A BRIEF REVIEW OF HYPERBARIC OXYGEN FOR STROKE REHABILITATION

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Oxygen is a natural gas that is absolutely necessary for life and healing. Purified oxygen is defined as a drug but is the most natural of all drugs. Oxygen under pressure is still the same gas but is more able to penetrate into parts of the body where the arterial flow is hindered - producing ischemia (loss of blood flow) and hypoxia (lack of oxygen). When oxygen under pressure is breathed by a patient in a sealed chamber it is termed a hyperbaric oxygen treatment (HBOT). The treatment lasts from 45 to 120 minutes during which time the person's body is surrounded by air pressure equivalent to the pressure produced by diving 16 to 33 feet underwater (7.35 to 14.7 pounds per square inch = 1.5 to 2 ATA).

In addition to raising the arterial levels of oxygen 10 to 15 times higher than that produced by normal atmospheric pressure, the pressure exerted within the body can and does exert therapeutic benefits on acute and chronically traumatized and swollen tissues.

The first suggestion that raised air pressures might be used in the treatment of human illness was made in 1664 by Henshaw in England. The first hyperbaric chamber to investigate the therapeutic action of compression of the air on the human body was described and built by Junod in 1834. Using 1 1/2 atmospheres of pressure, Junod was reported to have treated patients with paralysis with beneficial results. This pioneering work was not continued until 1965 when Ingevar and Lassen demonstrated positive results in 4 patients suffering from focal cerebral ischemia. Since then, numerous articles have been published demonstrating that hyperbaric oxygen is useful for the treatment of both acute and chronic stroke.

A sound physiological and anatomical basis for why hyperbaric oxygen improves acute and chronic stroke and brain damaged individuals has been developed over the past 100 years.

NEUROPATHOLOGY

In 1908, R. Pfeifer reported autopsy studies of human brains that had undergone exploratory punctures, months before their deaths. He recognized on the margins of the resulting brain injuries that the scars had numerous nerves and nerve fibers that were regenerating.

That these "marginal" neurons remain intact, alive and in place for more than the few months reported by Pfeifer was reported in 1934. Cyril B. Courville demonstrated the persistence of the processes of disintegration, of phagocytosis and repair in the brain of a 57 year old who had been shot in the head twenty-two years previously. Seriously damaged nerve cells had maintained their morphologic identity throughout this long period. In summarizing this case Courville stated, " Morphologically, crippled nerve cells may persist in the margins of wounds of the brain for many years." "Even after a prolonged interval the larger nerve fibers continue to show regressive change at the margins of wounds of the brain."

The concept of an ischemic marginal zone surrounding a central core of infracted brain tissue as a component of stroke induced damage was further developed by Astrup, Symon, Branston, and Lassen in 1977. Their baboon studies showed that electrical activity was lost at the periphery of a cerebral infarct when the blood flow fell below 15 ml/100g/min while neuronal death began to occur when blood flow fell to 6-8 ml/100 g/min. These low blood flow values may be used to define an area surrounding an infarct where the tissues remain alive but are not functioning called the "ischemic Penumbra". Dorland's Illustrated Medical Dictionary (28th ed., 1994) defines the ischemic penumbra as "an area of moderately ischemic brain tissue surrounding an area of more severe ischemia; blood flow to this area may be enhanced in order to prevent the spread of a cerebral infarction." Results have accumulated supporting the concept of the ischemic penumbra as a dynamic process of impaired perfusion and metabolism eventually propagating with time from the center of ischemia to the neighboring tissue. As mediators and modulators of this process, waves of depolarization, extracellular increases in excitatory amino acids, activation of Ca++ channels,

intracellular calcium deposition, induction of immediate early genes and expression of heat-shock proteins all play a role. (Heiss, WD, Graf, R 1994)

Spontaneous electrical activity is impaired when cerebral blood flow is reduced to about 60% of control. (Hossmann, KA et al 1980) (Moraweth RB et al 1979) Protein synthesis is suppressed 50% at a cerebral blood flow of 40% even before spontaneous electrical activity is impaired. (Mies, G. et al. 1991).

