allied academies

19th International Conference on
Neurology and Neurological Disorders
Melbourne, Australia | November 4-5, 2019

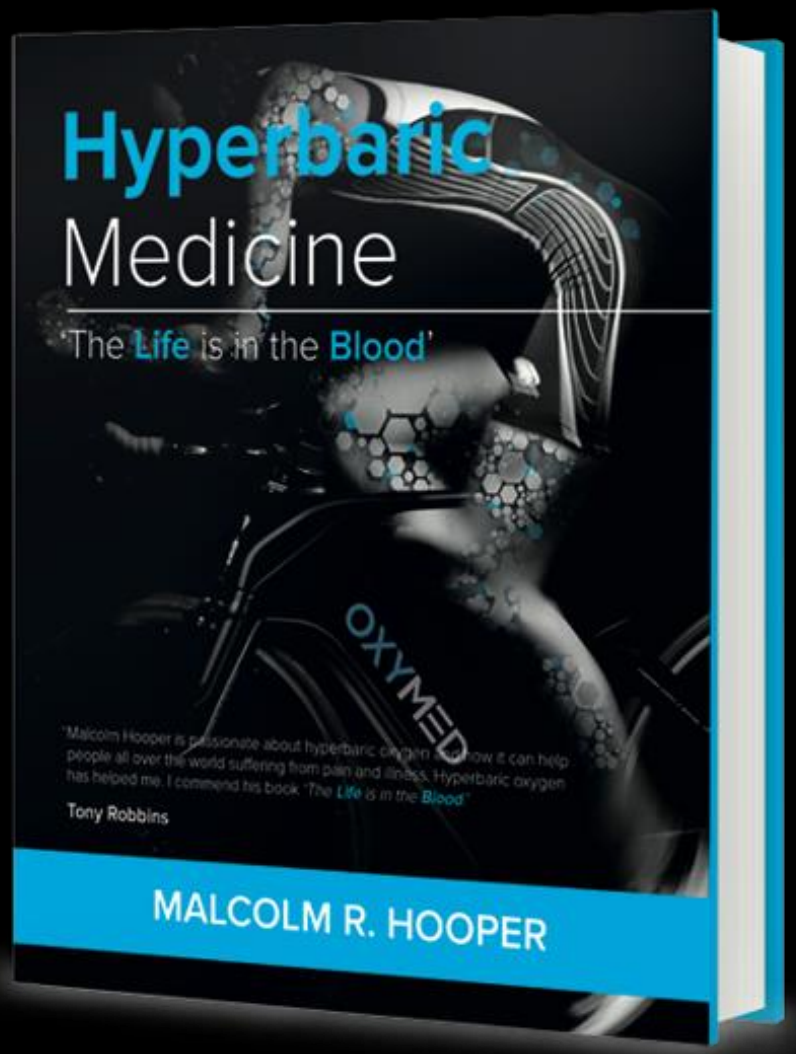
Malcolm R. Hooper ©
OXYMED Australia

Hyperbaric Oxygen Therapy

combined with **LOKOMAT**

Robotic Exoskeleton Walking assisting
Neuroplasticity in Brain and Spinal Cord disabilities

DISCLOSURES



Clinical Director OXYMED Australia

Malcolm R. Hooper B.AppSci, D.Acup, GradCert, GradDip, M.AppSci.

International Executive Director

* Hyperbaric Medicine International

** International Hyperbaric Medical Foundation

HYPERBARIC MEDICINE INTERNATIONAL

INTERNATIONAL HYPERBARIC MEDICAL FOUNDATION IHMF

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INSPIRATION

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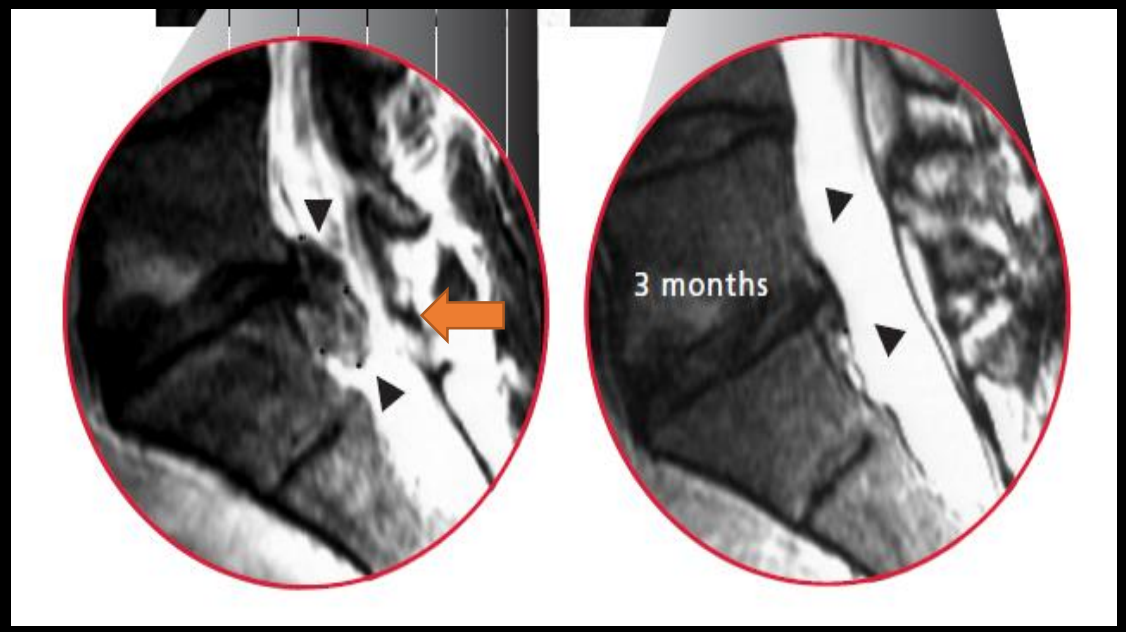
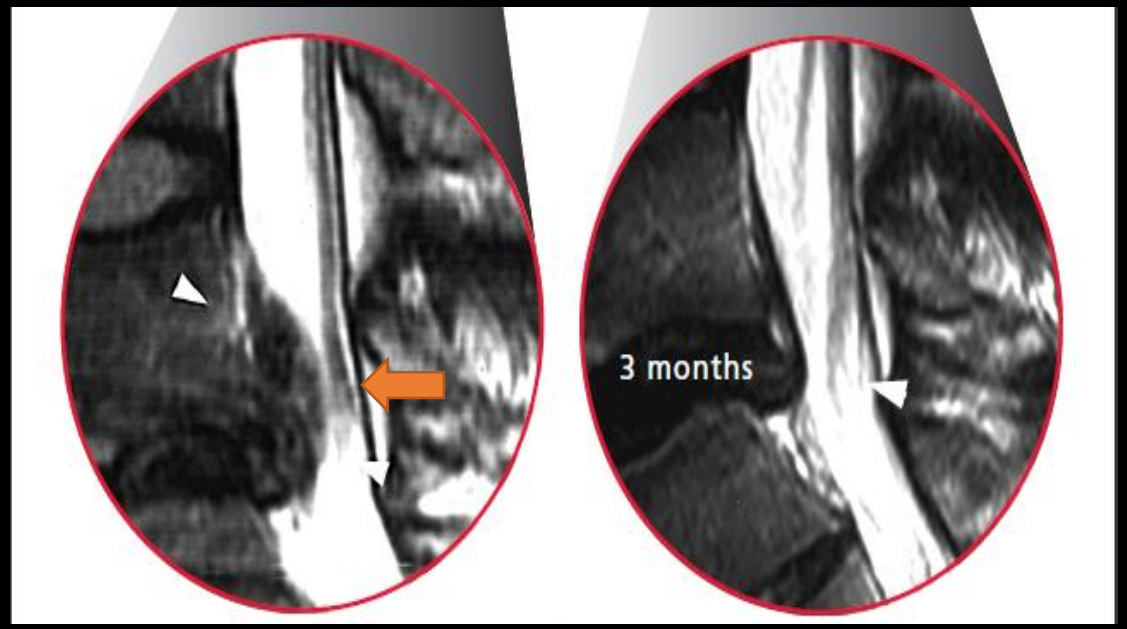
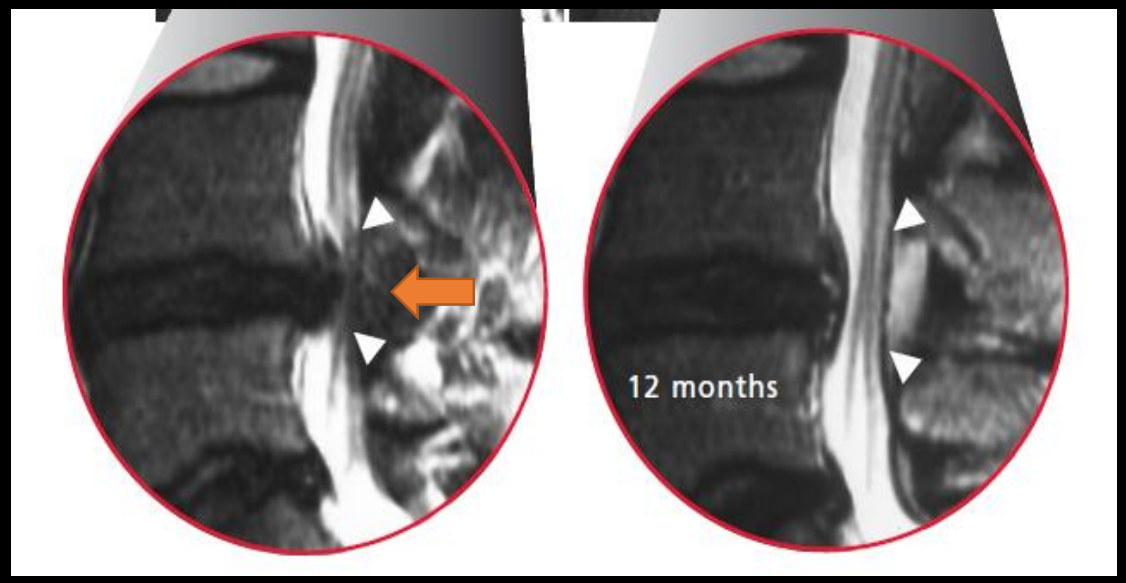
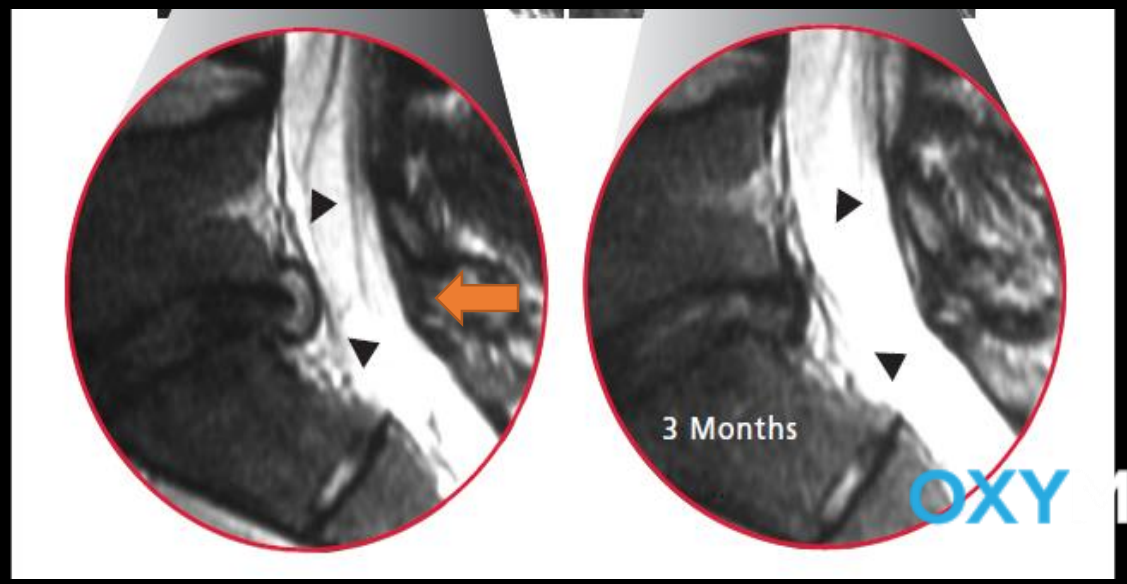
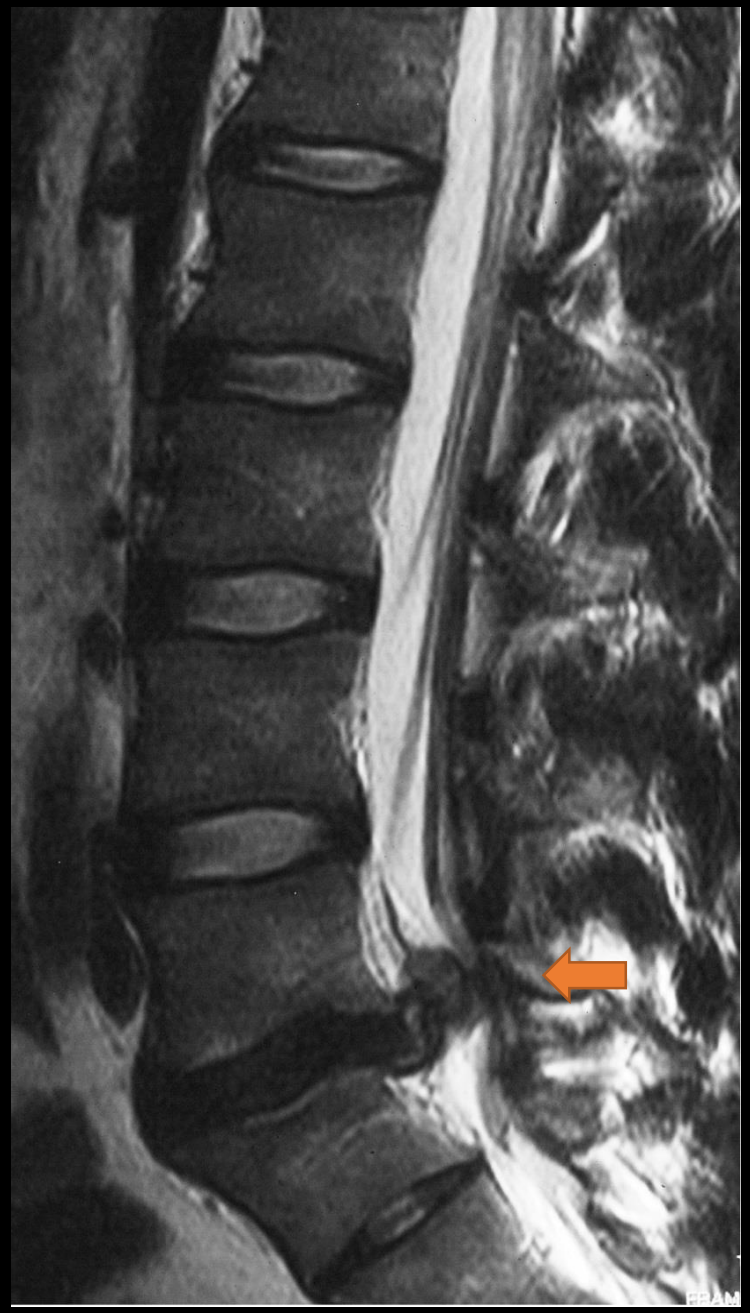
ORIGINATING WORK 1995-1997

