obeying the Universal Gas Laws, the most important of which is Henry's Law (2). Henry's Law states that the concentration of a gas in solution is proportional to the pressure of that gas interfacing with the solution. For example, the amount of oxygen dissolved in a glass of water is directly proportional to the amount of oxygen in the air. Similarly, the amount of oxygen dissolved in our blood is directly proportional to the amount of oxygen we are breathing. According to Henry's Law, there is a very small amount of oxygen dissolved in the liquid portion of the blood when breathing air (21% oxygen) at sea level. The remainder and majority of oxygen is bound to hemoglobin in the red blood cells giving a 98% saturation of hemoglobin. As we increase the amount of oxygen in inspired air by applying a nasal cannula or facemask of pure oxygen the final 2% of hemoglobin is quickly bound by oxygen. All of the remaining available oxygen interfaces with and is dissolved in the liquid portion of the blood. Once we reach 15 liters/minute of supplemental oxygen by a tight fitting aviator's mask or non-rebreather mask we have reached the maximum amount of oxygen that can be dissolved in blood by natural means. However, this is not the absolute limit. By placing a patient in an enclosed chamber, increasing the pressure above ambient pressure, and giving the patient pure oxygen we can cause an increase in dissolved oxygen in blood in direct proportion to the pressure increase.

At the point of three atmospheres absolute of pure oxygen (3 ATA), just slightly more than the amount the U.S. Navy has used for 50 years in the treatment of divers with decompression sickness, we can dissolve enough oxygen in the plasma to render red

blood cells useless. Under these conditions as blood passes through the tiniest blood vessels tissue cells will extract all of the dissolved oxygen in the blood without touching the oxygen bound to hemoblogin. This amount of dissolved oxygen alone can exceed the amount necessary for the tissue to sustain life. In other words, you don't need red blood cells for life at 3 ATA of 100% oxygen. This physical phenomenon was proven in a famous experiment in 1960 and published in the first edition of the Journal of Cardiovascular Surgery by Dr. Boerema of the Netherlands (3). Dr. Boerema anesthetized pigs, removed nearly all of their blood, and replaced it with salt water while he compressed them to 3 ATA. At 3 ATA in a hyperbaric chamber pigs with essentially no blood were completely alive and well. Dr. Boerema then removed the saline, replaced the blood, and brought the pigs to surface where they remained alive and well. This phenomenon has been proven effective in other experiments and is the basis for clinical use in extreme blood loss anemia (4). The best examples are Jehovah's Witness patients who have lost massive amounts of blood and because of religious proscription are unable to receive blood transfusions. These patients are kept alive over weeks with repetitive HBOT until their blood system is able to naturally produce enough blood to sustain life. This ability to maintain life without blood has obvious potential to battlefield casualties awaiting transfusion.

As a result of Henry's Law HBOT is able to exert a variety of drug effects on acute pathophysiologic processes. These have been well documented over the past 50 years and include reduction of hypoxia (5, 6), inhibition of reperfusion injury (7), reduction of edema (8), blunting of systemic inflammatory responses (9), and a multitude of others (10). In addition, repetitive HBOT in wound models acts as a DNA stimulating drug to effect tissue growth (11, 12). HBOT has been shown to interact with the DNA of cells in damaged areas to begin the production of repair hormones, proteins, and cell surface receptors that are stimulated by the repair hormones (13, 14). The resultant repair processes include replication of the cells responsible for tissue strength (fibroblasts) (15), new blood vessel growth (16, 17), bone healing and strengthening (18), and new skin growth (19).

To best understand the effectiveness and potential of HBOT one must understand basic disease processes, commonly referred to as pathophysiologic processes. Every insult or injury to living organisms, particularly human beings, is distinct and different, and can be characterized by the type of force, energy, or peculiar nature of that insult. For example, a blast force is different from a blunt force, an electrical injury, a toxic injury, a biological injury, infectious injury, thermal injury, nuclear injury, gunshot wound, stab wound, burn, or even a surgical wound. Regardless of the exact nature and idiosyncratic character of the injury, however, every acute injury has a common secondary injury called the inflammatory process (20). This secondary injury in fact causes more damage than the primary injury. Moreover, it is a universal process common to every human being regardless of race, color, creed, size, gender, or genetics. The beauty of hyperbaric oxygen therapy is its ability to powerfully impact the inflammatory reaction and its component processes like no other drug in the history of medicine.