Branston (et al 1974) demonstrated a deterioration in the amplitude of somatically evoked potentials at approximately 34% of control blood flow which is also the level of blood flow at which glucose begins to be utilized more rapidly due to oxygen-debt inhibition of mitochondrial metabolism and oxidative phosphorylation. Thus glycolysis is stimulated in order to maintain ATP levels. This produces lactic acid which accumulates because flow is reduced. Since ATP production by glycolysis cannot fully compensate for oxidative phosphorylation, AMP and purine levels increase and tissue adenylates are irreversibly lost either enzymatically or through blood clearance. Reduction in cerebral blood flow below 30 ml/100 g/min suppresses the adenylate cyclase and protein kinase C system (Tanaka K et al. 1993). The loss of adenylates, accumulation of lactic acid with a lowering of the pH and the formation of free radicals with subsequent oxidation of blood vessels walls, blood components and brain tissues results in induction of early response genes, expression of heat-shock proteins and diminished blood vessel wall and brain tissue protein synthesis and responsiveness (Paschen, W. et al 1992) (Newman, GC NIHR01Ns28429-02) Other studies have implicated a multifactorial interaction at the ischemic blood-endothelial interface of Factor VIII/von Willebrand factor, prostanoids, leukocytes, platelets, platelet-activating factor, leukotrienes, adhesion receptors, monocytes/macrophages, fibrinogen, viscosity and cytokines that can impair microvascular perfusion (Hallenbeck JM 1994) Disruption of the blood brain barrier occurs in focal cerebral ischemia (the animal model of stroke) and the degree of the disruption correlates inversely with cerebral blood flow. (Yang GY & Betz, AL 1994) Free oxygen radicals have been shown to disrupt the blood brain barrier in focal ischemia which allows large molecules to pass through into the brain. Free radicals inhibit rather than cause postischemic hyperemia.(Tasdemiroglu E. et al 1994) which is one more mechanism that causes stagnation of blood flow through the ischemic penumbral zone. When blood flow is further reduced to approximately 15%, synaptic transmission is abolished (Branston, NM et al. 1977) (Heiss, WD et al 1976), extracellular potassium increases and ATP falls proportionately.. A massive release of extracellular potassium occurs at blood flow levels below 10%, ATP is totally exhausted, neurons depolarize, cellular ion homeostasis breaks down and cell death occurs. (Astrup,et al. 1977. (Welsh, F.A. et al. 1978) (Paschen, W et al 1992)

The margins of an infarct are usually strikingly irregular. The explanation for this probably lies in the preservation of the circulation in some limited areas through better anastomosis of collateral vessels. (W. Freeman 1933) (Tamura A. et al. 1981), (Tyson GW)

The debate about the size of the penumbra revolves around the methods used to study it. The morphological evidence is much less than the size shown by autoradiography (rat-Tyson et al 1984; cat-Ginsberg et al, 1976) and this area is much less than that shown by functional assessment (Symon et al., 1976). Substantial areas of flow reduction beyond the infracted area(s) can be delineated by CT and MRI, while concurrently, oxygen utilization is decreased in these areas (Raynaud et al., 1987)(Benveniste H et al 1991). Repeat multitracer PET studies with human stroke victims have shown viable tissue in the border zone of ischemia up to 48 hours after the cerebrovascular attack. With few exceptions, these tissues suffer progressive metabolic derangement and had decreased cerebral metabolic rates of oxygen (-17.2% vs -26.1% as compared to normal mirror image regions of interests) within two weeks after the stroke. (WD Heiss et al. 1992). For many years cerebral ischemia has been thought to release glutamate from the hypoxic, damaged cells and this glutamate was thought to potentiate and propagate the initial hypoxic damage. Recently described, an alternative explanation for glutamate-mediated injury is hypoxia as well but caused by peri-infarct spreading depression-like depolarizations. These irregular depolarizations are thought to initiate or worsen hypoxic episodes (due to energy expenditures) and cause a further suppression in protein synthesis, a gradual deterioration in energy metabolism and a progression of irreversibly damaged tissue into the penumbra zone. Thus "interventions to improve ischemic resistance should therefore aim at improving the oxygen supply or reducing the metabolic workload in the penumbra region." (Hossmann KA 1994)