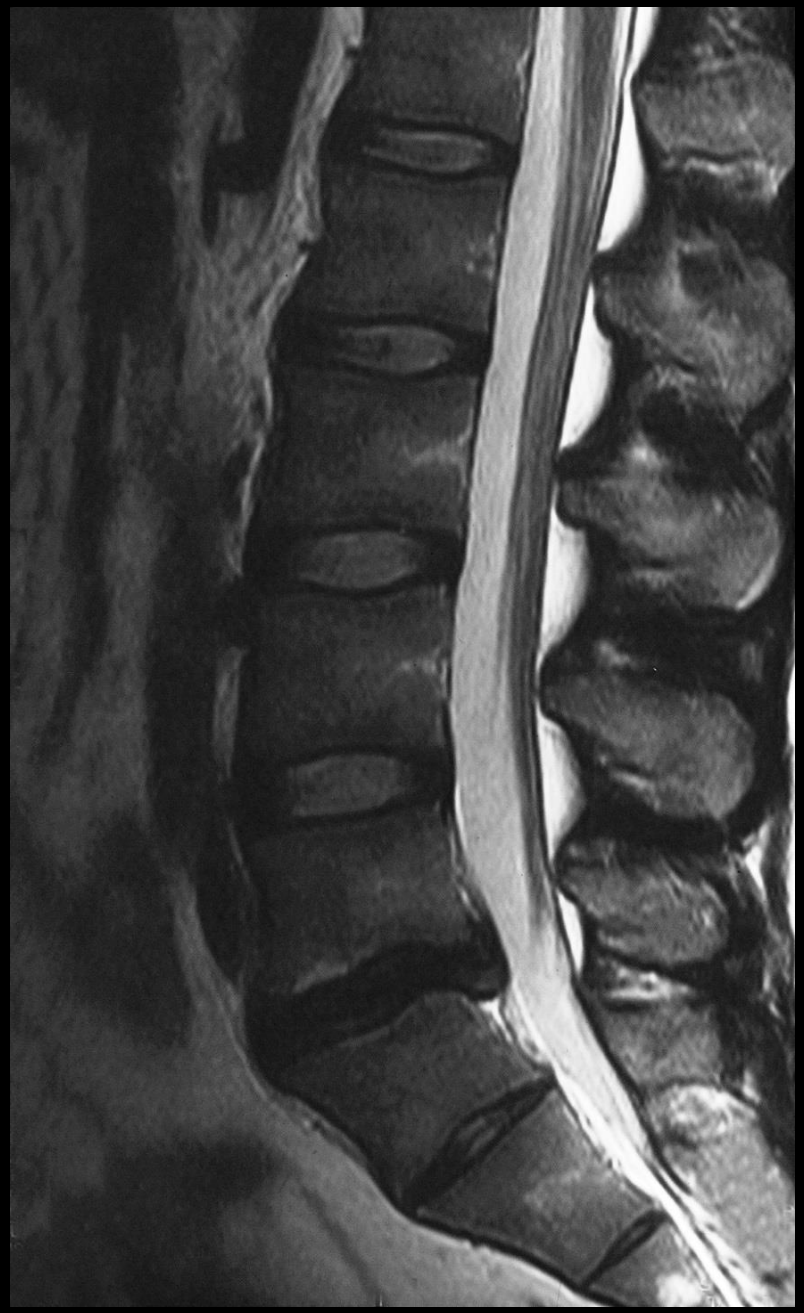












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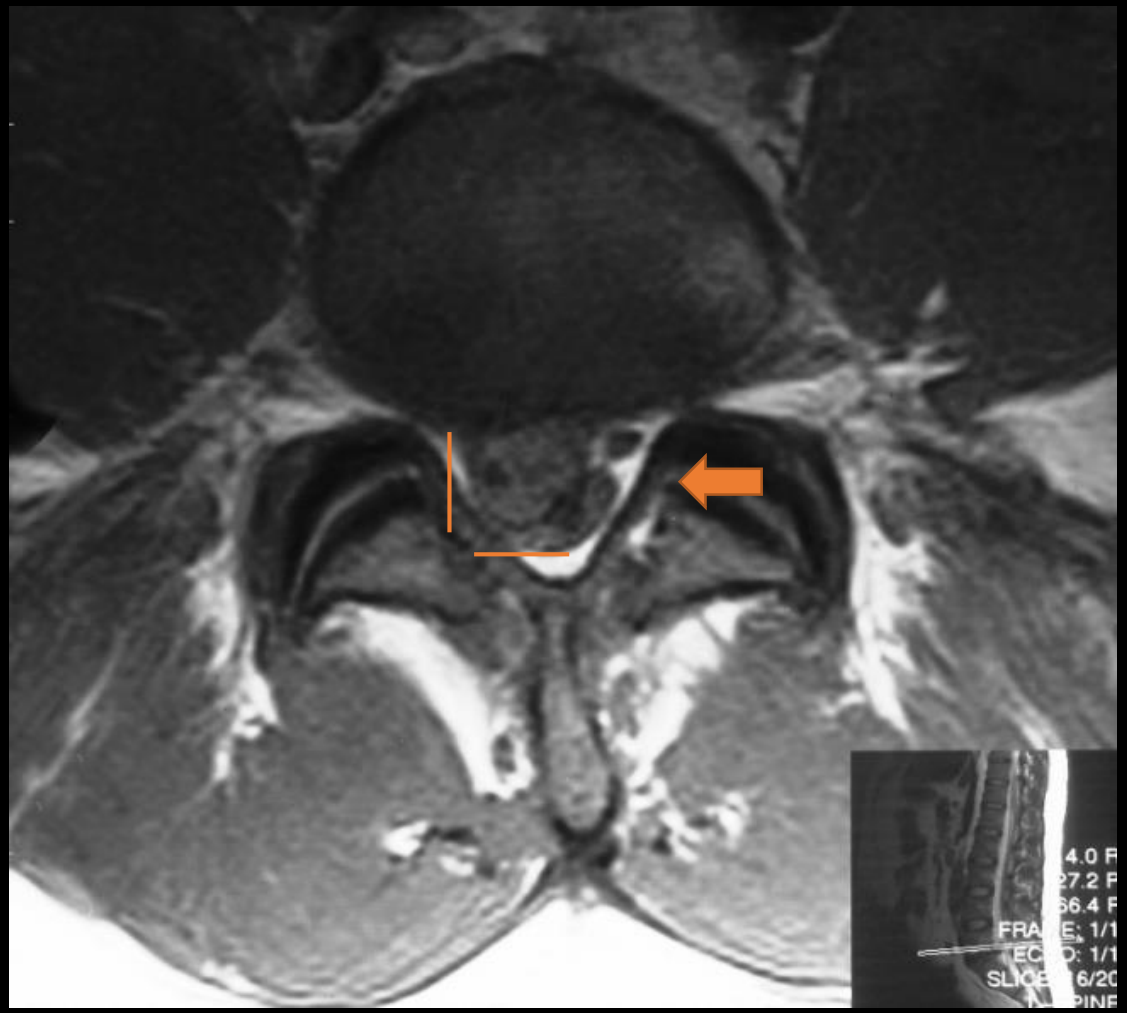
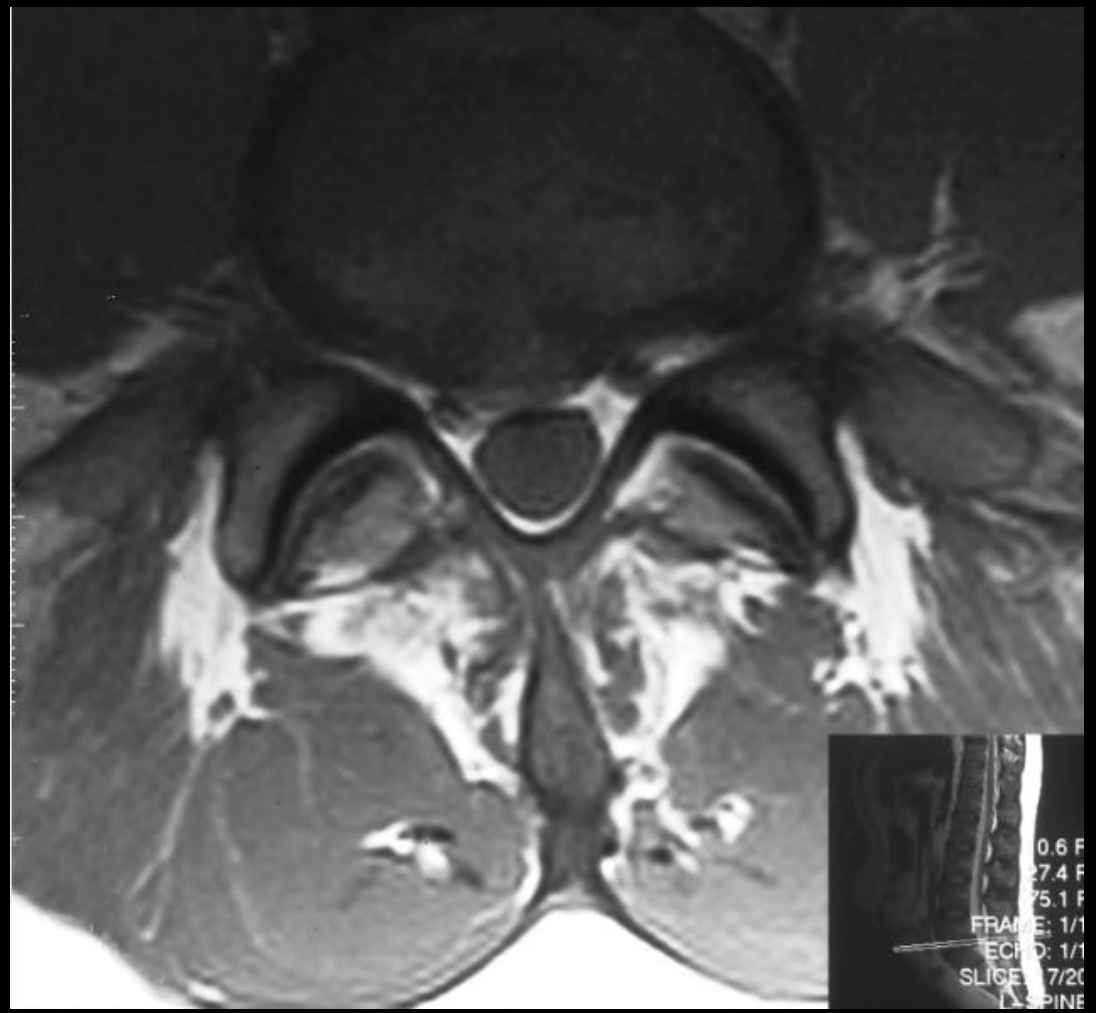
L5/S1 SEQUESTRATION





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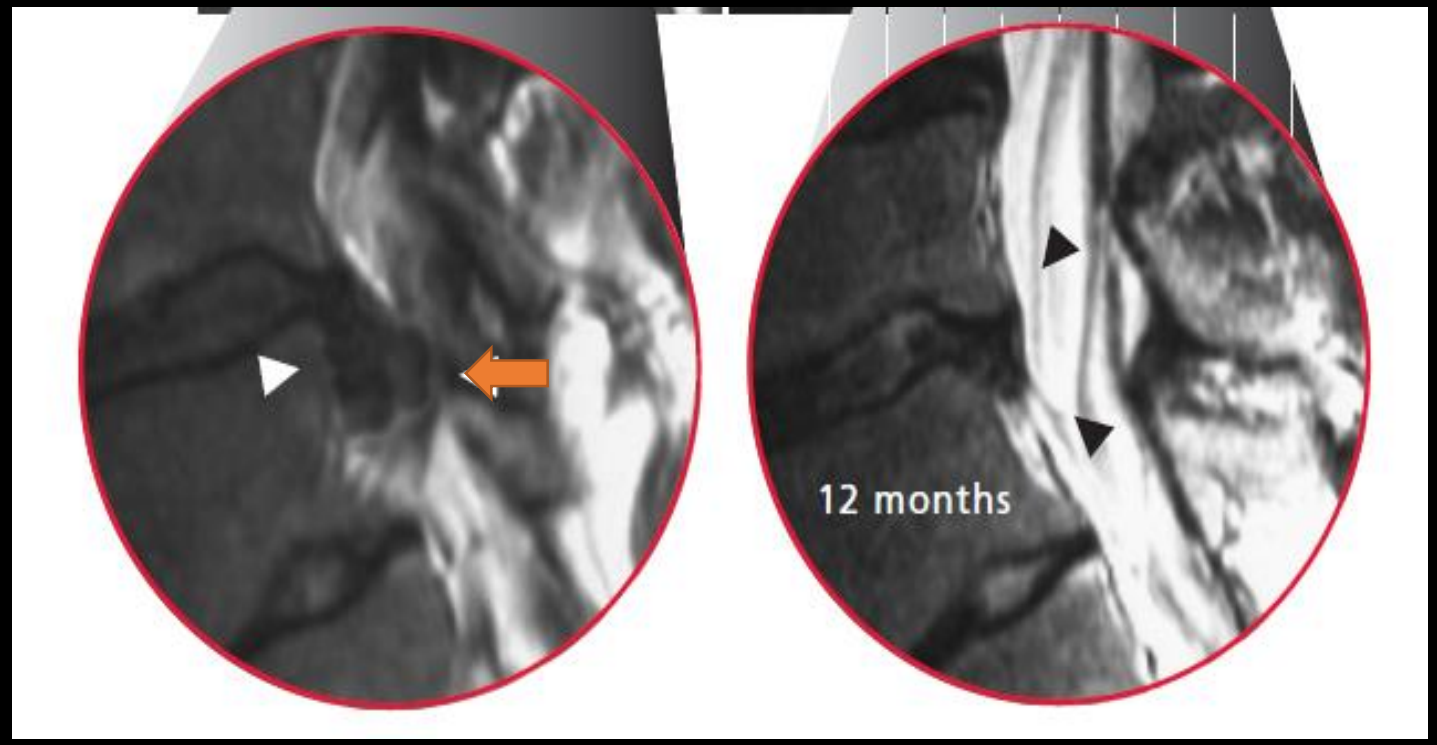

