

The use of Mild Hyperbaric Oxygen Therapy (mHBOT) to treat Neurological diseases

-A review by

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The following literature review has been undertaken to determine the effect of mild hyperbaric oxygen therapy (mHBOT), defined as atmospheric oxygen pressurised up to 1.5 ATA, on the following conditions:

- I. Alzheimer's Disease (AD)
- II. Autism Spectrum Disorder (ASD)
- III. Attention Deficit Hyperactivity Disorder (ADHD)
- IV. Cerebral Palsy (CP)
- V. Downs' Syndrome (DS)

In undertaking this research project, it is important to note that only clinical trials published post 2008 have been referenced for Hyperbaric and Mild Hyperbaric oxygen therapy.

In 2008, the Department of Undersea and Hyperbaric Medicine (UHM), a global and primary source of scientific information for hyperbaric physiology, defined new research guidelines to be applied to hyperbaric oxygen therapy (HBOT) research studies. The purpose was to ensure that HBOT research studies clearly outlined the independent variable of the HBOT treatment, ensuring environmental validity (Yildiz, Aktas, & Uzun, 2008).

Overview

The AirPod Oxygen Therapy delivers atmospheric oxygen pressurised at three pressure settings ranging from 1.1, 1.2 and 1.35ATA. The Airpod is classified as a mild HBOT (mHBOT) wellness device as it operates under 1.5ATA.

At this pressure setting, and using atmospheric oxygen, the AirPod delivers a highly effective therapy **without the risks** posed from medical grade (>1.5ATA) HBOT devices that use an external oxygen source. Whilst rare, the medical grade HBOT physiological complications include middle ear barotrauma, sinus barotrauma and oxygen toxicity which is only experienced above 2.0 ATA.

In addition, an external oxygen source that is used with HBOT medical devices presents a fire risk and requires additional resource and infrastructure to manage this risk.

As well as being a 'safer' therapy, a study published by the UHM shows that there is **no significant difference between the result observed under mHBOT and HBOT conditions** (Mukherjee, et al., 2014).



In summary, the literature review that follows uses comprehensive papers with sound experimental method and comes from credible, peer-reviewed sources. I personally believe that our therapies will have a substantial impact on alleviating the symptoms often associated with conditions such as ASD, AD, ADHD, CP and DS.



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Alzheimer's Disease (AD)

The brain consumes 20% of the oxygen taken in by the whole body. Of that, 90% of the oxygen used by the brain goes toward enabling mitochondria to produce energy to power all cerebral processing (Calvert, Cahill, & Zhang, 2007).

Over time, this sustained load places an immense amount of oxidative stress on the brain, compromising pathways and ultimately impairing the brain's ability to mediate important bodily processes. The mitochondrial dysfunction that follows compromises a cascade of 'follow on' reactions, ultimately increasing the rate of cognitive decline characterised by AD (de la Torre, 1997) (Devi, Prabhu, Galati, Avadhani, & Anadatheerthavarada, 2006).

More so recently, many healthcare professionals have started turning to m-HBOT and HBOT to alleviate the symptoms commonly associated with AD.

A study conducted by Shapira et al. (2018), uses a mouse model to explore the effects of HBOT on AD. Throughout this study, a marked increase in several aspects of AD pathology can be seen. They hypothesise that HBOT decreases the degree of oxidative stress to such an extent that it can help delay the onset of hippocampal atrophy, preserving the memory centres of the brain.

Under normal circumstances, in cases of cerebral hypoperfusion, the brain will activate several pathways that work to prioritise major functioning centres of the brain, compromising other 'less important' centres. Many of these 'protective' pathways can be attributed to causing many of the AD symptoms.

As a target of his research, Shapira et al. (2018), focussed on measuring the activity of these pathways. They found that such pathways (influencing inflammation, neurodegeneration, astrogliosis etc.) were downregulated in response to HBOT.