Focal cerebral ischemia is the animal model of stroke and in this model there is evidence for a reduction of the number of perfused capillaries in the affected penumbral areas. This loss of capillary perfusion is probably the result of a combination of changes that occur in the terminal capillary bed in the wake of the acute ischemic process. RBC aggregation, platelet aggregation, endothelial swelling, increased blood and plasma viscosity, etc are just some of the factors that contribute to the loss or decrease in the flow properties of red cells through ischemic tissue capillaries. Plasma, on the other hand, has been shown to reach all ischemic and post-ischemic capillaries and is able to pass through capillaries where red cells are no longer able to pass due to the constrictive and restrictive changes created by the ischemic process. (K.Kogure, K.A. Hossmann and B.K.Siesjo 1993) One of the mechanisms of action of hyperbaric

oxygen is to increase the oxygen solubility in blood plasma. It is possible to dissolve sufficient oxygen (. i.e. 6 vol% in plasma) to meet the oxygen needs of the brain. (K.K.Jain, 1996) Thus in the acute stroke patient, the use of hyperbaric oxygen is able to provide oxygen to ischemic neurons and to keep them alive while either endogenous or exogenous fibrinolytic mechanisms are brought to bear on the cerebral thrombosis that is causing the ischemia. This results in the salvage of the ischemic penumbra to a degree impossible with any other therapy.

CHRONIC STROKE REHABILITATION

With the injury to the brain, blood vessels are damaged or destroyed. The tissue that surrounds the area of outright necrosis has had its circulation compromised and may be only receiving a fraction of the blood flow and oxygen that it needs for optimum health. Thus a disruption in structure creates immediately a change (decrease) in function. This decrease in function remains for months or years and the neurons in these areas are said to be in "hibernation" or "sleeping". Hyperbaric oxygen treatments when given daily stimulates a process called "angiogenesis" or the formation of new blood vessels. New blood vessels form in the vicinity of the damaged tissues as a result of certain chemical signals (e.g. angiogenin) that are produced by the newly re-energized neurons, endothelial cells and macrophages and are then secreted into the surrounding tissues. These signals stimulate new blood vessels which slowly reconnect to the damaged tissues and within 60 days of daily treatments, the "sleeping" neurons wake up and resume their normal functions as the proper structures return back in place. The hyperbaric oxygen induced blood vessel repair results in a permanent structural change in the blood vessels that re-supply the previously damaged and nonfunctioning nerve tissue which was occurring due to diminished and inadequate blood flow. These new blood vessels improve the blood flow and oxygen delivery to the damaged brain tissues and this results in permanent improvements in the stroke and traumatically brain injured person. Clinically, what you see is the return to life of a previously paralyzed and useless limb or limbs, improvement in swallowing, speech, thinking (cognition), memory, etc. Quite obviously not all of the disabilities disappear since there was a central core of dead tissue that can not be revived. However, after the two months of therapy, these people may continue to improve for at least two years after their treatment with hyperbaric oxygen especially if they continue with physical therapy. This all occurs in patients who may have not seen any improvement in their conditions for years after their stroke even with the use of any and all other therapies indicating that the brain’s milieu intérieur has been altered for the better since the neurons are able to slowly re-establish their lost connections in ways not possible before hyperbaric oxygen.