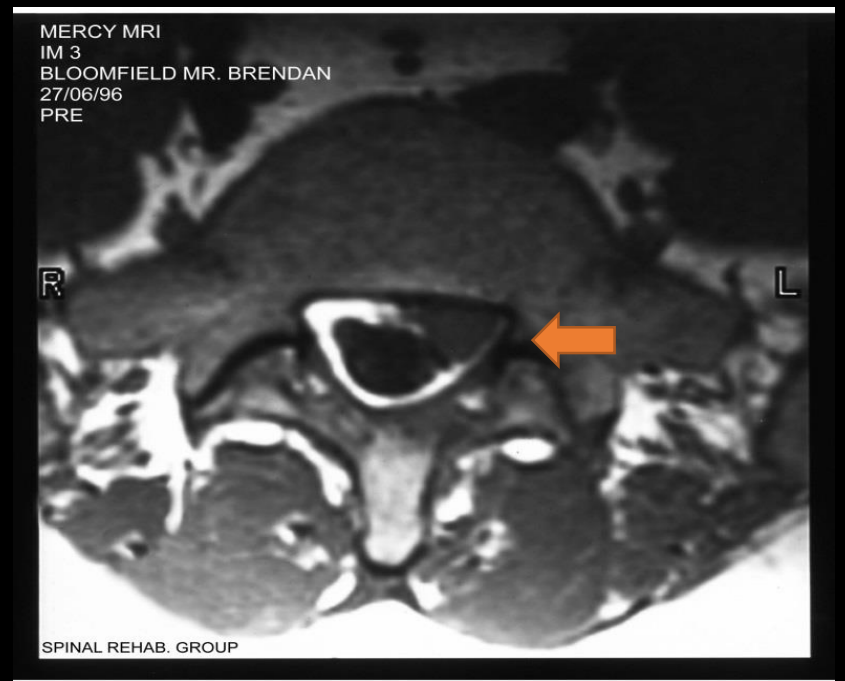

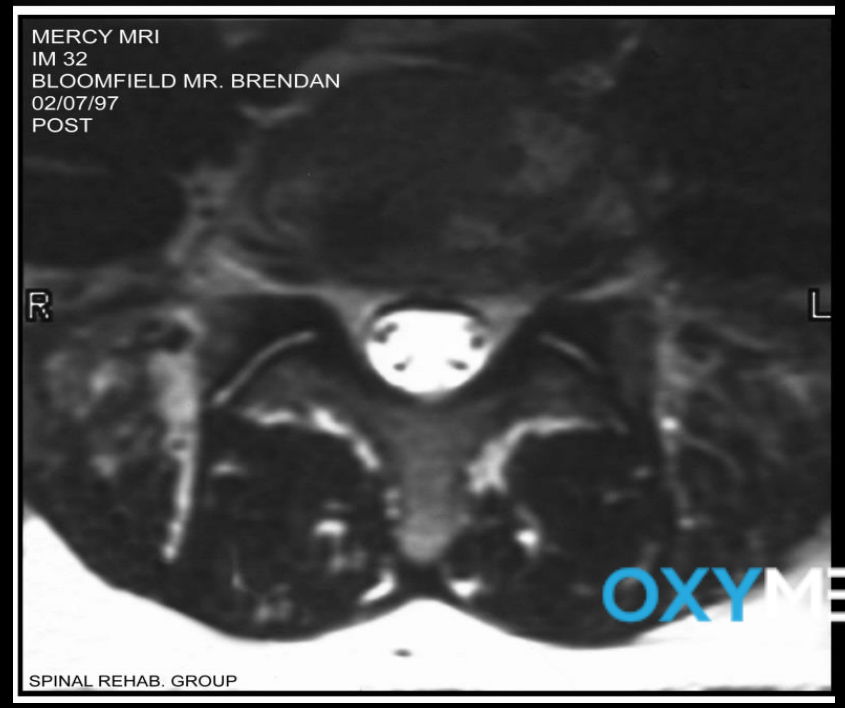

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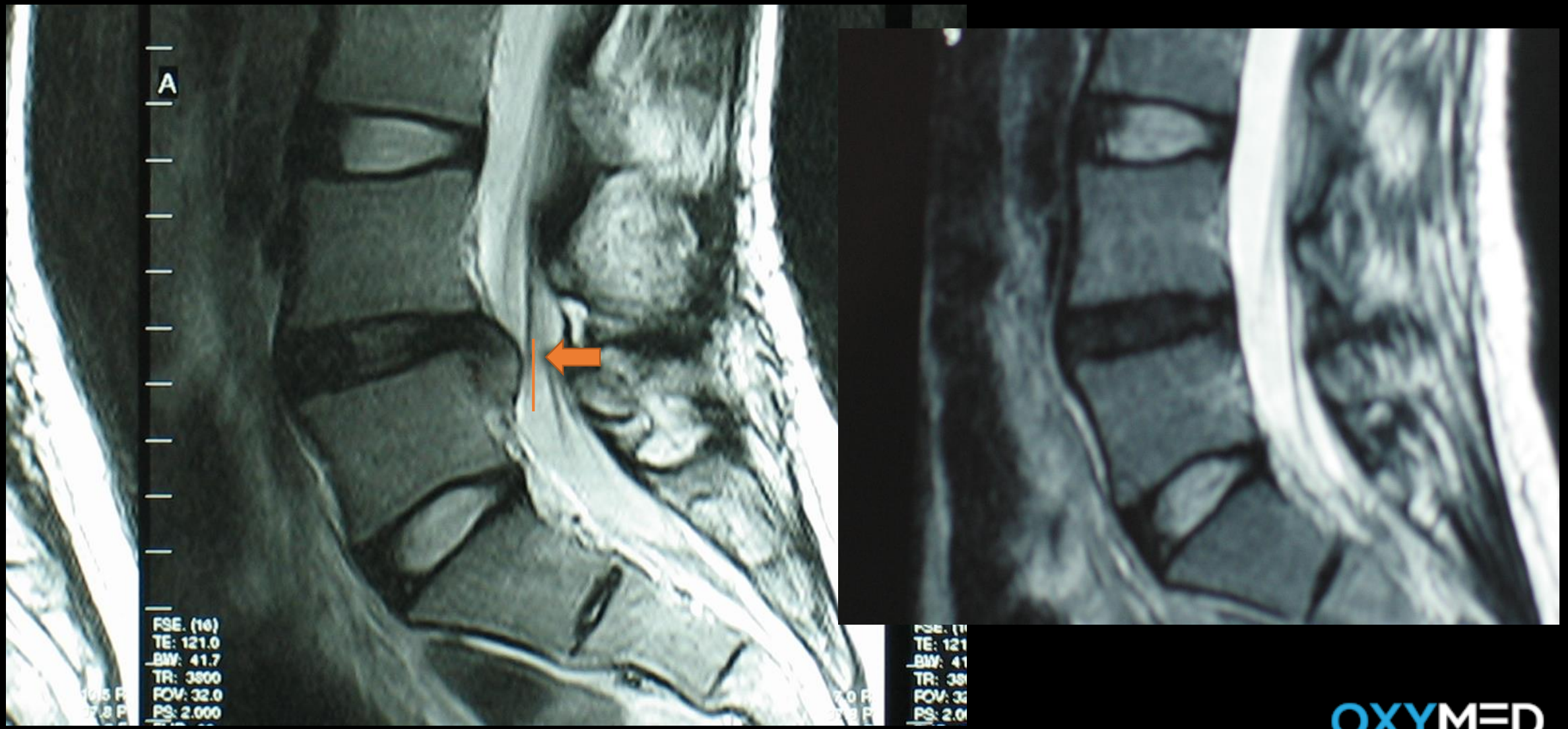
PRIOR DISCECTOMY - RECURRENT PROTRUSION



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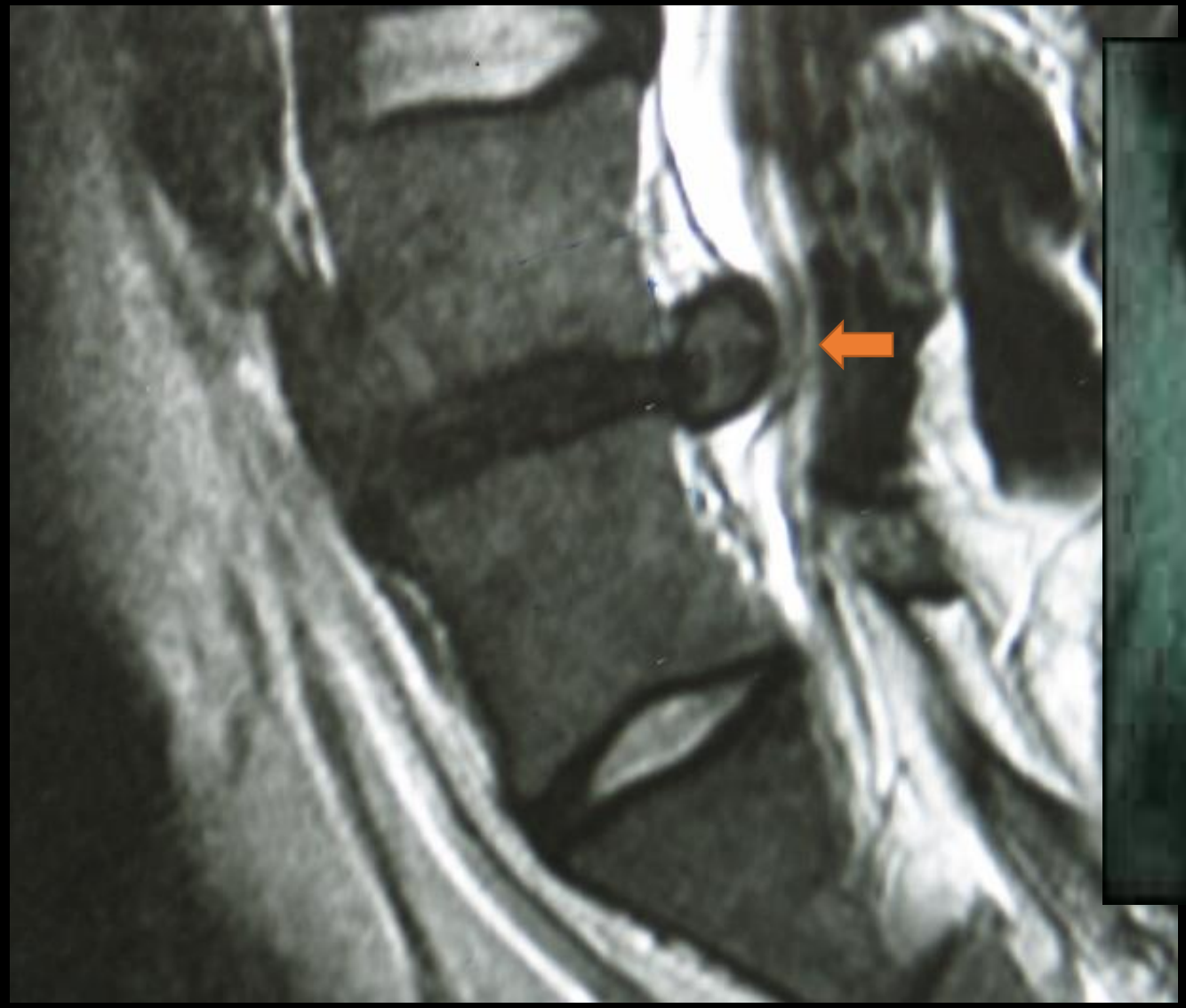
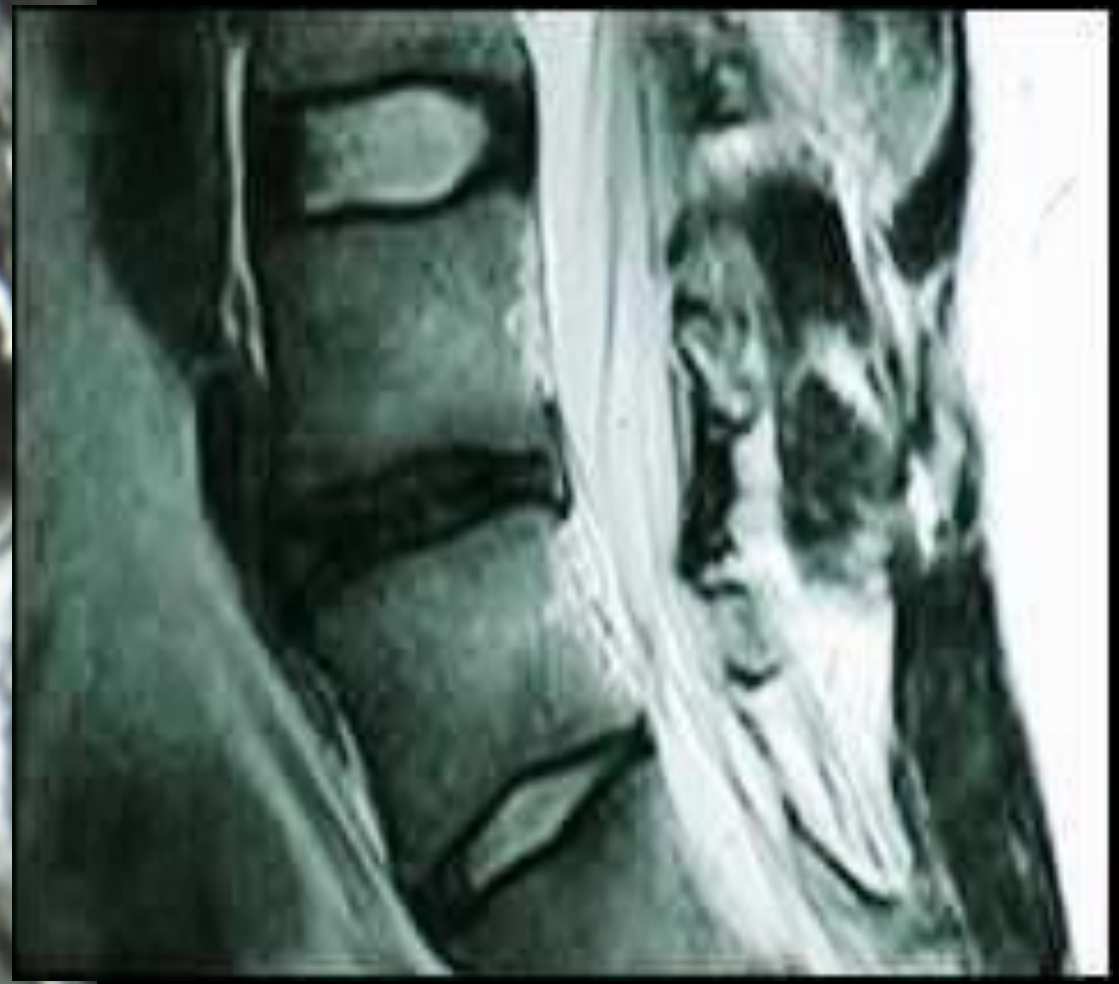
L4/5 PROTRUSION – 2 WEEK INTERVAL





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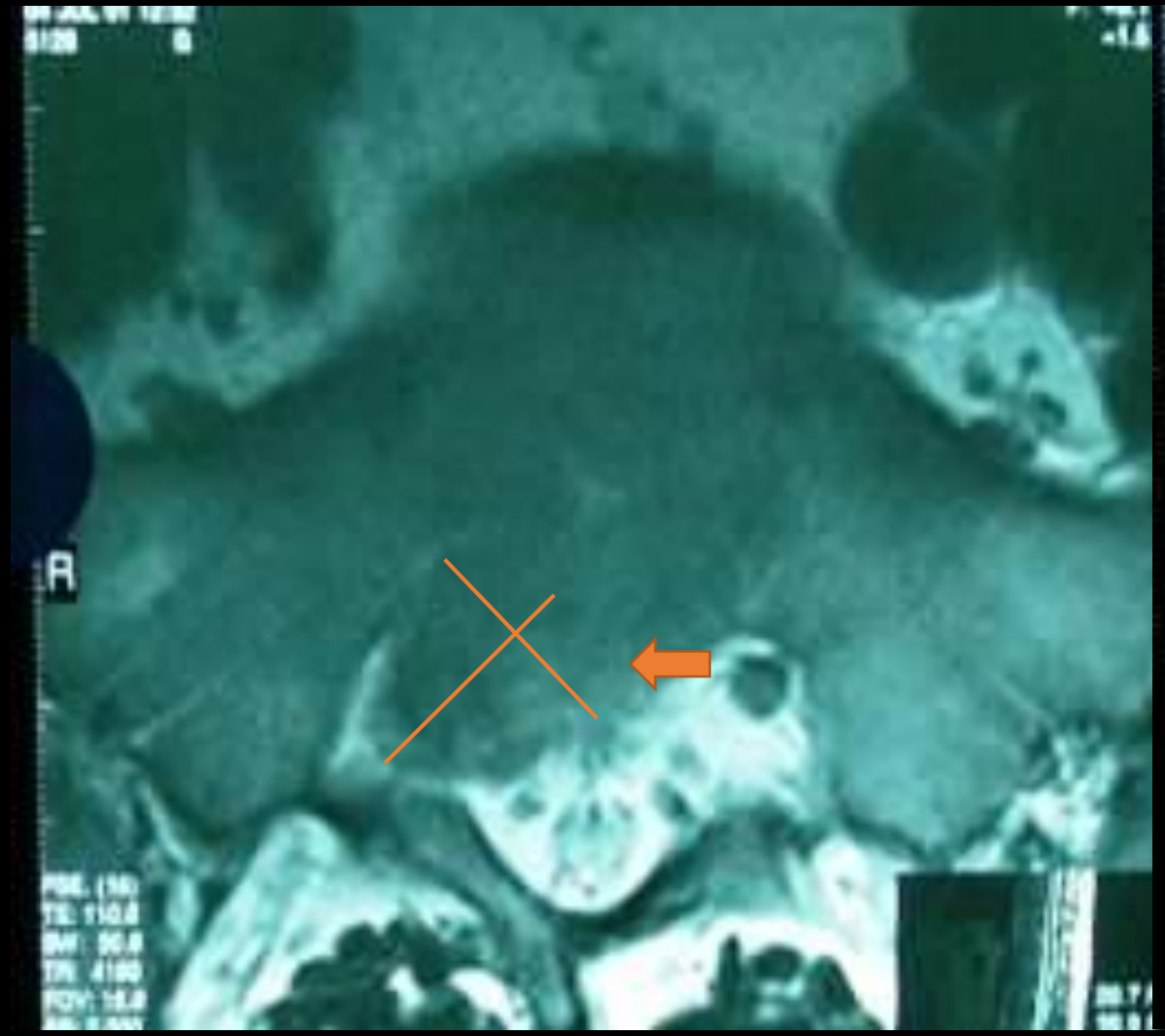
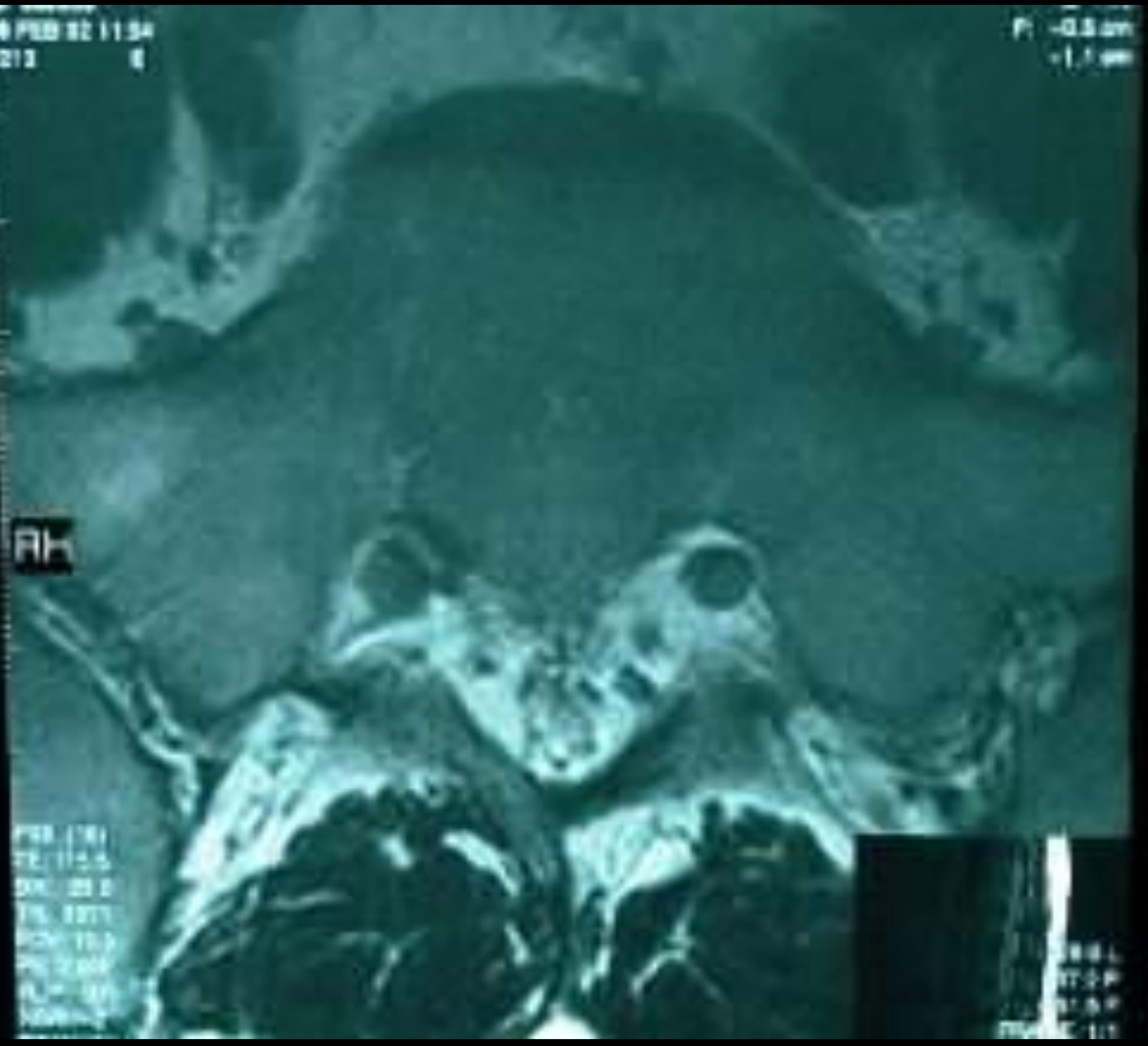
MASSIVE SEQUESTRATION L5/S1 DISC