Another protein marker known as TNF-a is also often used a diagnostic tool when working with neurological disorders and represents an important part in necrotic cascade pathways. This marker specifically is responsible for neurodegeneration (the death of neurons), in response to hypoxia. During this trial, the researchers noted a 60% decrease in TNF-a activity in response to HBOT.

In summary, this paper suggests that oxygen is an important rate-limiting factor for AD patients and proposes that HBOT must become considered as a viable treatment for treating neuroinflammation, even at late stages of the disease. These findings are consistent across the current literature with several other studies reporting similar data (Chen, et al., 2014) (Geng, et al., 2016) (Lavrnja, et al., 2015).



Autism Spectrum Disorder

Similar to Alzheimer's Disease, a large percentage (75%) of children affected by ASD are found to be affected by cerebral hypoperfusion (Zilbovicius, et al., 2000). As cerebral perfusion is proportionally linked to brain metabolic rate and function, the degree of hypoperfusion can be linked to the severity of autistic behaviours (Rossignol, et al., 2012).

At its core, any type of hyperbaric oxygen therapy is aimed at increasing the concentration of oxygen dissolved within blood. Hence, in such cases of hypoperfusion, whilst the cerebral perfusion pressure (CPP) remains constant, oxygen loading can be optimised by HBOT. Put simply, although the blood flow is still restricted, the blood is 'better quality' and so it can mitigate the hypoxic effects.

By allowing oxygen enrichment of the brain, oxygen can help to prevent the recruitment of many inflammatory signalling molecules. Rossignol et al. (2009), targets his study at such pathways and notes a significant decrease across the board in almost all inflammatory cytokine release.

In addition to this, he also notes a decreased level of VEGF. This particular hormone is responsible for forming new vessels within the brain and increasing membrane permeability which can lead to cerebral oedema, aiding inflammation. Without the spike in this hormone, it suppresses a substantial amount of inflammation. HBOT also results in increased vessel formation, but it does so through a different pathway, thereby avoiding the risk of cerebral oedema.

Throughout his paper, Rossignol et al. (2009), suggests that the prime target for such a treatment are children over the age of five (5) with a higher autistic severity. This is likely due to the fact that older children have a greater degree of cerebral hypoperfusion and are, therefore, more affected by oxygen-enrichment.

Rossignol et al. (2009) concludes his study by stating that "parents who pursue hyperbaric treatment for their child with autism can be assured that it is a safe treatment modality at the pressure used in this study (1.3ATA), and that it may improve certain autistic behaviours".

Follow up studies conducted by Rossignol et al. (2012) used Single Proton Emission Computed Tomography (SPECT) scanning in order to quantify the degree of change in oxygen perfusion within the frontal lobes (Please refer to Figure 1 on page 5).



Within this particular study, m-HBOT was administered at 1.3ATA, and a substantial increase in effective cerebral perfusion was noted.

One of the more unique advantages of m-HBOT in treating autistic behaviours can be seen when looking at the target demographic. m-HBOT is a non-invasive, relatively time-efficient treatment for a disorder that currently has very few modalities of proven treatment.