The inflammatory process begins with tissue injury. The injury can be as innocuous as apposition of tissues that normally do not interface against one another, such as spinal bony compression of a nerve root due to a degenerative disk. Most often, however, tissue injury results from much larger forces such as the type seen in military conflict. Once tissue is disrupted proteins, fat, other molecules, and disrupted tissue is exposed to the circulation. In addition, blood vessels are damaged both directly by mechanical forces and indirectly by tissue fragments that interact with the vessel walls. The net effect is bleeding from broken blood vessels and dilation of the unbroken blood vessels. As the vessels dilate, blood pressure forces the liquid portion of the blood out of the vessels. The extravasated fluid, now referred to as edema, exerts its own pressure that collapses blood vessels, leading to a reduction of blood flow. This compounds the reduction in blood flow already caused by disrupted blood vessels and bleeding. In addition, white blood cells in the circulation are attracted to the damaged tissue by molecules released from the damaged tissue. The white blood cells traverse the blood vessel walls in a process called emigration (21) and disgorge themselves of their digestive enzymes. These enzymes cause further tissue damage in an attempt to clean up the primary damage, but also cause constriction of blood vessels to limit further bleeding and leakage of fluid.

The cumulative effect of all of these processes, including tissue injury, fluid leakage, blood vessel disruption, bleeding, white blood cell accumulation, indiscriminate release of digestive enzymes, and blood vessel constriction is a reduction in blood flow and most importantly, reduction in the crucial element for sustenance of life, oxygen. With the reduction of oxygen, blood vessel walls become activated as do the white blood cell surface proteins. Activation of the white blood cell surface proteins results in their prominence from the cell surface in a manner similar to a sail rising on a sailboat. This drag slows down the white blood cells, resulting in their margination (22) to the walls of blood vessels in an area of injury. The white blood cells then stick to the walls of the blood vessels and generate tiny blood clots. This cascade of events is known as reperfusion injury (23). The white blood cells now emigrate and compound the process described above, resulting in greater reduction in blood flow and hypoxia. Thus, low oxygen leads to further tissue damage, leakage of blood vessels, clotting of blood vessels, and more hypoxia, in essence, the “vicious cycle” described by Holbach (24). This is the sequence of events at the site of every bullet, shrapnel, blast, blunt, electrical, etc. impact in every soldier injured in battle. Finally, if there is enough bleeding, clotting of blood vessels, and blood vessel leakage of fluid in the body to drop blood pressure the entire body becomes activated by hypoxia, undergoes reperfusion injury, and the soldier experiences shock, a critical point of no return for most human beings.

In the past 12 years scientific research has unequivocally shown that the only drug to completely or nearly completely reverse the reperfusion injury process is hyperbaric oxygen. In multiple experiments with different animal models, different organ systems, different types of blood flow reduction or absence (e.g., heart attack, stroke, cardiac arrest, carbon monoxide, tourniqueting of an extremity, etc.) timely HBOT within hours of reperfusion injury has been shown to completely or nearly completely reverse

reperfusion injury (25). The mechanism of action has been partly elucidated and shown to be an effect on the white blood cell surface proteins and the inside lining of the blood vessels to which the white blood cells stick (26, 27). The net result is a reduction in clotting, blood vessel leakage, and an increase in oxygenation. In addition, HBOT has been shown to constrict blood vessels (28), thus reducing bleeding and leakage of fluid that causes swelling and further compression of blood vessels. This breaks the vicious cycle described above. Simultaneously, due to its ability to dissolve large amounts of oxygen in the liquid portion of the blood, oxygen enriched plasma is able to reach damaged areas of tissue not accessible by normal blood flow and restore oxidative function to these areas. The net result is a dramatic reduction in the secondary injury process, improved viability of tissue that would otherwise die, and salvage of the tissue and patient.

The goal of the DoD-BIRR Battle Project is to use timely hyperbaric oxygen therapy to hyperacutely interrupt the inflammatory reaction and its injurious cascade, reverse hypoxia that results from disruption of blood vessels and bleeding, restore and prolong tissue viability, and prevent the secondary injury processes that are so devastating. HBOT is uniquely suited to battlefield casualties for its beneficial effects on five processes or conditions: acute severe traumatic brain injury (TBI), extremity wounds with crush injury and compartment syndrome, burns, acute hemorrhage, and reperfusion injury.