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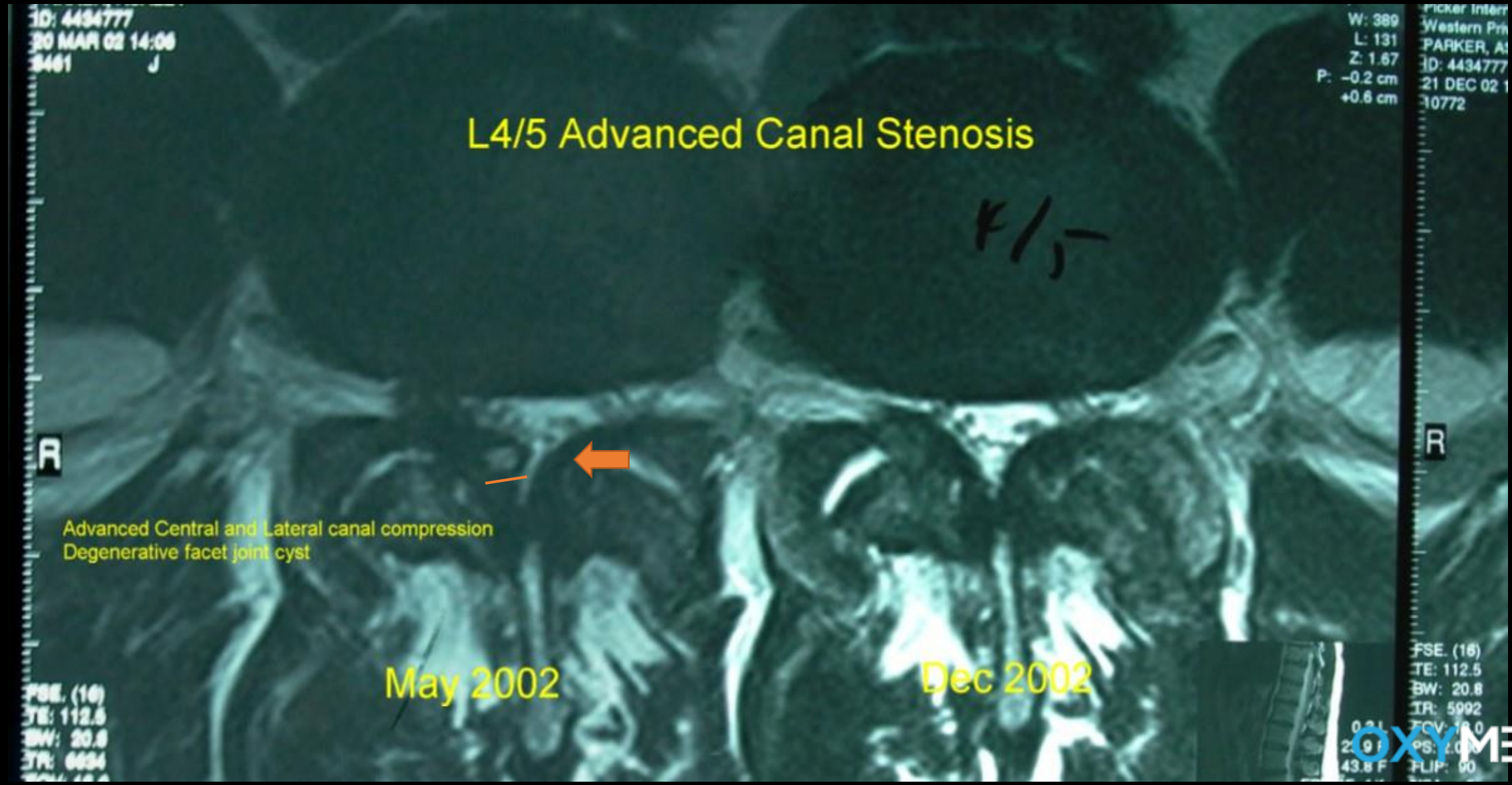
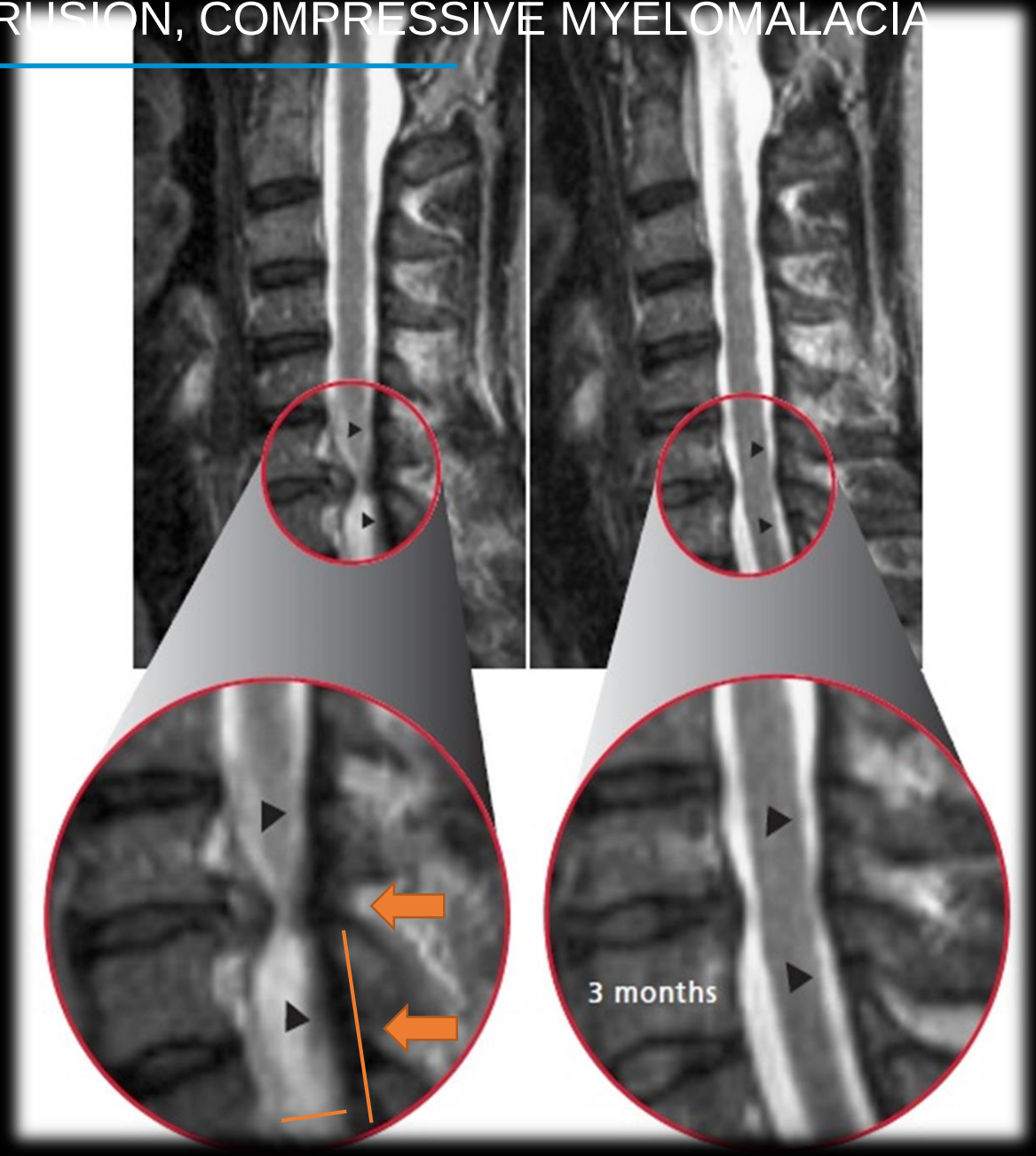
CANAL STENOSIS, FACET JOINT CYST



DISC PROTRUSION, COMPRESSIVE MYELOMALACIA



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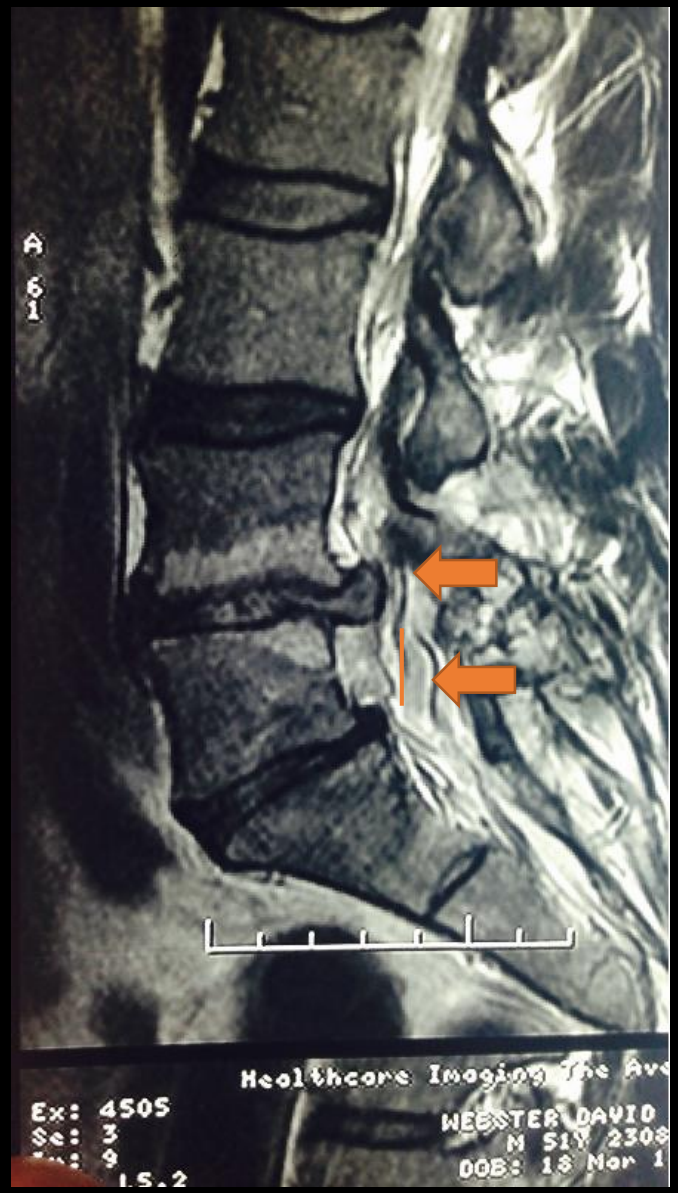
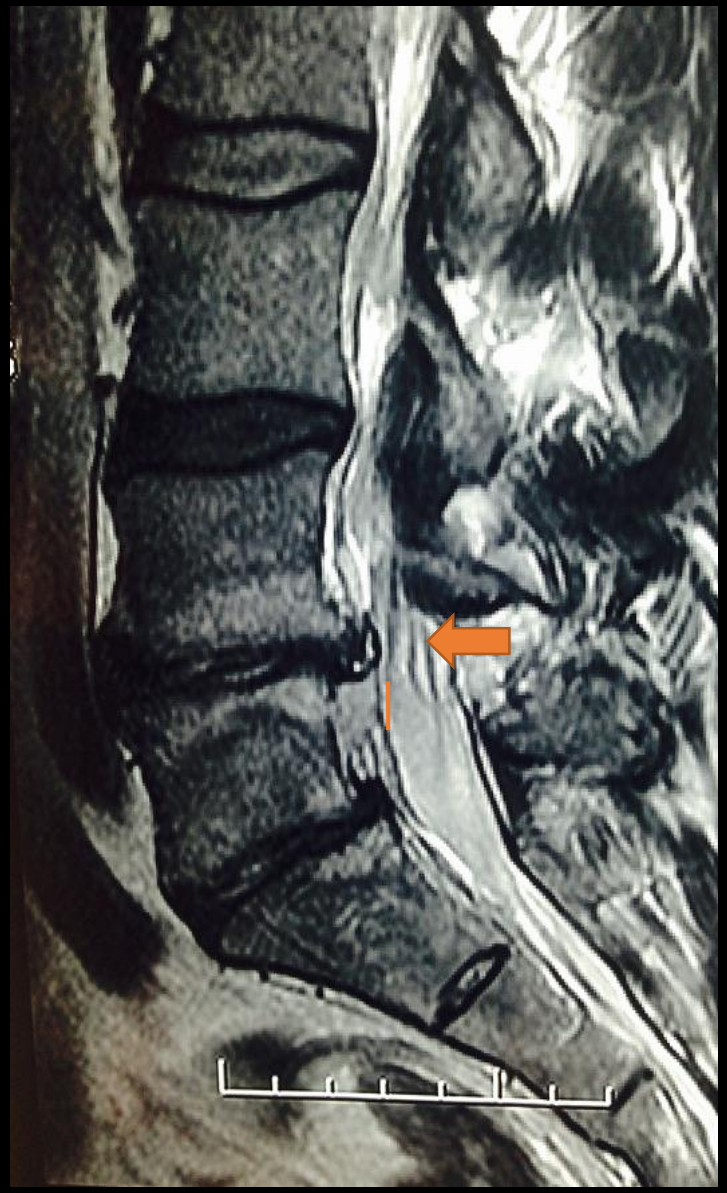
COMPLEX FAILED SURGICAL SYNDROME (FBSS)





