

Chamber of Hopes for Brain Repair

Hyperbaric oxidative treatments bring new hopes of brain repair from strokes, traumatic brain injuries and even metabolic disorders.

Reflections on a recent article published in PLoS ONE:

By Efrati *et al*:

“Hyperbaric Oxygen Induces Late Neuroplasticity in Post Stroke Patients - Randomized, Prospective Trial”

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By Eshel Ben-Jacob

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Currently, stroke is the leading cause of inability to maintain independent life among adults in the US. Every year, more than 800,000 people in the US suffer a stroke. With the aging of the population, the severity of the problem posed by stroke (and brain injuries mainly due to home accidents) is expected to increase. Experts agree that novel methods to repair and protect the brain from damage caused by strokes, traumatic injuries and metabolic disorders (which can lead to dementia and Alzheimer) are needed more than ever before.

New Hopes

New results by a team headed by *Dr. Shai Efrati* of *Asaf Harofeh* Medical Center and *Tel Aviv University* suggest that hyperbaric oxidative treatment (HBOT) should be employed to repair the brain from strokes and traumatic brain injuries (TBI). The results imply that in the future, the HBOT might also be exploited to protect the brain from dementia and Alzheimer (for reasons explained further below). The team illustrated and analyzed the dramatic improvements in brain function and quality of life following two months of HBOT treatment, in Seventy-four participants, 6-36 months after the stroke, whose condition was no longer improving prior to the treatment. Yet, the neurological functions and life quality of almost all the patients (over 95%) were significantly improved after the HBOT sessions. Analyses of brain imaging (by SPECT scans) showed that the treatment led to an increase in brain activity in brain locations with neurons that stayed alive but did not have sufficient energy (blood supply) to function (generate firing of signals).

Granted new freedom

When asked, many of the patients say that the treatment gave them back the freedom they lost due to the stroke (or TBI). The patients' relatives say that their loved ones returned to them. They also mention the new freedom by being relieved from the time and economic pressure imposed by the need to take continuous care of disabled people. Going from the patients and the families to the national level, billions of dollars will be saved every year once HBOT is adopted as routine to treat stroke and TBI patients. Right now, the total cost of stroke in the US is *over \$50 Billion per year*. The cost of two months HBOT care per person is only about \$5-10K.

The objection by the medical community

The current study did not discover the fact that HBOT can repair stroke damage. It has been first discovered almost half a century ago (in the early 60s). The discovery has first been considered anecdotal but slowly gained an increasing attention. There has been a "burst" of interest and reports about the beneficial effects of HBOT on stroke and TBI in the late 90s. However, the results were either ignored or severely questioned by the medical community. Consequently, the practice of HBOT to treat stroke and TBI has been shunted primarily to private clinics. While still helping patients who could not find relief otherwise, it caused many in the medical community to dismiss the use of HBOT for brain repair and to actively convince patients not to explore this option. I had many conversations with MDs who shared with me the extent to which they are antagonized by the idea. Almost all of them were so convinced that there is "no reason" it should work, that they did not want to waste the time and hear about the results and what is the underlying brain's thermodynamics and metabolism management that can explain the effect.

Challenging the paradigm

I explain further below the negative reaction of the medical community. In short, the main reason I think has to do with the fact that the findings challenge the leading paradigm as they demonstrate beyond any doubt that neuroplasticity can still be activated months and years after acute brain injury, thus revealing that many aspects of the brain remain plastic into adulthood. It is always hard to accept a new paradigm, and even more so when the paradigm is associated with the brain. Another reason is that it is "too simple" – there is such a high diversity of strokes and they vary from person to person. So the idea that this wide spectrum of complex cases can all be greatly improved simply by putting the patients under high pressure and high oxygen levels seems too much like "magic" that is hard to accept. This is not the only example of powerful solutions that have been dismissed for a long time. For example, the metformin that was shown to be effective for diabetes 2 in the late 50s was approved for use in the US only in 1995, and within a year it became the most widely used drug for diabetes 2.

Are we at a turning point?

Although the FDA defines compressed oxygen as a drug, the use of HBOT to treat stroke and TBI patients does not require FDA approval. What hinders the practice is the negative perception in the medical community at large along with many formal

declarations by various medical organizations that there is no proof that it works. Hopefully, the new study and consequent studies will change this unfortunate state of affairs. The fact that most stroke and TBI patients are deprived of the benefits of HBOT treatment seem to me a major ethical issue that must be discussed and reconsidered by the medical community as soon as possible.

The new treatment

Intensive therapy and rehabilitation programs for post-stroke patients are considered essential for maximizing the patients' quality of life. Unfortunately, these programs are often just partially successful. In the current study, the seventy-four participants spanning 6-36 months post-stroke were divided into two groups: a treatment group that received HBOT from the beginning of the study, and a cross group that had a control period of two months with no treatment followed by a two month period of HBOT treatment. Treatment consisted of 40 two-hour sessions five times weekly in high pressure chambers containing oxygen-rich air (pressure of 2Atm – the pressure sensed when diving down to 10 meters). The figure shows the combined results in terms of improvements in the physiological parameters.