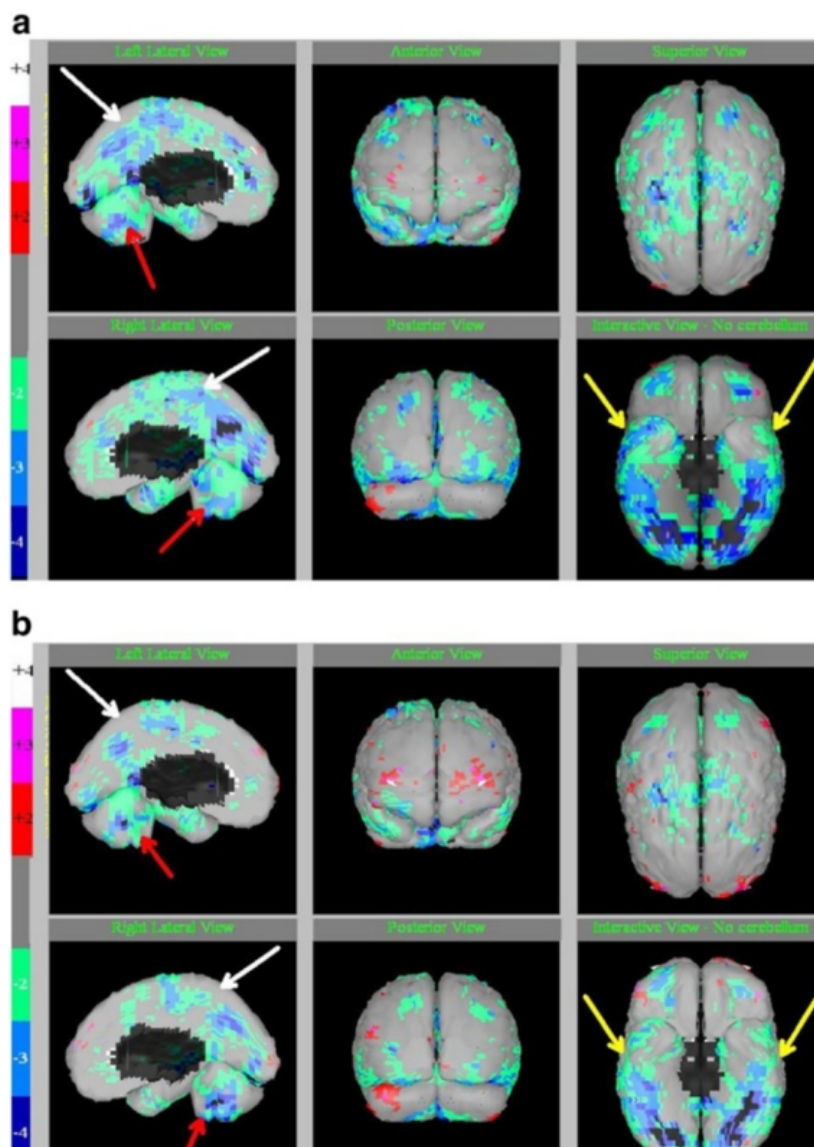


Figure 1. SPECT scan images in a 12 year old boy with autism (a) before and (b) after 80 sessions of HBOT at 1.3 atm. Legend: minus 2 (green) to minus 4 (blue) standard deviations indicate the magnitude of regional hypofunctioning (hypoperfusion). White arrows indicate improvement in deeper cortical hypoperfusion patterns. Red arrows on sagittal slices show the midline cerebellum hypoperfusion and improvements after HBOT. Yellow arrows on the “underside” view show the temporal lobe hypoperfusion with improvements after HBOT



Attention Deficit Hyperactivity Disorder (ADHD)

Attention Deficit Disorders (ADDs) are a chronic condition often diagnosed in adolescence. While the precise cause of ADDs are still debated, current literature correlates many cases to genetic influence and CNS dysfunction.

Currently, there is no cure, however there are many effective medications such as psychostimulants that can help to mitigate the symptoms over short periods of time.

The application of m-HBOT to treat ADDs is slightly more experimental than its popular use in conditions like ASD and there are many avenues for further research.

A comprehensive study conducted by Ezra, Dang & Heuser (2011) however, provides a new perspective on this potential treatment.

In this study, 15 subjects who developed ADD and a slowing of reaction time at the time of exposure to mold toxins were identified. Deficits in attention span and reaction time were documented not only by taking a careful history, but also by performing a Test of Variables of Attention (TOVA). The TOVA test provided an objective measure of these variables.

After 10 sessions of m-HBOT, a statistically significant improvement in both measures was observed.

After performing a paired-*t* test, this study found that participants reported a significant increase ($p > 0.05$) in attention span and reaction time after bouts of mHBOT when compared to baseline (Figure 2 please refer to page 7).

The principle behind how m-HBOT and HBOT works to elicit such results is still debated, however, it is presumed to stem from three main sources.