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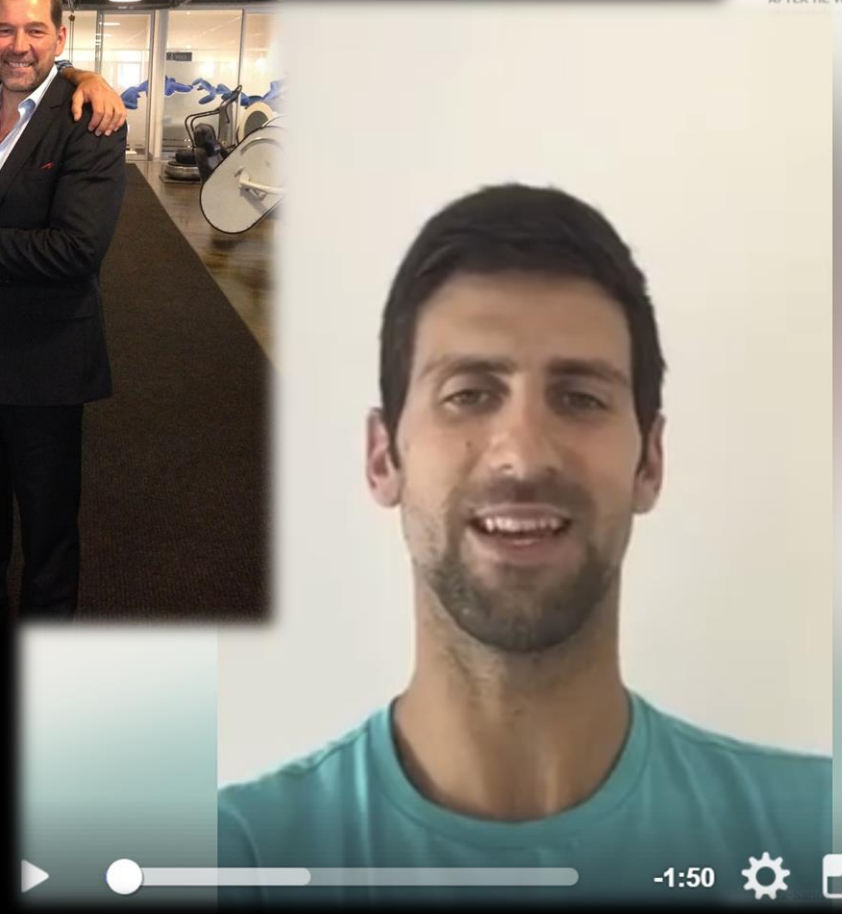
INTERNATIONAL ATHLETES (2010-2019)



SPORTS

Tennis Players Get an Oxygen Fix

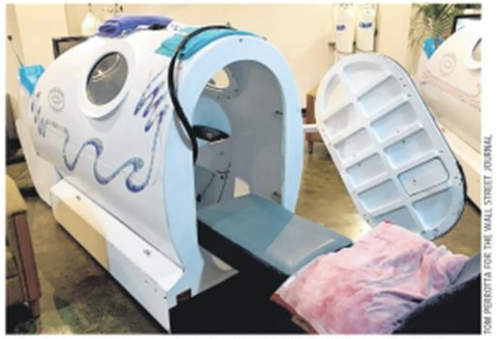
To aid recovery, tennis pros in Melbourne rent hyperbaric chambers

BY TOM PERROTTA

Melbourne, Australia

AFTER HE WON a four-hour, 32-min-

WILLIAM WEST/AGENCE FRANCE-PRESSE/GETTY IMAGES



TOM PERROTTA FOR THE WALL STREET JOURNAL

Left, Novak Djokovic uses hyperbaric oxygen therapy to help with recovery. Above, a pod at the HyperMED clinic in Melbourne, Australia.

ar, doubles star Mike Bryan be-
me a pod regular. His twin brother,
b, tried it too, though just once.
"It's great," Djokovic said. "It
ould get out there more, not just
r athletes."
Mike Bryan said: "It just helps re-
very. I felt a little better doing it."
Bryan also likes the VacuSport, a
ng tube with a skirt that seals a
yer's legs in a vacuum and flushes
tic acid. There is also a cryother-
y chamber, which cools to minus
0 degrees Fahrenheit for a few
inutes. HyperMED's website has a
ture of Milos Raonic, the Cana-
an star, standing in its chamber.
Oxygen sessions last anywhere
om an hour to two hours and cost
0 Australian dollars (US$105).

Mattek-Sands said the benefits are subtle but valuable. "It's not like you walk out of there feeling like Superman or anything," she said. "You sleep pretty good that night, I'll say that. You crash and you dream pretty heavy."

The facility is run by Malcolm Hooper, a former chiropractor, who sat in Djokovic's box in Rod Laver Arena Thursday evening as the world No. 1 beat Roger Federer and earned a spot in Sunday's Australian Open final, the sixth of his career. Hooper's clients include people with cerebral palsy, traumatic brain injuries and disabilities, as well as other athletes. During the Open, he opens his clinic day and night depending on players' needs. "Two, three in the morning, whatever the requirements are," he said.

Top athletes around the world, including football, basketball and soccer stars, use hyperbaric oxygen therapy. Djokovic said he only uses hyperbaric pods in the U.S. and Australia, because access and regulations are challenging in Europe. He said there is still a stigma about oxygen therapy, that it gives athletes who use it an unfair advantage.

"It's very sensitive, especially in the European part of the world," he said. "I wish I can have this all over the place, I wish."

Mattek-Sands said she would be thrilled if the sport's major tournaments provided pods on site. "It's just kind of the new wave for the future," she said.

Hyperbaric therapy doesn't suit everyone. Andy Murray has tried it and decided it isn't for him, according to a representative. Some question its merits. A paper published last year in PeerJ, a peer-reviewed journal, found lower lung cancer incidence among people living at high elevations, which suggests oxygen could be a driver of cancer. Kamen Simeonov, an MD-PhD trainee at the University of Pennsylvania and co-author of the paper, wrote via email, "Basically, it's exposing yourself to risks with no logical reward."

Hooper, who is an affiliate member of the International Hyperbaric Medical Association, said he has seen gains in his patients, and that research suggests hyperbaric treatment can help many ailments. "Every athlete has a growing list of injuries that may benefit," he wrote in an email.

Hooper's chiropractic license was suspended for two years in 2013 after a dispute with a former cerebral palsy patient in part over the effectiveness of treatment, though the Chiropractic Board of Australia viewed Hooper's "conduct as an error of judgment rather than a defect in character," and that he was a "true believer in the treatment that was being given." (He said he hasn't practiced as a chiropractor for 20 years and no longer has a need for the license.)

Hooper also was treating Aussie Rules football players in 2013 when they separately came under investigation for the possible use of banned substances. A Court of Arbitration for Sport panel that imposed a two-year ban on 34 players earlier this month made no mention of Hooper in its findings and didn't assign him any fault. Hooper says he tells all his clients about his history. Justin Sands, the husband of Mattek-Sands, said Hooper has been open since they first met.

"He's been nothing but an upstanding, good guy," Sands said.

Sands, who played college football in the U.S., said he used hyperbaric therapy in his playing days. He says he's surprised so few tennis players use it, given the grueling demands of the game. It might even be useful, he said, for the tour's traveling husbands and wives, though for other reasons. "It's great for a hangover," he said.

GAME CHANGER - PR

PR presented 6-years post injury, classified as a **C6/7 complete**

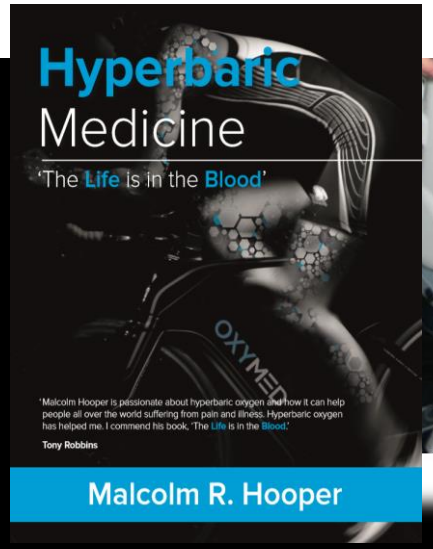
“Hyperbaric Oxygen Therapy creates a ‘fertile neurovascular platform’ for emerging stem cell, immunotherapies and nanotechnology techniques.

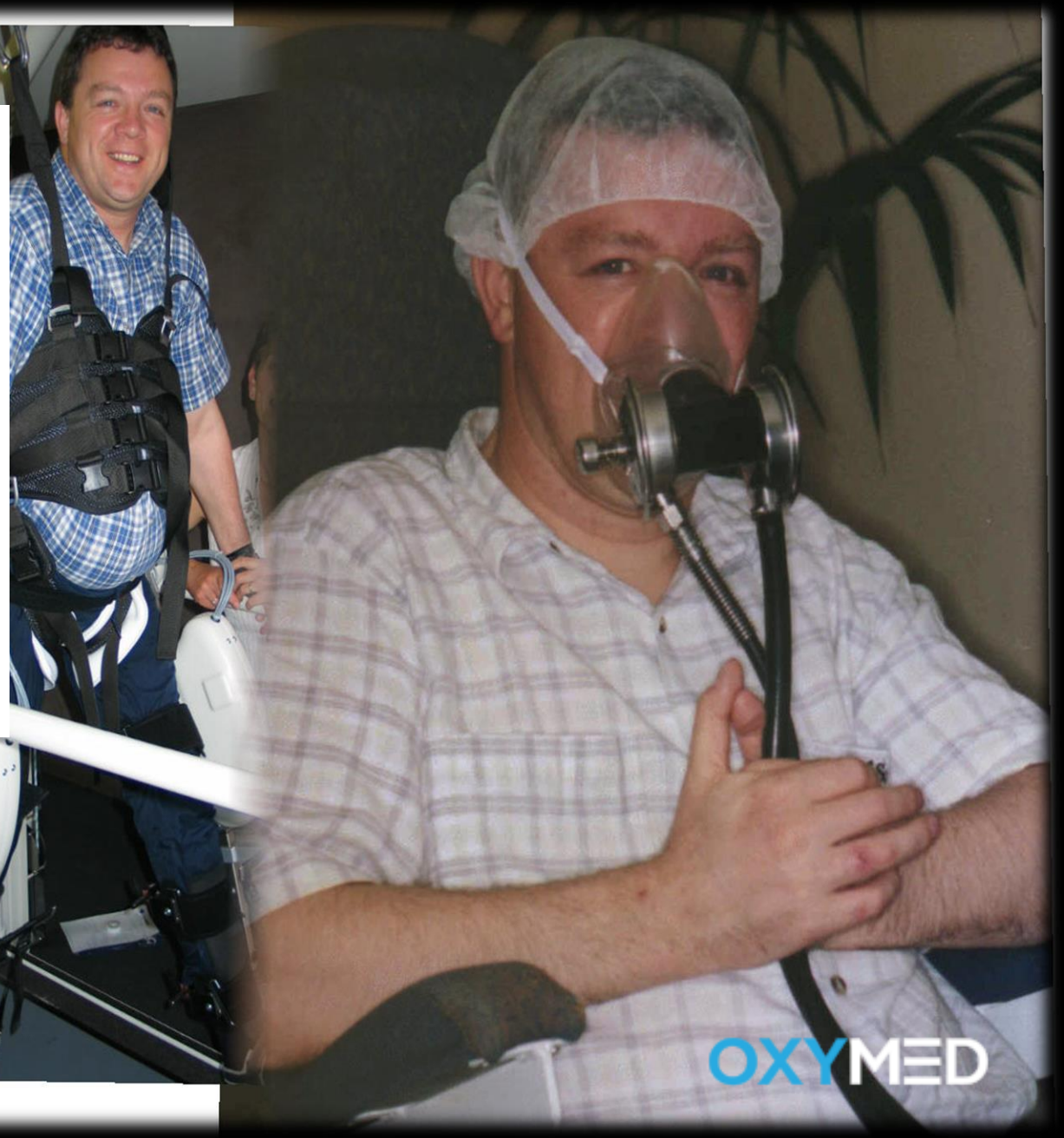
The impact and success of these and future procedures are dependent on the integrity of the underlying supporting neurovascular bed.” (Hooper 2005).

* HBO acts as a 'catalyst' promoting immune modulation

* HBO results in increased blood flow by fostering the formation of existing and new capillary dynamics (neovascularization) activating damaged and dormant nerve cells (penumbra state)

* HBO accelerates neuroplasticity





CASE STUDY IM

Young Isabel has never walked.

* At 8-months age Isabel, was operated on for a benign tumour resulting in her becoming a **T4 complete paraplegic.**

OXYMED

SYRINGOMYELIA, CORD ATROPHY, BENIGN FIBROUS MASS

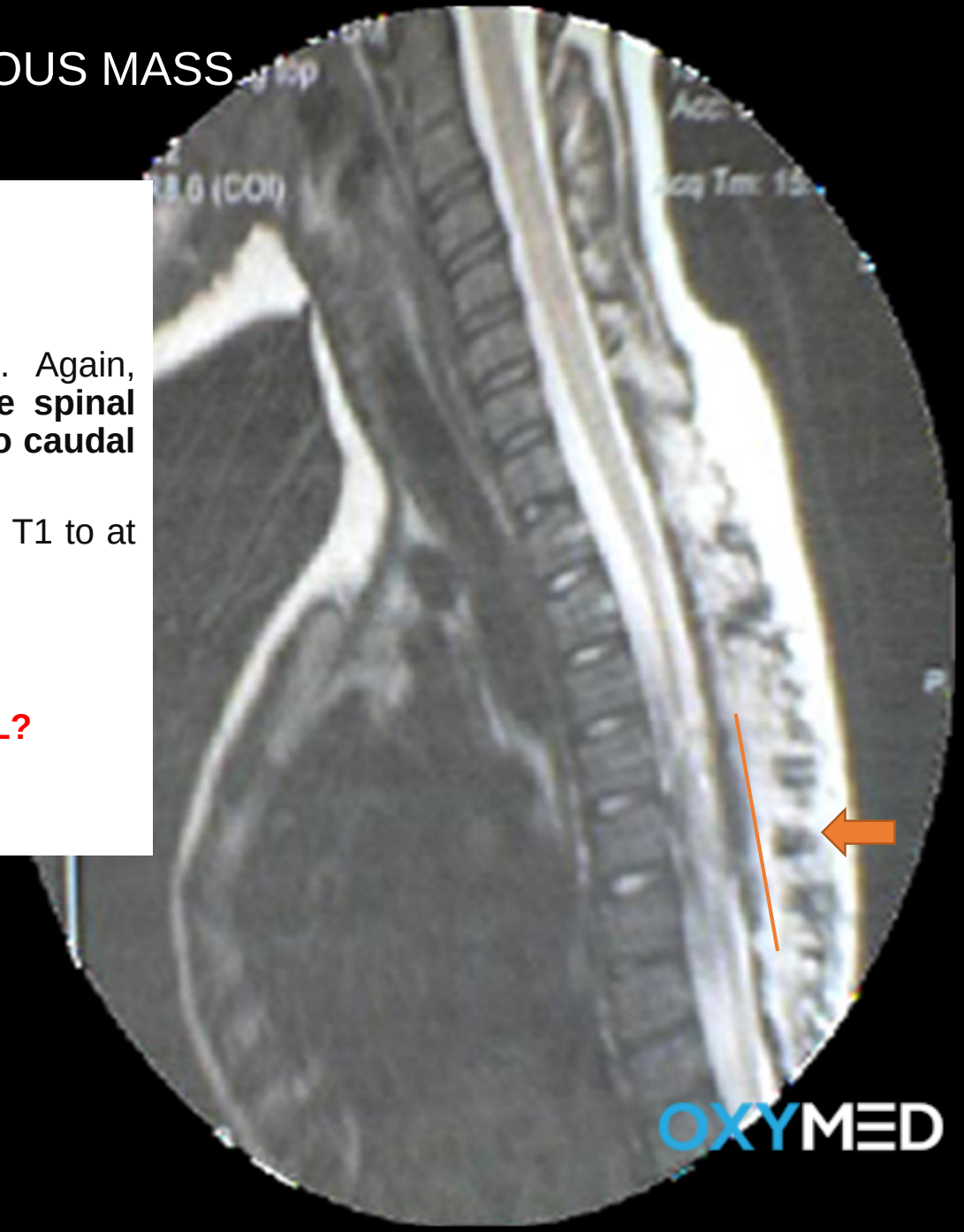
Prior to commencing HBOT LOKOMAT (2007)

MRI 13-03-07:

“Comparison is made with the last examination dated 10-10-05. Again, demonstrating the **enhancing intraspinal lesion posteriorly in the spinal canal at the level of T4-T6**. It is again seen to measure **2.8cm cranio caudal and 1cm AP**.