The literature for HBOT in acute severe TBI is amongst the strongest in hyperbaric medicine. HBOT effects on brain injury pathophysiology have been well-documented (29-37). In humans Holbach (38) demonstrated improved glucose metabolism in acute severe TBI patients with one HBOT. He followed this study with a controlled trial of HBOT in TBI patients with the acute mid-brain syndrome (24). Using 1-7 HBOT's, he demonstrated an overall 55% reduction in mortality and 81% improvement in short-term outcome (10d post TBI). These dramatic findings were duplicated in the largest study performed to date, the Rockswold study in 1992 (39). Rockswold showed that HBOT induced a 47% reduction in mortality overall and a 59% reduction for the most severely injured, nearly identical to Holbach. Rockswold followed his study with two additional studies that reinforced their and Holbach's findings. The first one in 2001 (40), showed that a single HBOT improved brain metabolism (similar to Holbach-38) and re-coupled brain blood flow and metabolism in severely injured human brain FOR THE FIRST TIME IN THE HISTORY OF SCIENCE AND MEDICINE.

This was a profound discovery and was consistent with all of the previous animal and human experimentation performed with HBOT in acute TBI. The second study, an animal study (41), proved that HBOT could increase oxygen consumption, brain tissue oxygen levels, and mitochondrial function (the organelle that is the energy center for every cell in the body). Additional randomized controlled studies by Artru (80) and Ren (81) at somewhat higher pressures have shown the same result as Rockswold and Holbach. Taken collectively the multitude of animal and human studies strongly argue that HBOT delivered within hours to days of acute severe TBI unequivocally reduces mortality and improves outcome. The reduction in mortality has never been equaled by

any therapy in the medical armamentarium except possibly the ambulance, or in the case of the military, the helicopter. Adding HBOT to helicopter evacuation of casualties should further decrease morbidity and mortality of injured soldiers. This is the foundation of the DOD-BIRR Project.

The second important impact of HBOT in acute battlefield trauma is the effect on extremity injuries which include crush injury, major blood vessel disruption, and compartment syndrome. Extremity gunshot, blast, and other high force military injuries cause massive tissue destruction, hypoxia, and swelling. This swelling leads to what is called compartment syndrome where the various muscle compartments that are bound by their dividing tissues (fascia and bone) increase in pressure and occlude blood vessels. The subsequent lack of blood flow causes more hypoxia leading to the "vicious cycle" described above in traumatic brain injury. A vicious cycle in the extremities results in death of the tissue, loss of function, and often loss of limb. This sequence of events is often complicated and worsened by disruption of major blood vessels that further lowers oxygen levels. Multiple animal studies have demonstrated a benefit of HBOT in crush injury, lack of blood flow, and compartment syndrome (42-47).
A human study in 1987 (48) reinforced these results by showing limb salvage in traumatized extremities with low blood flow who were at risk for amputation after failed surgical therapy. Stronger studies in 1989 (49) and 1996 (50) duplicated the previous animal and human data. In particular the study by Bouachour (50) in open fractures and crush injuries demonstrated significantly improved complete healing and bone healing with a reduction in additional surgical procedures. Actual application to extremity war injuries has been reported by three separate authors with good results (51, 52, 53). Most of these studies, especially the war studies, involved damage to major blood vessels with its accompanying loss of blood flow and oxygen until surgical repair was complete. Despite this arterial damage, the net result in most of the studies is a reduction in major amputations. Very likely HBOT ameliorates compartment syndrome by reducing edema and reversing hypoxia. Its most profound effect, however, maybe on prevention of compartment syndrome by impacting reperfusion injury. Reperfusion injury is a normal feature of direct tissue injury, but it can be compounded by the secondary reperfusion injury from tourniqueting a massively bleeding extremity. HBOT delivered within the first few hours of injury could significantly inhibit reperfusion injury (7, 25, 26) and prevent the major delayed complications of R.I.: infection, compartment syndrome, and amputation. In addition, HBOT could prevent the reperfusion injury that occurs during surgical repair of the injured extremity as the extremity is tourniqueted during surgery to allow blood vessel reconstruction and bone repair.
HBOT has shown benefit in acute thermal burns since 1965 when Wada discovered that burned patients treated for carbon monoxide poisoning from a coal mine fire experienced accelerated healing of their burns (54). Since that time a plethora of studies in animals has shown improved healing (55), reversal of hypoxia (56), reduction of inflammation/reperfusion injury (57, 58), burn edema (59, 60, 61, 62), increased rate of skin growth (63), improvement in the blood vessels (63, 64, 65), prevention of progression of deep second degree burns to third degree burns (62, 65, 66, 67), reduction in burn shock (68)and a decrease in infections (55). Studies in humans have mirrored the animal literature with clear or likely benefit in 19 of 21 studies (69),