- 1) HBOT has the ability to increase oxygen perfusion deeper tissues, even despite vascular or neural trauma.
- 2) The stimulation of superoxide dismutase (SOD) in response to HBOT. This antioxidant acts as a free radical scavenger and mobilises white blood cells to potentiate germ-killing antibiotics.
- 3) HBOT has been linked to increasing the rate of reconstruction of lower order motor neurons, making it an effective strategy for the treatment of several neurodegenerative diseases (Ezra, Dang, & Heuser, 2011).



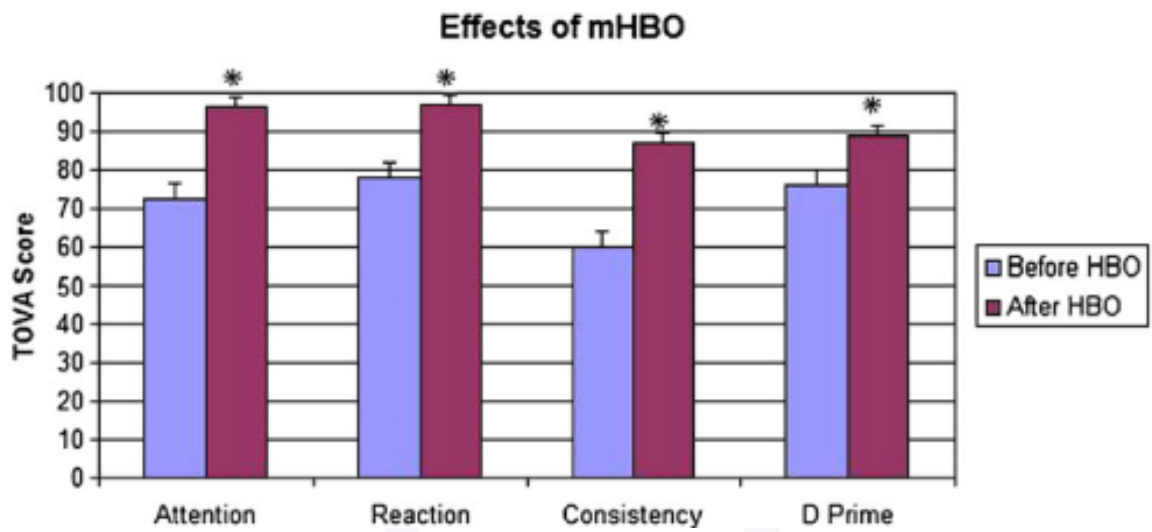


Figure 2. TOVA Score before and after 10 sessions of mHBOT (1.3ATA). (n=15). Paired-*t* test conducted to determine validity, significant changes are denoted by '*'. Each subject was compared individually to their own trial before the treatment to allow for varying degrees of competency. The TOVA scale denotes deviation from standard scores exhibited by TOVA controls where 100= no abnormality



Cerebral Palsy

Cerebral Palsy (CP) is a neurological disorder characterised by poor muscle control and poor neuronal development leading to several issues involving cognition.

The primary cause commonly associated with the development of CP are poor *in utero* conditions such as hypoxia or a compromised nutrient delivery. This typically results in a lesion in the posterolateral frontal areas of the brain which cause severe functional deficits in movement. In addition to the immediate site, and as a result of poor electrical communication within the lesion, we can see a ring of underdevelopment around it known as the 'ischemic penumbra' (Astrup, Siesjo, & Symon, 1981).

Whilst the neurons directly within the lesion are untreatable, the neurons within the penumbra report long-term viability even past birth (Neubauer, Gottlieb, & Kagan, 1990), with some cases reporting viability up to the age of 60.

What this means is that although we are unable to totally ameliorate the functional effects of CP lesions, we are able to delay, if not completely stop, the progression of the disorder.

The following summary is comprised of three (3) different studies that facilitate a multidisciplinary analysis of m-HBOT to treat CP in both rat models and human models.