* The T2 imaging again shows **cord atrophy with hydromyelia** from T1 to at least the inferior border of the lesion”.

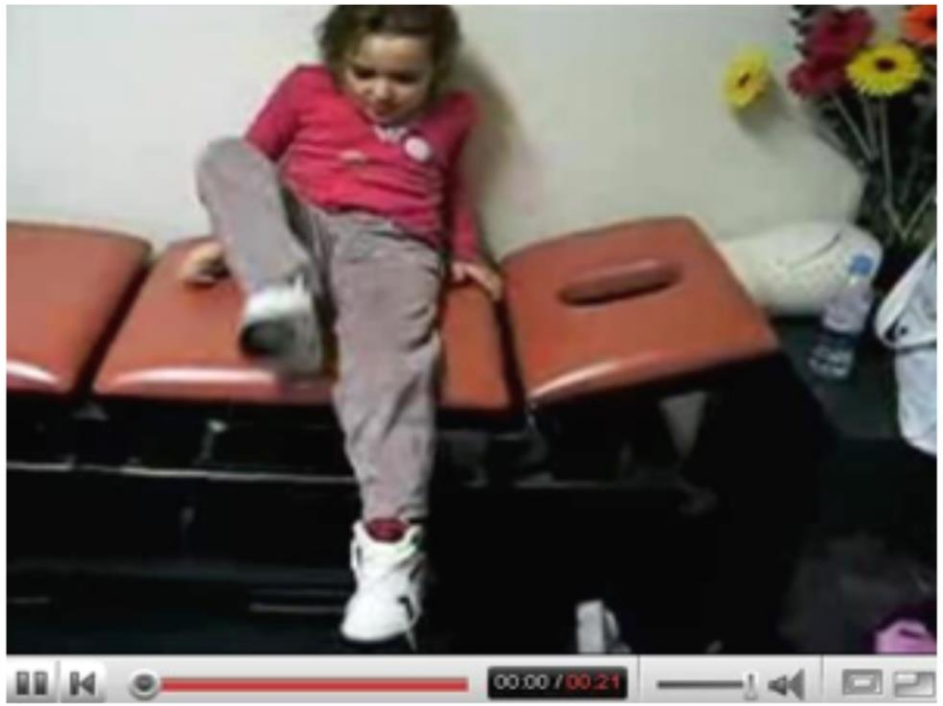
WHAT ARE THE PROSPECTS OF RECOVERY FOR YOUNG ISABEL?



CHANNEL 7 NEWS (2007)

https://youtu.be/f6ICtNzU6gM

https://youtu.be/ZfzWSKIKcvM



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CASE STUDY KP

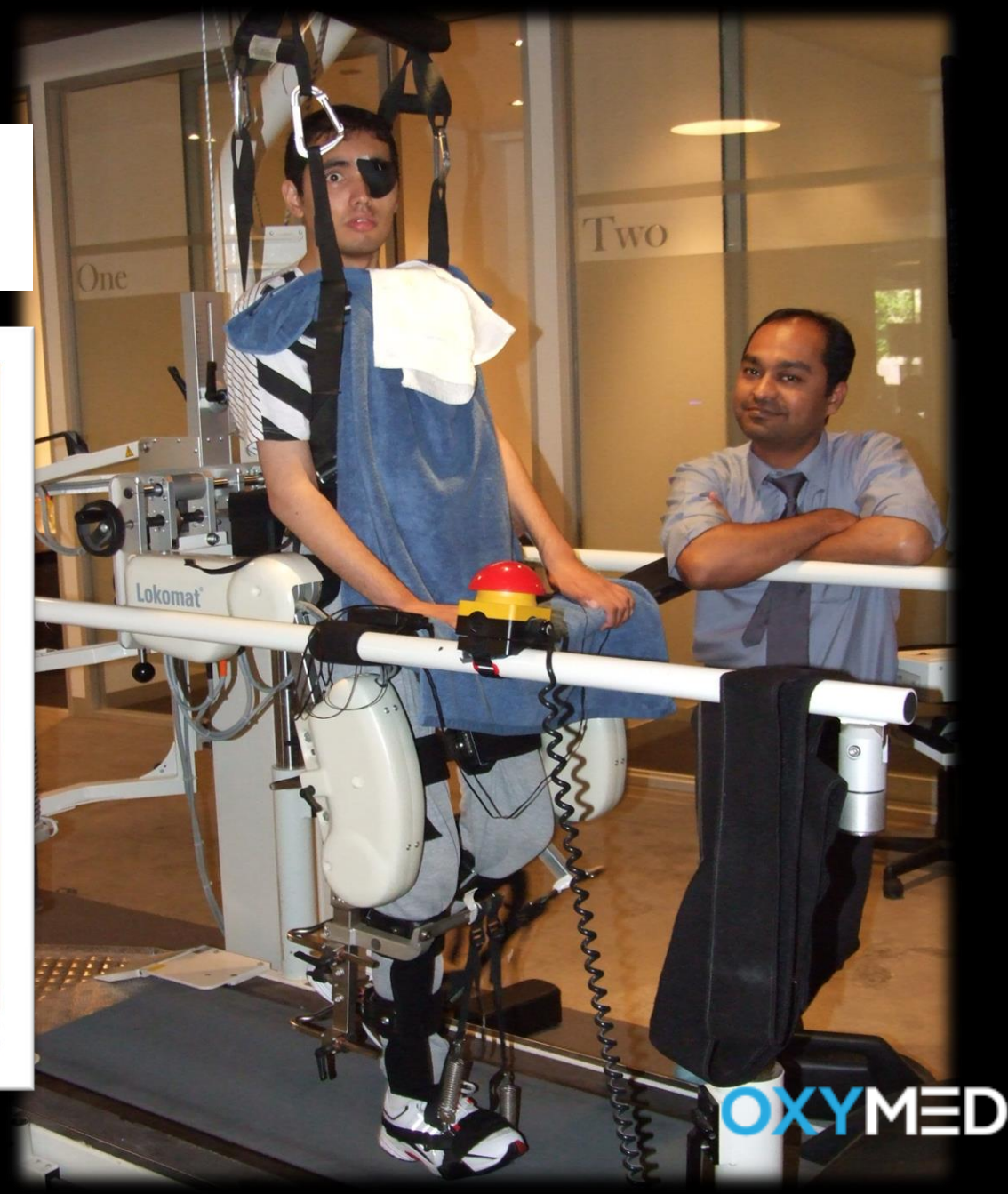
Kyle suffers a T12 spinal cord injury being told he would “never walk again”.

https://youtu.be/tml5KjZEBp0?t=5

CASE STUDY MB

Marco suffered a massive stroke due to an extensive arteriovenous malformation (AVM).

https://youtu.be/OMqty6COs8E?t=39



CASE STUDY CB

Young Chloe – near drowning victim.
https://youtu.be/3XCL1mocf1c

THE EVOLUTION OF HYPERBARIC OXYGEN

* **Alexander The Great 320 BC**, Bosphorus Straits in a glass barrel during the siege of Tyre.

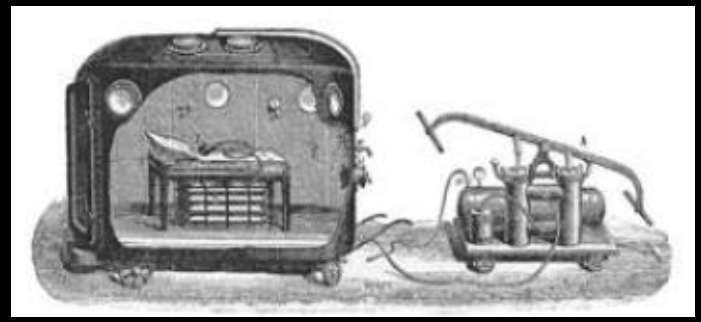
* **Leonardo Da Vinci** 1500's made sketches of diving vessel chambers

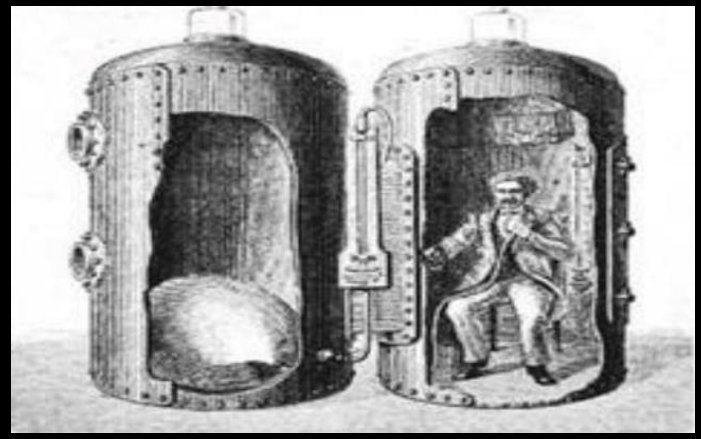
* **1620**, the Dutch inventor Cornelius Drebbel developed the first true diving bell. This vessel had the ability to be compressed to 1 atmosphere but had no supplementary Oxygen.

*** 1662**, British physician Henshaw - chamber fitted with a large pair of organ bellows, with valves paced so that air could either be compressed into the chamber or extracted from it. In the 'domicilium' **increased pressures were used for the treatment of acute disease**, and **reduced pressures for the treatment of chronic diseases**.

* **1691**, Edmund Halley, after whom the comet is named, improved diving bell chambers by devising a method of ***replenishing the air supply***.

* **1830's**, France led the new fashion in Hyperbaric Medicine. Hyperbaric chamber exposures of between 2 and 4 atmospheres absolute were stated to **increase the circulation to the internal organs, improve the cerebral blood flow, and produce a feeling of well being**.





BROOKLYN BRIDGE – CAISSON WORKERS

*__1700 - 1830's Brooklyn Bridge New York, construction workers__, miners and tunnellers would use a *sealed box filled with compressed air called a caisson, to work underwater or at great depths.* This allowed them to work safely with a supply of air. The workers became known as **Caisson workers**, or just 'caissons'. As the amount of work increased and more and more workers were using these Caissons, there was an increase in reports of illnesses such as dizziness, cramping, sharp pains in the joints and abdomen and even death. The understanding for this was not understood and it became known as mysterious malady. *One strange mystery to them was that the symptoms seemed to disappear when the worker returned to the pressurised chamber*. Of course, we now see these as classic symptoms of **decompression illness** or as it's known to divers today **'the bends'.**

* **1834-1837**, Junod, Tabarie and Pravaz built a large hyperbaric chamber using it to treat a variety of ailments. The chambers were promoted and used specifically for **pulmonary diseases, including tuberculosis, laryngitis, tracheitis and pertussis, as well as apparently unrelated diseases such as deafness, cholera, rickets, metrorrhagia and conjunctivitis**.

* **1877**, Fontaine developed the first **mobile hyperbaric operating theatre**, and by this time hyperbaric chambers were available in all major European cities being advertised as comparable to **health spas**.

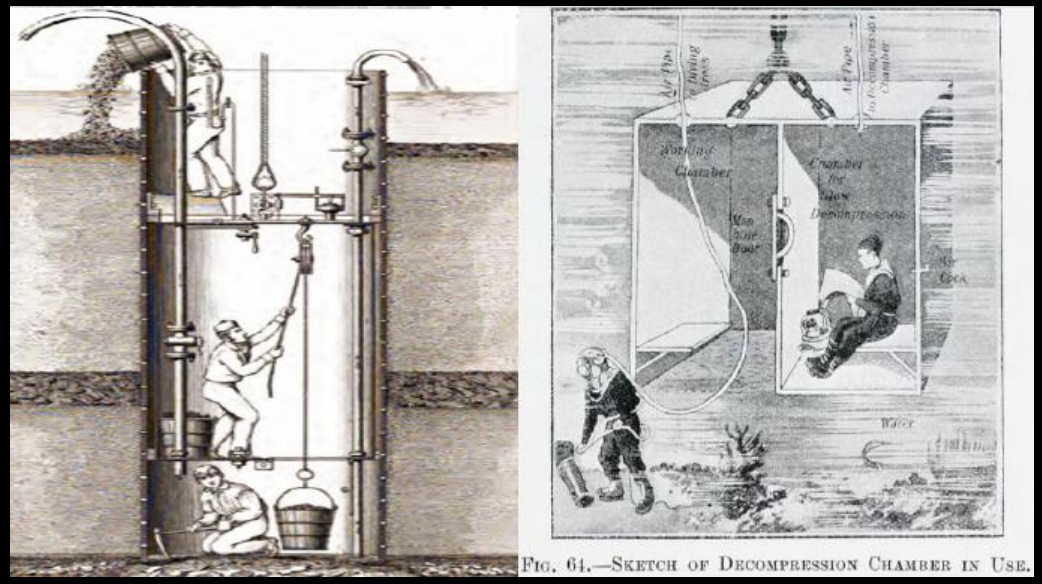


Fig. 61.—Sketch of Decompression Chamber in Use.

EVOLUTION OF HBOT

* **1850s** Hyperbaric chambers flourished across Europe and known as **“Pneumatic Institutes”**

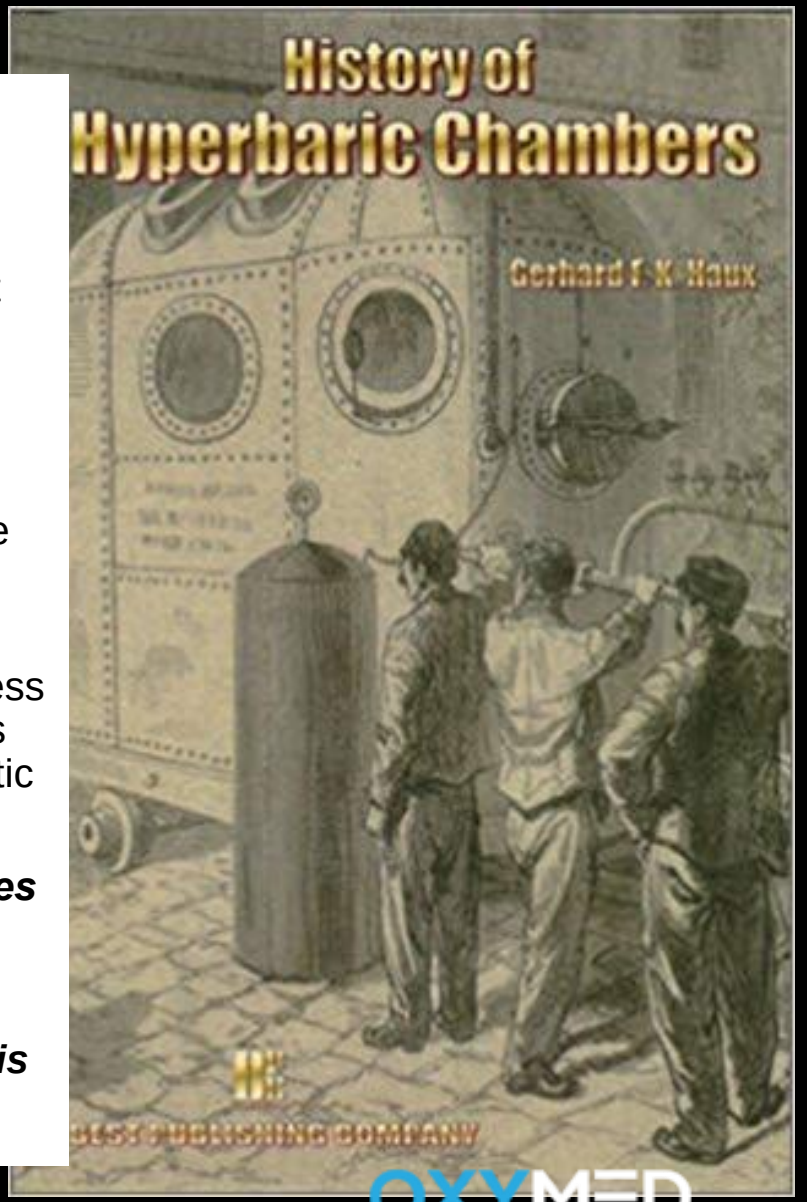
* **1860**, The first hyperbaric chamber was constructed in Canada.