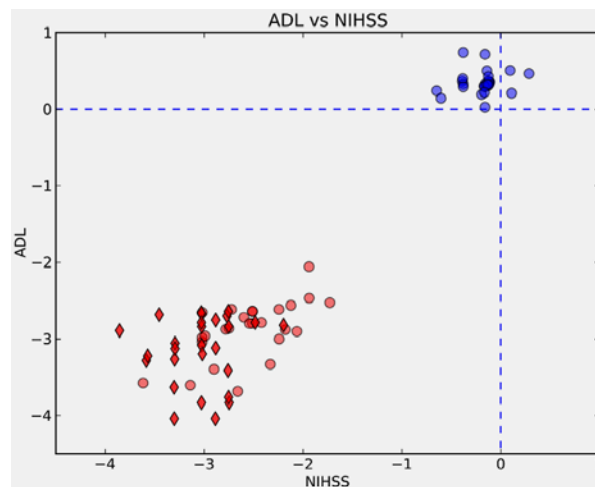


Figure1: Changes in the neurological evaluations. Each circle and diamond shows the changes (statistically normalized) in the NIHSS (NIH stroke scale) and the ADL (activity of daily living) of the patients over a period of two months. Blue circles correspond to the changes during the two month control (when no treatment was given). The changes are close to zero (no changes) which provides confirmation that the patients were at chronic stage. Red circles correspond of the changed during the two months that these patients were treated. Red diamonds correspond to changes during two months of treatment of the additional group of patients. We see that the results for the two independent groups are similar – both indicate significant improvements (negative changes mean improvement). (Courtesy of Dr. Efrati)

As evident from the graph, the results show dramatic improvement. Yet, the current study aimed at “proof of concept” that HBOT can benefit stroke patients, so all patients underwent 40 HBOT sessions. Based on the accumulated clinical experience, more sessions of HBOT may be needed, at least for some patients, in order to obtain the maximal improvement effect.

A new paradigm with new hopes

During most of the 20th century, the central paradigm has been that neuroplasticity can only be activated during childhood and during a limited time window following brain damage. The dramatic improvements in the stroke patients with chronic late stage brain damage imply reactivation of neuronal activity in stunned areas (brain regions in which the activity stopped following the stroke). Stroke damages the blood flow in the brain and causes various degrees of brain injuries. Most severe is cell death (necrosis). However, surrounding necrotic tissue, where cells are entirely lost, there are also quiescent regimes of neurons that are impacted by metabolic dysfunction. They have the energy to stay alive but not enough for full activity (firing of electric signals). These are the brain locations that HBOT targets. By increasing the supply of energy (oxygen), it leads to the formation of new blood vessels and, in parallel, enables the inactive neurons to become active and form new links with neurons inside and outside the damaged areas. To confirm the reactivation of the quiescent areas, the researchers evaluated the anatomical features and functionality of the brain using a combination of CT scans to identify necrotic tissue and SPECT scans to determine the metabolic activity level of the neurons surrounding damaged areas. The research was based on the idea that damaged brain areas with non active but live neuron regions can be activated by providing the cells with high oxygen. Comparison of SPECT scans before and after treatment revealed increase in neural activity in the quiet live neurons. Examples of CT and SPECT scans are shown in Figure 2.

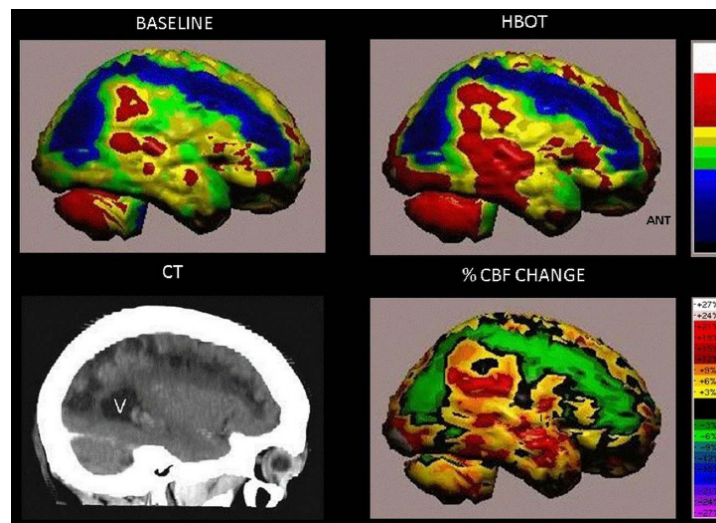


Figure 2: SPECT (the colored pictures) and CT (the B&W picture) of a patient suffering from left hemiparesis due to ischemic stroke that occurred 26 months prior to treatment. The upper two images show the infarcted brain (deep blue color) involving the right antero-postero-lateral frontal, right superior-parietal and right parieto-occipital regions. Curved sagittal view in CT (bottom left) shows the anatomical stroke area (V = posterior horn of right ventricle). The peri-infarct region shows improved perfusion as demonstrated by SPECT image (right upper image). Quantitation of the cerebral blood flow (CBF) change (before and after treatment) is demonstrated in the right lower image. (Courtesy of Dr. Efrati)