A study conducted by Yang et al., (2008), talks about the ability of m-HBOT to facilitate new stem cell proliferation, specifically in brains with a history of hypoxic brain damage.

Using a rat model, Yang et al., (2008), not only induce this successfully, but track the maturation of such neurons in areas of trauma. A key finding is that 28 days after the treatment commenced there was a +57% increase in the number of mature neurons between the HBO group and the control group.

Yang et al., (2008) focus not only on the amount of neurogenesis, but on the percentage of these neurons that reach maturation (Figure 3 and 4.).

In the past, neurons that have been induced into proliferation have not reached this stage of development and could therefore be redundant.

In this study, it is shown that m-HBOT is able to create an environment that allows the neurons to reach maturation, presenting as a more long-term sustainable treatment than acutely inducing neuron proliferation.



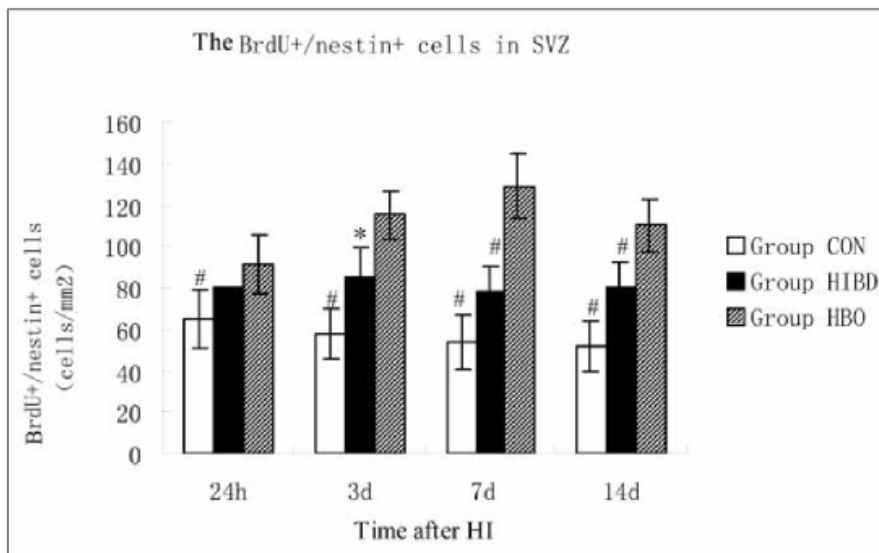


Figure 3. The amount of successful neuronal maturation after hyperbaric intervention (HI) causing endogenous stem cell proliferation (n=180). Paired-t test conducted to determine validity, significant differences from HBO group are denoted by '*' (-p<0.05) and '#' (-p<0.01). BrdU+ and Nestin+ cells are used as a measure of neuronal maturation.

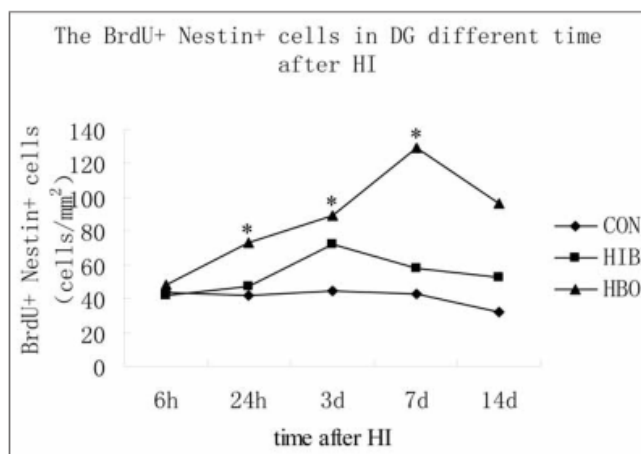


Figure 4. The rate neuronal maturation after hyperbaric intervention (HI) causing endogenous stem cell proliferation (n=180). Paired-t test conducted to determine validity, significant improvements from the previous time point are denoted by '*'. Each subject was compared individually to their own trial before the treatment to allow for varying degrees of competency. BrdU+ and Nestin+ cells are used as a measure of neuronal maturation.