*** 1861**, The first such chamber in the United States was built by Corning in New York to treat **nervous disorders.**

* **1879** a fully equipped **mobile hyperbaric operating room** was available in hospitals, sanatoriums, and even in private homes. It was claimed that patients recovered from anesthesia more rapidly when in the chamber. **Cyanosis and asphyxia** were reported to be less, or absent. **Post-anaesthetic excitement and vomiting** were markedly decreased. The mobile chamber was recommended to facilitate the **reduction of hernia, and for patients with asthma, emphysema, chronic bronchitis and anemia.**

* **Twenty-seven operations** were performed within a 3-month period in this chamber. Success was so great that a large hyperbaric surgical amphitheatre which would hold 300 people was planned, but never actually came into being. **Fontein** had an accident whilst at the Pneumatic Institute which resulted in his death, the first physician martyr to Hyperbaric Medicine.

* **1885**, British Medical Journal (BMJ): ***“The use of atmospheric air under different degrees of atmospheric pressure, in the treatment of disease, is one of the most important advances in modern medicine and when we consider the simplicity of the agent, the exact methods by which it may be applied, and the precision with which it can be regulated to the requirements of each individual, we are astonished that in England this method of treatment has been so little used”.***



EVOLUTION OF HBOT

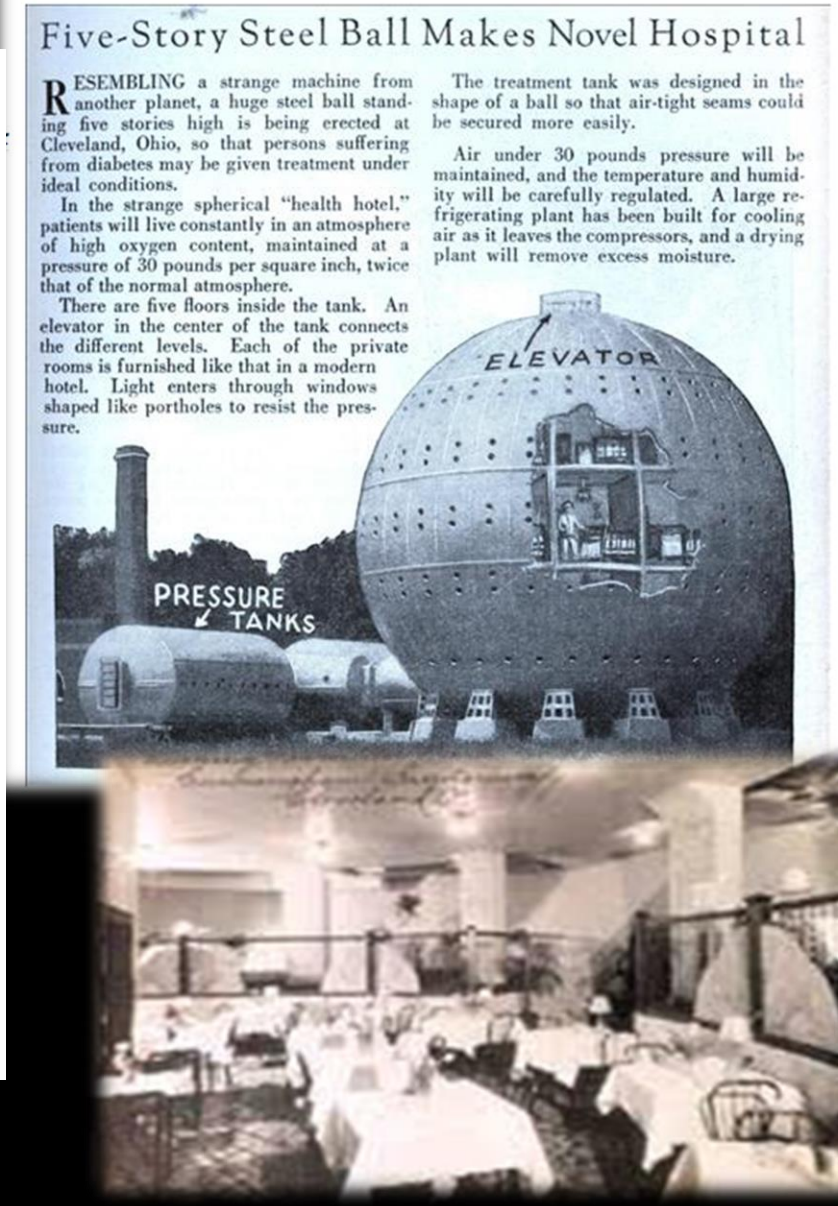
* **1920's** Cunningham first used his chamber to treat the victims of the **Spanish influenza epidemic** that swept across the USA during the closing days of the First World War.

* Cunningham had observed that mortality from this **disease was higher in areas of higher elevation,** and he reasoned that a barometric factor was therefore involved. He claimed to have achieved remarkable improvement in patients who were **cyanotic and comatose**. One night however, a mechanical failure resulted in a complete loss of compression and all his patients died. This tragedy was a sobering lesson but ultimately did not deter Dr Cunningham.

* His enthusiasm for hyperbaric air continued, and he started to treat diseases such as **syphilis, hypertension, diabetes mellitus, and cancer.** His reasoning was based on the assumption that **anaerobic infections** play a role in the etiology of all such diseases.

* **1928**, Dr Cunningham, in Cleveland constructed the worlds largest chamber – five stories high and 64 feet in diameter. Each floor had 12 bedrooms with all the amenities of a good hotel. At that time it was the only functioning hyperbaric chamber in the world. As the publicity surrounding his treatments grew, Dr Cunningham was repeatedly requested by the **Bureau of Investigations of the American Medical Association** (AMA) to document his claims regarding the effectiveness of Hyperbaric Therapy.

Five-Story Steel Ball Makes Novel Hospital (Jan, 1929)



Five-Story Steel Ball Makes Novel Hospital

RESEMBLING a strange machine from another planet, a huge steel ball standing five stories high is being erected at Cleveland, Ohio, so that persons suffering from diabetes may be given treatment under ideal conditions.

In the strange spherical "health hotel," patients will live constantly in an atmosphere of high oxygen content, maintained at a pressure of 30 pounds per square inch, twice that of the normal atmosphere.

There are five floors inside the tank. An elevator in the center of the tank connects the different levels. Each of the private rooms is furnished like that in a modern hotel. Light enters through windows shaped like portholes to resist the pressure.

The treatment tank was designed in the shape of a ball so that air-tight seams could be secured more easily.

Air under 30 pounds pressure will be maintained, and the temperature and humidity will be carefully regulated. A large refrigerating plant has been built for cooling air as it leaves the compressors, and a drying plant will remove excess moisture.

AMA 1928 POSITION ON THE ‘TANK TREATMENT’

* Apart from a short article in 1927, Cunningham made no efforts to describe his technique in ‘accepted’ medical literature. He was eventually censured by the AMA in 1928 in a report that stated:

“Under the circumstances, it is not to be wondered that the Medical Profession looks askance at the ‘tank treatment’ and intimates that it seems tinctured much more strongly with economics than with scientific medicine. It is the mark of the scientist that he is ready to make available the evidence on which his claims are based.”

* The Cunningham chamber was ‘*dismantled in 1937 and scrapped for war efforts’.*

* **1937** – the year that Cunningham’s “air chamber” hotel was demolished – Bhnke and Shaw used hyperbaric Oxygen for the treatment of **decompression sickness**.

* **1960** Boerema - **The Life Without Blood**.

* **1966** The first **stroke victims** treated using HBOT.

* **1967 Undersea and Hyperbaric Medical Society** (UHMS) was founded

* **1970** The first **Multiple Sclerosis** patient treated using HBOT.

* **1988 International Society of Hyperbaric Medicine**.

* **1997/8 The International Hyperbaric Medical Foundation** (IHMF) and **International Hyperbaric Medical Association** (IHMA).

* **2000** Hyperbaric Medicine approved as a subspecialty of emergency and preventative medicine.

Dr. Ite Boerema

Life without blood

(A study of the influence of high atmospheric pressure and hypothermia on dilution of the blood)

by

I. BOEREMA (*), N. G. MEYNE, W. K. BRUMMELKAMP, S. BOUMA, M. H. MENSCH, F. KAMERMANS, M. STERN HANF and W. VAN AALDEREN

(from the Surgical Department of the University of Amsterdam)

When in 1948 we (first at research) started our experiment on hypothermia[1] [2] our ultimate aim was to reduce the metabolism of a warm-blooded animal to such an extent that all the physiological processes would almost come to a standstill.

If successful, this would enable the heart to be clamped off for a period long enough to allow for a major intracardiac operation to take place. When, however, we presented our results to the Netherlands Society of Surgeons in 1950 this aim had not been achieved by any means. In a hypothermic animal at about 27° C., the circulation could be stopped with good chances of survival for about twice as long as in a normothermic animal. The gain in time, about 100 per cent, was relatively great, but absolutely it was very modest, amounting to about five minutes; the reason for this was that below 20° C the physiology was altered too much and the normal harmony of life processes disturbed too much to allow for continuation of life or normal recovery by warming up.

Efforts to achieve safe conditions at a lower level of hypothermia so as to gain a greater period of time for clamping off the heart failed until recently, at any rate for animals with the same weight as human patients. So in 1956 we presented a series of experiments which showed that it was possible to clamp off the circulation for a greater length of time without lowering the temperature further than 27° C.[3] [4] We operated on the animal in a pressure chamber at an absolute pressure of three atmospheres. The animal breathed pure oxygen, the investigators naturally breathed air.

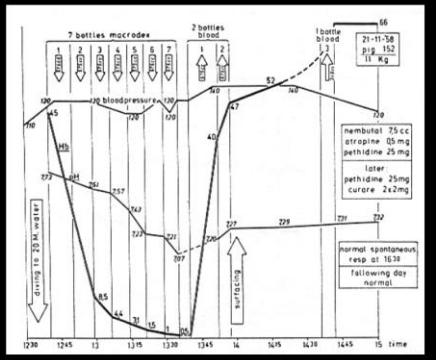
Through the combination of inhaling pure oxygen and being under three atmospheres of pressure, the whole body was supersaturated with oxygen in physical solution.

(*) Professor of Surgery.

Again we are much indebted to T.N.O. (Institute for Applied Physical Research) for financial aid, to the staff of the Mijnenlinest of the Royal Dutch Navy at Den Helder and to our adviser on technical matters, P. Beime.

— 133 —

« LIFE WITHOUT BLOOD »
BOEREMA 1960



Hyperbaric oxygen.
20 m depth.
0,5 % hématocrit

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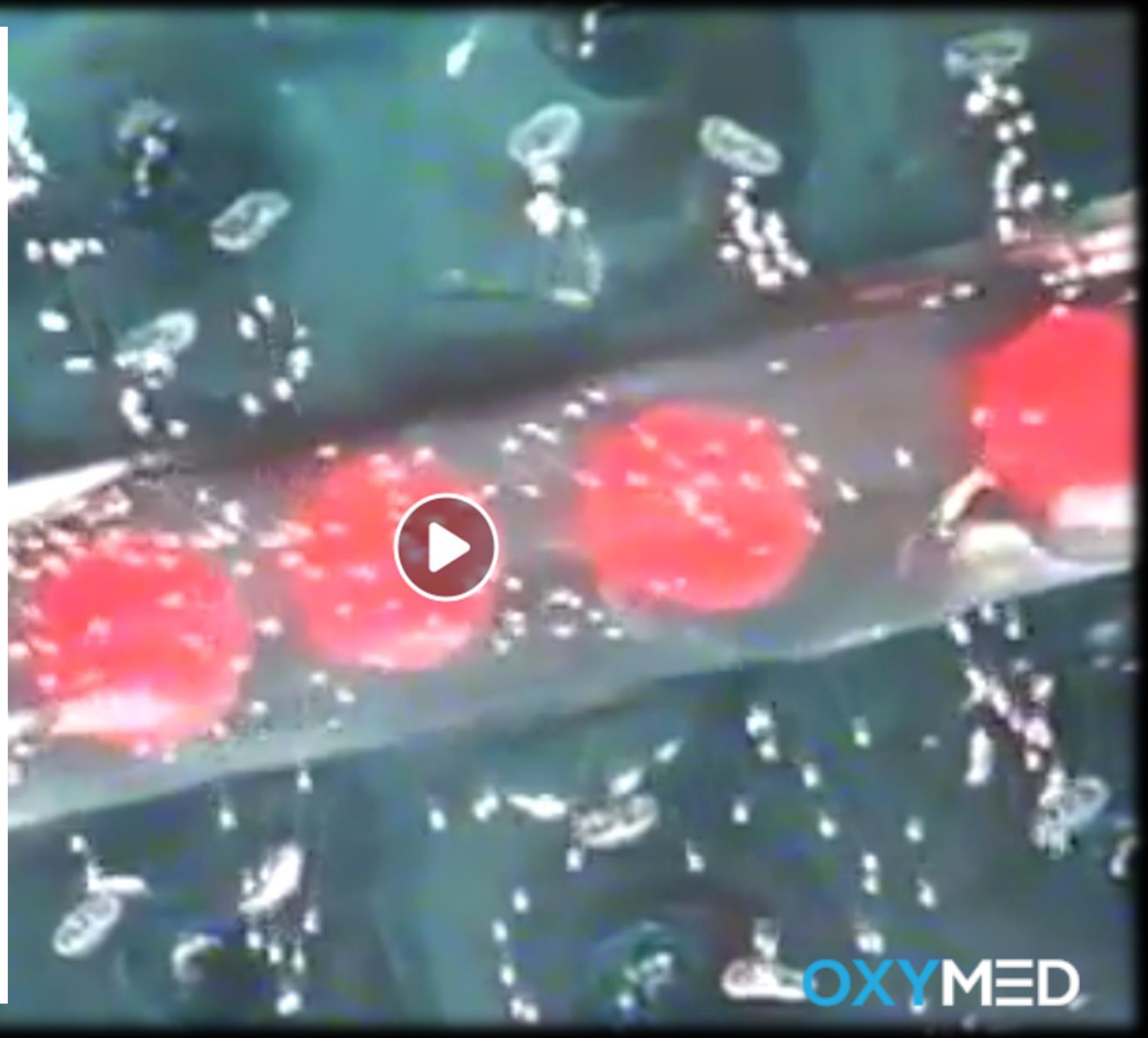
WATERSHED MOMENT – ‘LIFE WITHOUT BLOOD’

* In **1960** Prof. Boerema surgeon and physiologist in Amsterdam, was the first to experience the mechanism of action of hyperbaric oxygen by publishing the results in the famous scientific article: **"life without blood"**.