The brain's energy management

The brain receives 15% of the cardiac output, 20% of the total body oxygen consumption, and 25% of the total body glucose utilization. Still, this relatively high energy is only sufficient to keep five to ten percent of the neurons active at any given time. Fuel sources are not transferred from the blood directly to the neuron. Other cells that constitute the majority of the cells in the brain, the glia, are in charge of energy management. Some special glia cells also regulate the blood flow in the brain, directing it towards areas with high neuronal activity and away from areas with low activity. The regeneration process following brain injury, which involves complex tasks such as building new blood vessels and rebuilding connections between neurons, requires much energy. This is where HBOT treatment can help. The tenfold increase in oxygen levels during treatment supplies the needed energy for building new blood vessels, new connections between neurons and stimulation of inactive neurons for facilitating the healing process. , The idea that HBOT can help brain repair, though reasonable, has been rejected by the medical community until now since the brain energy management has additional challenging aspect that has been largely overlooked. To simplify the explanation, I take a detour from brain function to sport.

Aerobic and anaerobic exercises

It is widely recognized that sports for good health requires both aerobic exercises – long and more moderate physical activity - and anaerobic exercises – short time intervals of intense activity. What lies behind these activity modes is the fact that muscles, as other cells, can generate energy in two ways: 1. Respiration (also called oxidative respiration), in which energy is generated from sugars (but also from other fuels such as proteins and fats) in a complex process somewhat similar to complete combustion, and can be performed only when oxygen is available. This process is slow but has high efficiency, and the end products are energy, carbon dioxide and water. 2. Glucose fermentation (also called anaerobic fermentation), in which glucose is processed without oxygen. This process is fast but has low efficiency and generates also lactic acid. To provide the fast energy needed during intense exercise, muscles use anaerobic fermentation. The “burning” sensation in the muscles following intense exercise results from the lactic acid byproduct. Lactic acid can be processed by the liver but can also be used as a fuel for oxidative respiration by the muscles. This is why it is recommended to continue for some time with mild exercise following intense workout.

Aerobic and anaerobic functions in the brain

The brain’s energy management also involves interplay between oxidative respiration and anaerobic fermentation. The energy generated by oxidative respiration is sufficient for the neuron to maintain the basic activity but not while being engaged in dedicated task performance. Unlike the muscles that rely on anaerobic fermentation for extra energy, the neurons use respiration for extra energy. However they do so by using more efficient fuel – lactic acid that is provided to them by the glia. The glia cells use anaerobic fermentation under normal conditions so they can generate lactic acid to feed the neurons when needed. Since high concentration of lactic acid can be toxic, the glia cells provide this fuel to the neurons only when needed and when it can be used. Thus, to maintain the brain in good health it is important to perform both *aerobic and anaerobic brain "exercises"*.

Breaking the vicious circles

A vicious feedback loop of energy management occurs at the chronic stage following brain injury: to save energy, glia divert blood flow from the quiescent brain locations to the active ones, starving the former of oxygen; to avoid toxicity in the absence of oxygen, the glia do not feed the neurons in these locations lactic acid, denying them the alternative energy source. The HBOT breaks this vicious circle: the ten folds higher oxygen level (achieved during treatment) triggers the glia to provide the neurons with lactic acid, which enables them to start firing. This ignited activity, in turn, leads to strengthening the connections between the neurons in the damaged area and building new connections, and consequently the blood flow in the brain is re-balanced accordingly.

The complexity of the energy management in the brain has begun to be fully appreciated only recently and there are still many open questions. I assume that this is one of the main reasons that the value of HBOT in brain repair has been ignored so far. Previous studies, lacking the recently-acquired insights into brain functioning, were designed in a way that led to conflicting results. Such an example is the use of HBOT at the early-acute phase immediately after stroke, when the normal activity of the glia is distorted by stress factors. Another example is raising the pressure to 2.4Atm. As every diver knows, dives with oxygen tanks are limited to 10 m, where the pressure is 2 Atm. Higher concentrations of oxygen may have a toxic effect. HBOT with 2.4Atm may give rise to toxicity and put extra stress on the glia, diverting them from anaerobic fermentation, thus limiting their ability to feed lactic acid to the neurons.

Hopefully, the convincing evidence presented in the current study will change this state of affairs, which denies millions of stroke and TBI patients the simple therapy that can give them back their life.

Looking ahead

The new findings have important implications that can be of general relevance and interest in neurobiology. Although this study focused on stroke patients, the findings bear the promise that HBOT may serve as a valuable therapeutic practice in other brain disorders such as dementia and Alzheimer. It is now understood that many brain disorders are related to impaired energy management in the brain (metabolic disorder), usually at older age when blood circulation and other body functions becomes less efficient. Being able to activate neuroplasticity, one can deduce that HBOT might also be used to reverse early stage of dementia and radically slow down the progress of Alzheimer. More daring is the idea to go a step further and envision the use of HBOT as “anti brain-aging” - brain maintenance and improvement at advanced age.