As with the previous disorders within this review, the main function of HBOT is to increase the ability of the blood to deliver the nutrients to areas that are 'harder to reach' by increasing the pressure of oxygen within the blood.

A study conducted by Efrati et al., (2013), used SPECT (single positive emission computed tomography) to capture the degree of change in perfusion pressure when exposed to HBOT.

Figure 5 utilises data obtained from HBOT administered at 2.0ATA however Efrati et al., (2013) notes similar effects when administered at 1.3ATA. Figure 5 also shows an immense amount of improvement in the basal ganglia region. This region is arguable the most region for the regulation of movement second only to the primary motor cortex.

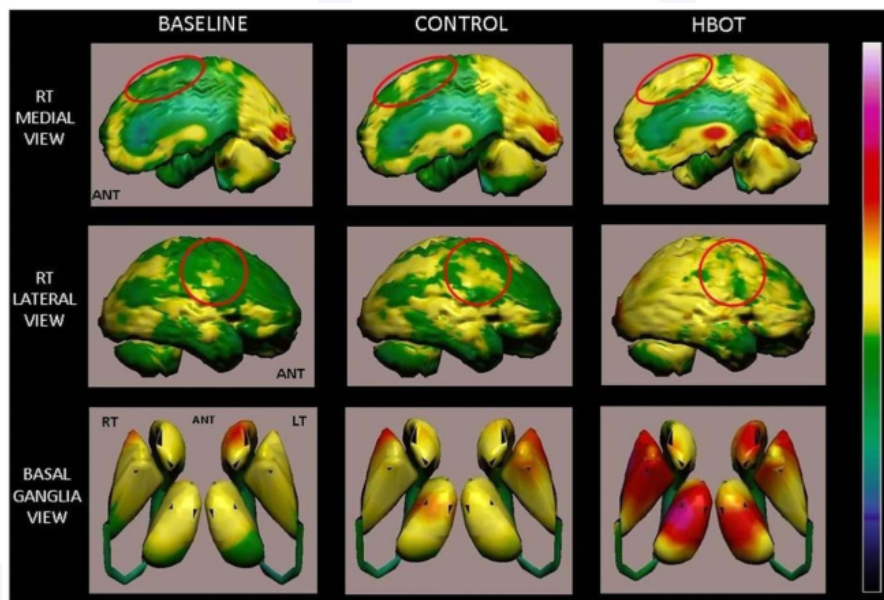


Figure 5. Volume rendered Brain SPECT perfusion maps following HBOT.

The results shown are of a patient suffering from hemiparesis. The HBOT column shows disappearance of the perfusion deficits demonstrated at the end of the control period. The colour bar provided displays the ascending degree of perfusion (Black → White)



A study conducted by Mukherjee et al., (2014) at the UHM targeted their research at the functional effects of HBOT on CP rather than the underlying physiology. They took 150 children that suffered from CP and separated them into four groups (Table 1.).

	A (control)	B	C	D
<i>HBOT conducted at</i>	-	1.3 ATA	1.5ATA	1.7ATA
<i>Supplemental O₂?</i>	-	No	Yes	
<i># of sessions</i>	-	40		
<i># of participants</i>	-	40	32	58

Table 1. Distribution of sample size. Mukherjee et al., (2014)

In this experiment, group B most similarly resembles our AirPod Oxygen Therapy as it is conducted at 1.35ATA and does not require supplemental oxygen.

Throughout the course of the study, gross motor function measure¹ (GMFM) tests were conducted on the participants to assess their level of functionality.

As shown by the data, there was a significant amount of functional improvement in all of the different levels of HBOT administered (Figure 6.).

More interestingly, however, statistical testing conducted found that there was not a significant level of difference between the degree of functional improvement noted in the three (3) treatment groups.

What this means is that whilst our product does not use supplemental oxygen and is not graded as a medical device, it mitigates the risks commonly associated with high-grade HBOT yet does not compromise on the amount of functional benefit to our clients.