demonstrating a drastic reduction in healing time for deep second degree burns (70-73). The effect on third degree burns (all layers of the skin) is less apparent since modern burn care has evolved to early surgical removal of burned tissue. Immediate HBOT in these cases, however, could likely minimize the amount of questionable second degree burned tissue that would be inadvertently excised with the third degree burn. This could be important in burns of the face, ears, hands and feet where tissue preservation is critical. Lastly, early intervention with HBOT has reduced the cost of burn treatment (73). Hyperacute HBOT at a battlefield MASH station should duplicate the civilian experience and have a dramatic impact on the treatment of burned soldiers.
The fourth significant impact of HBOT on military casualties would be in the treatment of massive hemorrhage. As mentioned above in the example of Jehovah's Witness patients HBOT can be used as a blood substitute until definitive treatment is available (74). A large volume of animal and human studies consistently show better survival with HBOT (75) in profound hemorrhage. Relying on Henry's Law and Boerema's experiment, massive amounts of oxygen would be delivered to exsanguinating soldiers by its dissolution in the soldier's plasma. In the 1960's major hospitals in the United States and Europe utilized Henry's law to hyperoxygenate babies with congenital heart disease undergoing cardiac surgery. In the absence of the soon to be invented heart-lung bypass machine the dissolved oxygen provided surgeons longer operating times during cardiac standstill. In a MASH unit soldiers could be rapidly compressed to 3 ATA on 100% oxygen in hyperbaric chambers while awaiting or in the process of receiving blood transfusions. Using air breaks between oxygen administration periods they can remain at this pressure for 3-4 hours, 3-4 times per day (75). The reduction of time in the shock state would pay dividends in decreased morbidity and mortality. In addition, in times of mass casualties that overwhelm the blood supply and surgical capabilities, HBOT could be delivered until blood is available or while the soldier is in flight to another MASH. Alternatively, critical soldiers with massive ongoing bleeding could be placed in a hyperbaric operating room and receive the benefits of life without blood while time is bought for surgical control of bleeding and blood transfusions. The natural extension of this application is to those soldiers who have cardiac arrest from massive hemorrhage. Should this event occur even minutes before or after arrival at the MASH unit soldiers could be compressed on oxygen while IV's are placed, volume and blood are infused, and bleeding is controlled. The precedent has been set for this in resuscitation from cardiac arrest in a drowned diver with decompression sickness 22 minutes after loss of consciousness (76) and guinea pigs 15 minutes (77) and swine 25 minutes post induced cardiac arrest (78). While the human case was a partial exsangination and the animals had normal blood volume they suggest an untapped potential for application to soldiers. The time has come to introduce to the military medical therapeutics arsenal both this potential and the more certain application to near-exsanguinated soldiers or soldiers in shock.
The fifth area of impact for HBOT in acute military casualty treatment is reperfusion injury. As mentioned above, reperfusion injury is a ubiquitous process post injury. Specifically, it is a secondary injury that occurs upon restoration of blood flow (23). In the case of battlefield injuries it occurs with any blunt, blast, bullet, shrapnel, stab, electrical, burn, or other wound. In addition, it causes tissue destruction post resuscitation from shock, upon release of any tourniquet placed to control bleeding in

the field or in the operating room, and upon restoration of blood flow to re-attached limbs. HBOT's effect on reperfusion injury has been argued to be a generic drug that applies regardless of the affected organ system or species (25). It appears to also be a dominant mechanism in the prevention of brain lipid peroxidation in the swine resuscitation experiments above (79). When delivered in timely fashion after injury it protects the body from further reperfusion injury should the soldier have to undergo surgery or have other complications. Coupled with the known effects on bone healing and the ability to salvage marginally viable tissue HBOT has the potential to significantly reduce major amputations. Overall, HBOT's effect on reperfusion injury could be huge in military casualty management.

In conclusion, HBOT is one of the most powerful drugs known to man. Simultaneously, HBOT delivers the substrate of life, oxygen, for which there is no substitute. HBOT has profound beneficial effects on injury pathophysiologic processes that are common in military casualties. Moreover, it has been shown to positively impact traumatic brain injury, compartment syndrome, burns, hemorrhage, and reperfusion injury. These injuries and injury processes comprise the bulk of battlefield casualties. With timely intervention of HBOT the morbidity and mortality of injured soldiers should substantially improve as they have in their civilian counterparts. Past foreign military experience strongly suggests this benefit in extremity wounds and its our conviction that United States soldiers deserve nothing less. This is the goal of the DoD-BIRR Project.

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