Outcome in stroke may be predicted to some degree by the volume of tissue affected. Comparative functional volume obtained by single photon emission computerized tomography (SPECT) often indicates a larger region of recoverable tissue than CT.(Mountz, JM 1990) This functional volume of the infarct size can be demonstrated to decrease after one to several hyperbaric oxygen treatments (Neubauer, 1990, 1992) and this increase in blood flow to the area of infarction that occurs as a result of hyperbaric oxygen can serve as a clinical test to determine if there is salvageable neurons still present in the penumbra. Presumably, if the test (SPECT first, then HBO then repeat SPECT) is positive, the person should receive benefit from the use of a series of hyperbaric oxygen treatments because of the revitalization of the ischemic penumbral tissues.

This is a good test if the test is positive since we are generally assured that the person will experience improvement with hyperbaric oxygen. However, what if the test is negative? Since the literature and clinical experience predicts that between 80 to 90 percent of stroke victims will be helped by hyperbaric oxygen, perhaps the SPECT scan may be missing some other fundamental mechanism by which hyperbaric oxygen is helping these people improve. For example, when rat’s forebrains are made ischemic for 10 minutes and then after 1, 2, 3 weeks and 3 months their cerebral glucose utilization is measured, generalized reductions in glucose utilization is found throughout the majority of gray matter indicating that widespread alterations of functional activity prevail in postischemic brains beyond the selectively vulnerable regions. (Beck T, et al 1995) Following acute, localized lesions of the central nervous system, arising from any cause, there are immediate depressions of neuronal synaptic functions in other areas of the central nervous system remote from the lesion. These remote effects result from deafferentation, a phenomenon known as "diaschisis". (Von Monakow C. 1914)

After an interval of time, which will vary directly with the severity of the lesion, functional recovery may occur to some degree due to synaptic reactivation of neurons. This is favorably influenced by rehabilitation. Diaschisis most commonly manifests itself by such neurological signs as impaired consciosness or cognitive impairments including dementia, dyspraxias, dystaxias, dysphasias, incoordination and sensory neglect. The nature of diaschisis has been demonstrated by widespread depressions of local cerebral blood flow and metabolism extending far beyond the anatomical lesion. Von Monakow pointed out that development of diaschisis is enhanced by latent circulatory disorders in both the affected and unaffected areas of the brain. Recovery of function is associated with recovery of local perfusion and metabolism. (Meyer, JS,et al 1993)

More recently PET scans have shown that diaschisis does not independently add to the clinical deficit in human cerebral infarction but represents part of the damage done by the stroke. (Bowler JV et al. 1995) "Diaschisis is a functional phenomenon that correlates with both stroke severity and infarct hypoperfusion volume" (Infeld B; et al.1995)

In another PET scan study of 31 patients with infarcts involving the frontal sensorimotor cortex, 23 had persistent diaschisis up to 5 years after onset while the remaining 8 had the diaschisis recover without recovery of oxygen metabolism in the infarcted area (implying that tissue in the ischemic penumbra did recover and this is what allowed for recovery of the diaschisis). (Miuura H; et al.1994.)

Thus if functionless ischemic penumbral tissue can be "re-activated" and be made to function again, a coresponding amount of the areas of diaschisis will be returned to normal with normal blood flow and function returning.

In a number of studies in normal dogs, monkeys and Man, hyperbaric oxygen has been shown to diminish cerebral blood flow from 1 to 29% (average 14.7%) which some people have claimed to be detrimental to a stroke or brain injured patient. All of these studies were done in normal non-brain injured subjects while the studies that were done in brain injured patients all showed an increase in cerebral blood flow (Jain, 1996 page 239). Dr. K.K. Jain states, "Vasoconstriction and reduced cerebral blood flow do not produce any clinically observable effects in a healthy adult when pressures of 1.5 to 2 ATA are used. ..The effects of HBO are more pronounced in hypoxic/ischemic states of the brain. HBO reduces cerebral edema and improves the function of neurons rendered inactive by ischemia/hypoxia. The improvement of brain function is reflected by the improved electrical activity of the brain."

For abstracts of scientific studies that investigated the effectiveness of hyperbaric oxygen therapy for acute and chronic stroke in humans, please see our HBO Abstracts webpage that follows.

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