¹ GMFM: This test includes activities that measure the subject's ability to walk unassisted, maintain an stationary position with resistance and others.



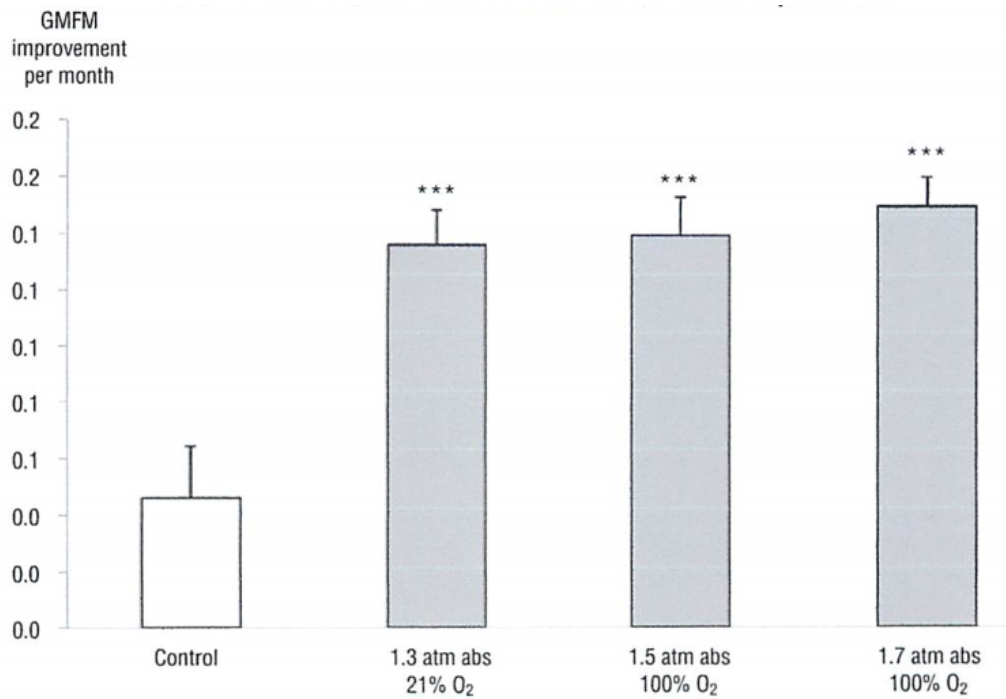


Figure 6. **Amount of improvement in motor function as measured by GMFM after hyperbaric intervention.** Paired-t test conducted to determine validity, significant improvements from the previous time point are denoted by '*'. Each subject was compared individually to their own trial before the treatment to allow for varying degrees of competency.



Downs Syndrome

Downs Syndrome (DS) is a genetic disorder that is caused by a chromosomal abnormality that occurs during development *in utero*. The disorder is commonly associated with a mild-moderate intellectual disability which has a variety of follow on effects in the fields of motor function, behavioural adaptation and other developmental malformations.

Shortly after the chromosomal abnormality *in utero* occurs, the body undergoes a series of irreversible physical changes. Because of this, there is no cure, and so far, there is limited research pertaining to the ability of m-HBOT or HBOT to alleviate the symptoms commonly associated with DS. For this reason, this research review will look at the ability of HBOT to increase the quality of the nutrition provided to the foetus *in utero*.

The following articles cited can be separated into two categories:

- 1) the factors that have been linked to increasing the occurrence of DS births and
- 2) how HBOT can help to mitigate these factors.

A study conducted by Salehi et al., (2006), uses a mouse model to explore how cholinergic neuron degeneration can contribute to the cognitive dysfunction noticed in DS. He establishes a link between the neurodegeneration experienced in DS to that experienced in Alzheimer's Disease.

Because of this, we can look at the potential ways that HBOT can help to decrease the rate of neurodegeneration or increase the rate of neurogenesis as a potential preventative mechanism *in utero*. Mu, Krafft & Zhang, 2011, comment that HBOT not only increases the rate of neurogenesis, but also can help to prevent cell death within the primary affected areas of the brain (Figure 7.).



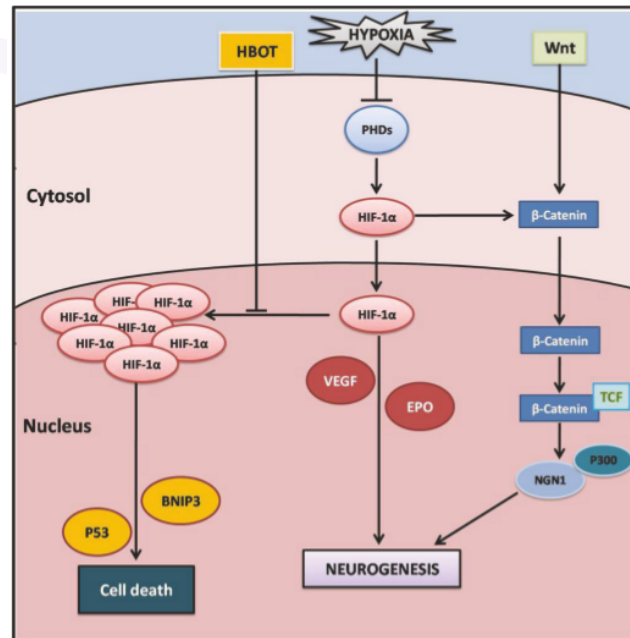


Figure 7. Under normal circumstances HIF-1α worked to mobilise pro-apoptotic markers which increase cell death. In HBOT, this pathway is inhibited, and the Wnt pathway, responsible for neurogenesis, is upregulated.

In 1995, Busciglio & Yankner published a study that suggested the underlying primary cause of DS was the increased generation of oxidative stress. They highlight that the increased amount of oxidative stress placed on the system directly leads to a broad range of metabolic issues within the neurons and supporting structures of the basal forebrain.

Whilst these effects are locally noticed in the brain, oxidative stress can compromise regular function all around the body, including placental nutrition (Eldar-Geva, Hochberg, deGroot, & Weinstein, 1995). The literature that supports the use of HBOT in order to mediate oxidative stress is abounding, and widely appreciated as a viable treatment (Thom, 2009).

Just like the other types of cells in our body, neurons require energy to function too. This energy is formed in mitochondria and requires the input of oxygen. Quite often if there is either a large demand for energy, or a low supply of oxygen, these mitochondria undergo oxidative stress and can begin to lose function. Without an adequate amount of energy, many neurons in crucial areas of the brain die off. By increasing the pressure of oxygen within the blood, HBOT lowers the degree of oxidative stress that the mitochondria experience, therefore



decreasing the amount neuronal death that is commonly associated with DS *in utero* (Dave, et al., 2003).

One thing that further exacerbates the amount of neuronal death are toxic reactive oxygen species (ROS). ROS are released as a part of a local inflammatory response within the brain, and work to 'shut down' certain pathways to 'protect the brain' (Thorpe, Fong, Alic, Higgins, & Dawes, 2004). Quite often in neurodegenerative diseases however, ROS can be produced inorganically as a false response, leading to the further breakdown of crucial pathways. One niche aspect of our AirPod Hydroxy treatment is that we also administer hydrogen in the chamber to neutralise these reactive oxygen species. Hydrogen is a powerful antioxidant and can help to scavenge free radicals in areas of high ROS activity.

This review ultimately suggests that although HBOT cannot cure DS, the literature suggests that if a woman undergoes m-HBOT (>1.35ATA), it will increase the degree of placental nutrition to lower the amount of risk factors commonly associated with the occurrence of DS births.

It is worth noting, however, that parental observations support anecdotal accounts of their child's improvement in several domains of DS in response to HBOT. Please refer to the paper titles 'Anecdotal Evidence'.



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