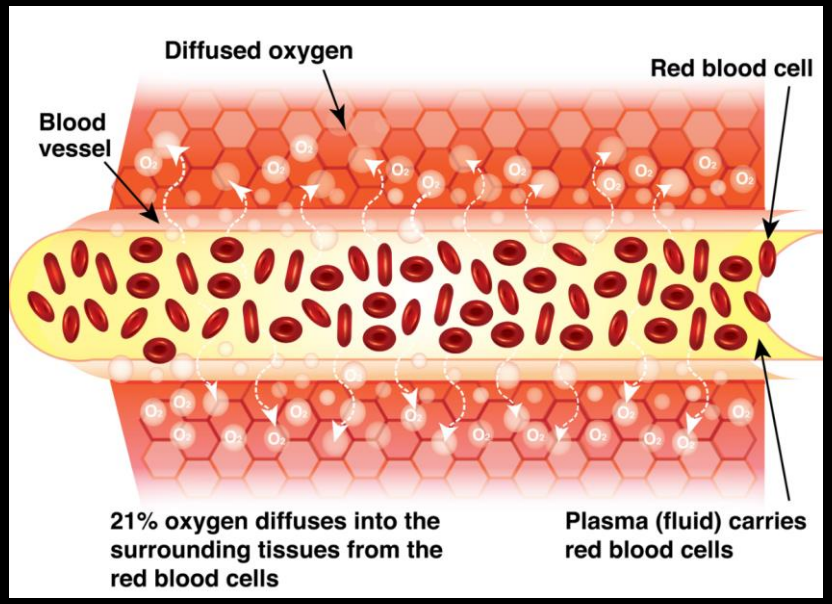
* **Henry’s Law of Partial Pressure**: formulated by William Henry in **1803** regulating the solubility of gases in solvents - *"At a constant temperature, the amount of a gas that dissolves in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid."*

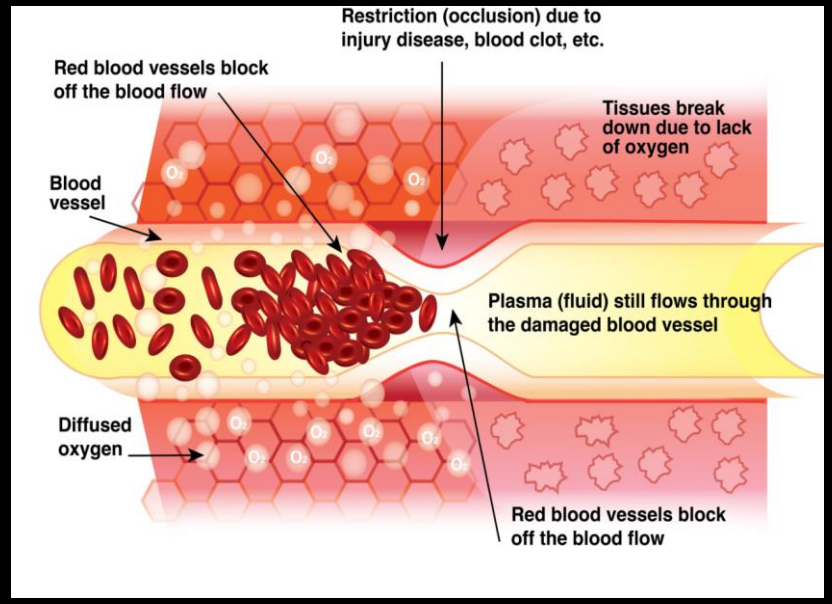
* At 3ATA, the pigs breathed pure oxygen and the **plasma was physically saturated of oxygen not related to hemoglobin.** The molar fraction of dissolved oxygen in the plasma was so high that the ‘*presence of red blood cells was completely obsolete’*, making it possible to maintain all vital functions despite the pigs.

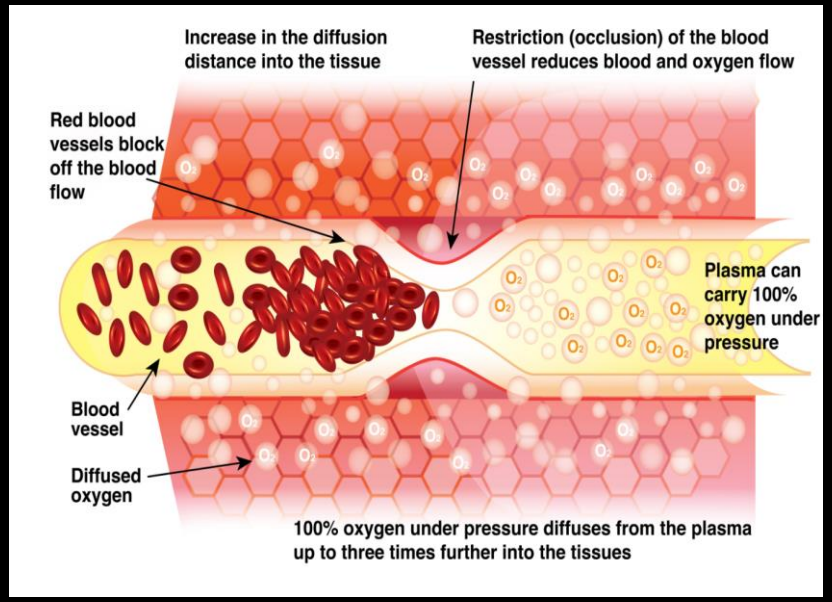
* **‘This experiment had great world relevance and poses medical-scientific bases for the studies of current hyperbaric and underwater medicine’.**

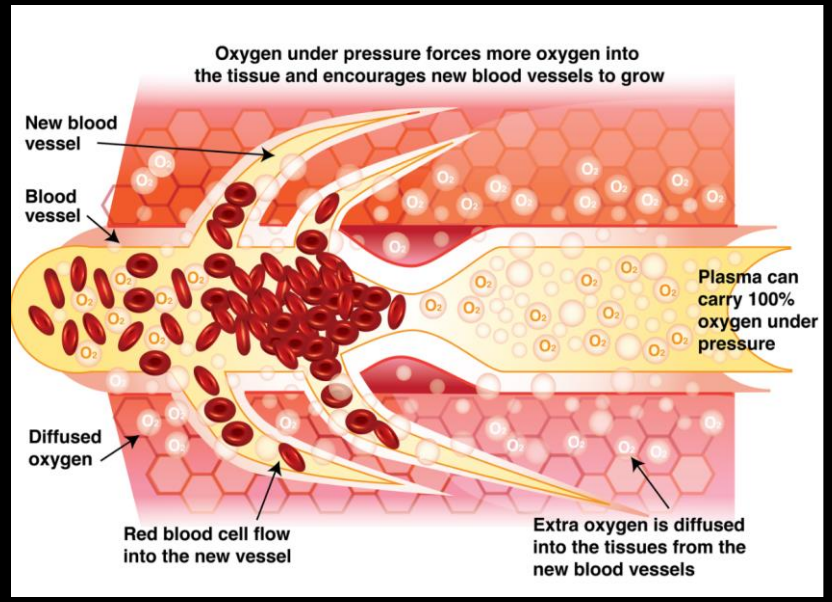


HYPERBARIC 101 – DIFFUSION GRADIENT UNDER PRESSURE









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FDA VS INTERNATIONAL RECOGNISED CONDITIONS (OFF-LABEL)

USA FDA funding is restricted to **14 approved conditions.**

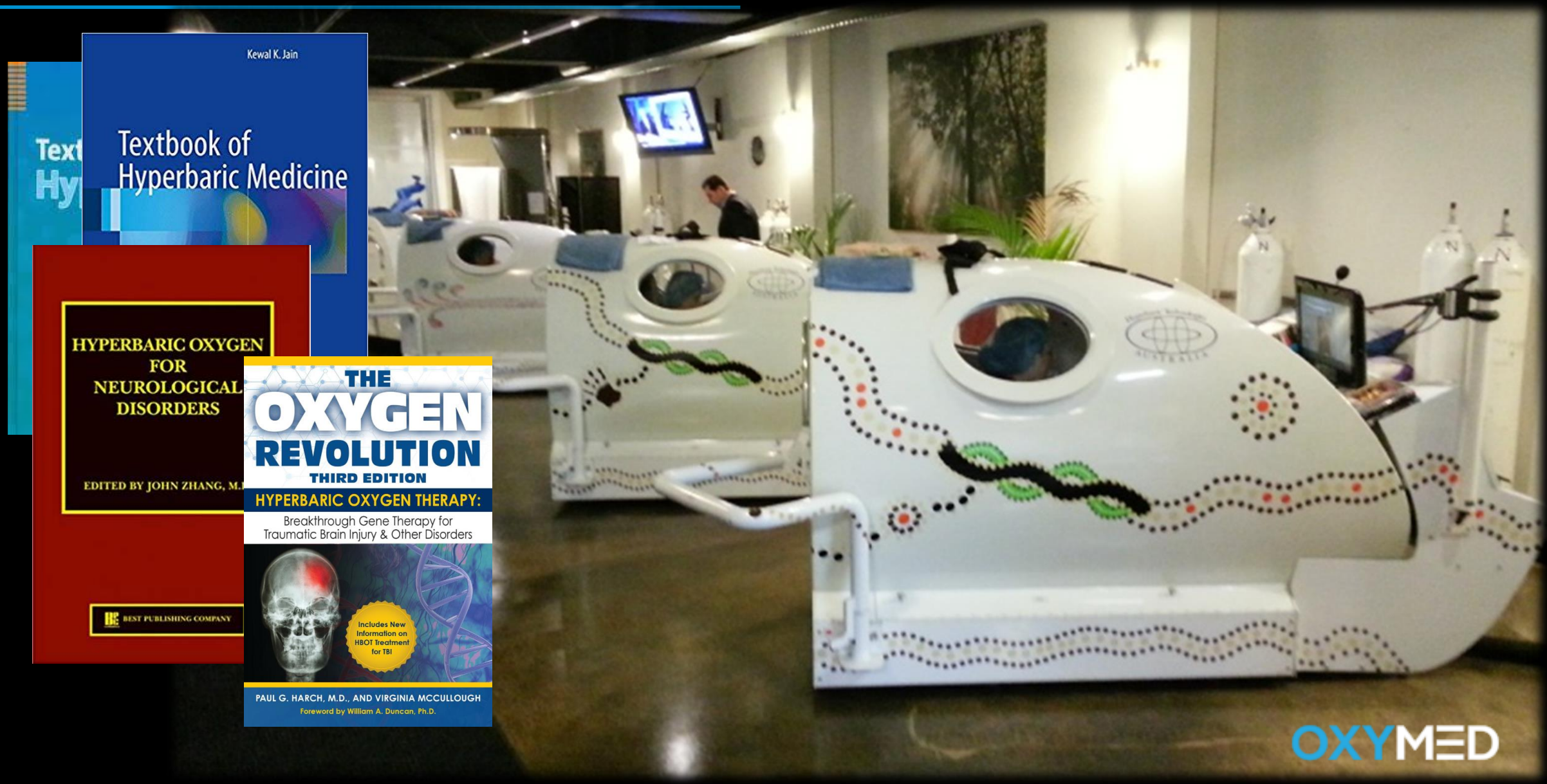
- Air or gas embolism,
- Carbon monoxide poisoning
- Enhancement of healing in diabetically derived illness such as diabetic foot, diabetic retinopathy, diabetic nephropathy
- Exceptional blood loss (anemia)
- Intracranial abscess
- Clostridal myositis and myonecrosis (gas gangrene)
- Crush injury, compartment syndrome, and other acute traumatic ischemias
- Decompression sickness
- Necrotizing soft tissue infections (necrotizing fasciitis)
- Osteomyelitis (refractory)
- Delayed radiation injury (soft tissue and bony necrosis)
- Skin grafts and flaps (compromised)
- Thermal burns
- Actinomycosis
- Cyanide poisoning
- Delayed radiation injury (soft tissue and bony necrosis)
- Sudden Sensorineural Hearing Loss

* **AUST** – Medicare funding is limited to **6 conditions.** * **UK** – NHS funding is limited to **3 conditions.**

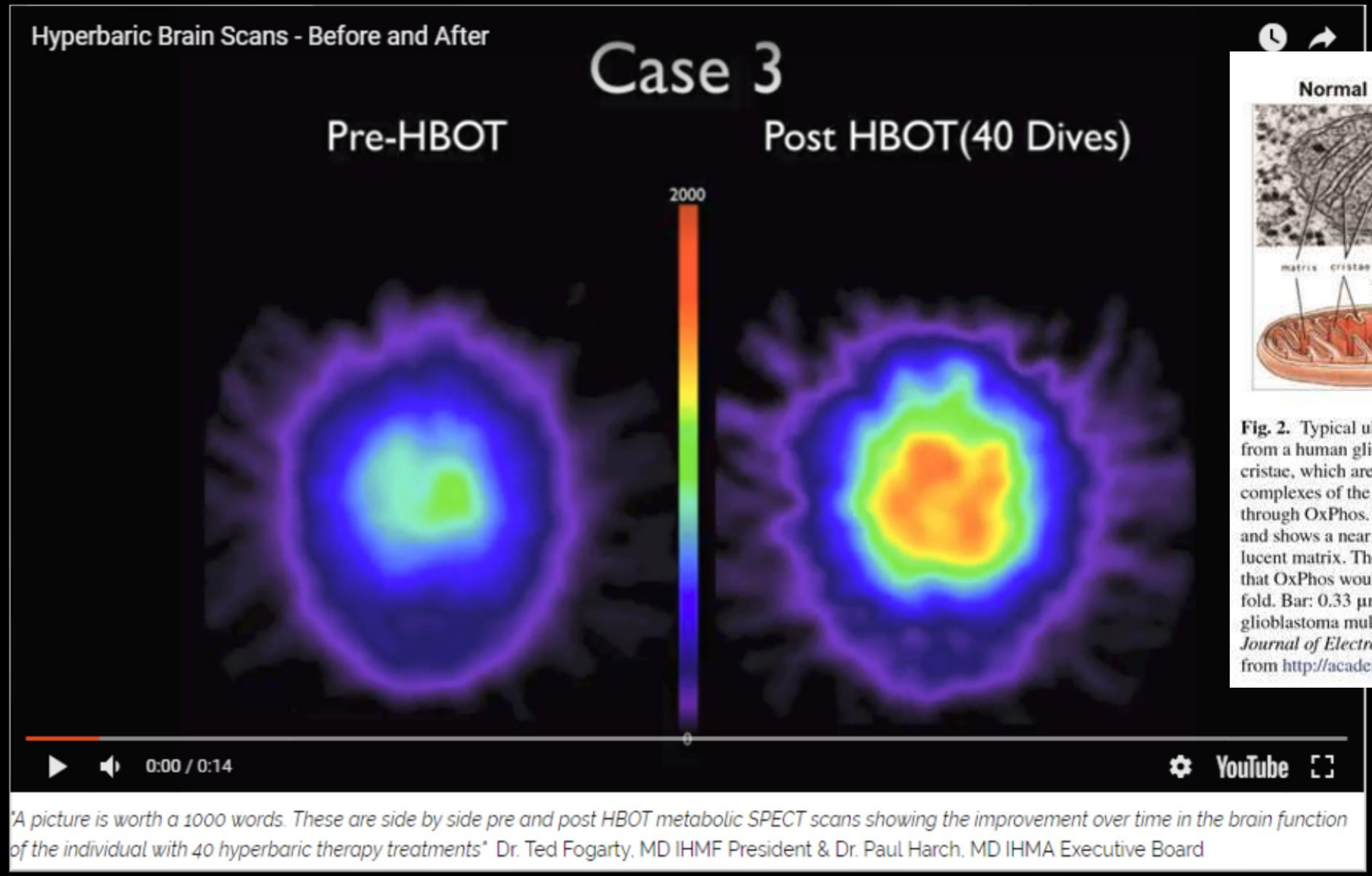
* **2013**, **China** reports over 5000 chambers labelling **Primary Emergency Conditions** and **Secondary Adjunctive Conditions**. The Qingdao, 22nd academic meeting approved *“new indications to include diseases that were directly or indirectly caused by hypoxia and/or ischemia or a series of conditions that are related to hypoxia and/ or ischemia in the evolution of the disease process”.*

* **2019**, Hyperbaric Medicine International formed with the amalgamation of the IHMA and the National Hyperbaric Association (NHA) to reflect the international recognized conditions (currently in excess of 70-conditions).

HYPERBARIC OXYGEN THERAPY TODAY



SPECT IMAGING PRE AND POST HBOT



"A picture is worth a 1000 words. These are side by side pre and post HBOT metabolic SPECT scans showing the improvement over time in the brain function of the individual with 40 hyperbaric therapy treatments" Dr. Ted Fogarty, MD IHMF President & Dr. Paul Harch, MD IHMA Executive Board

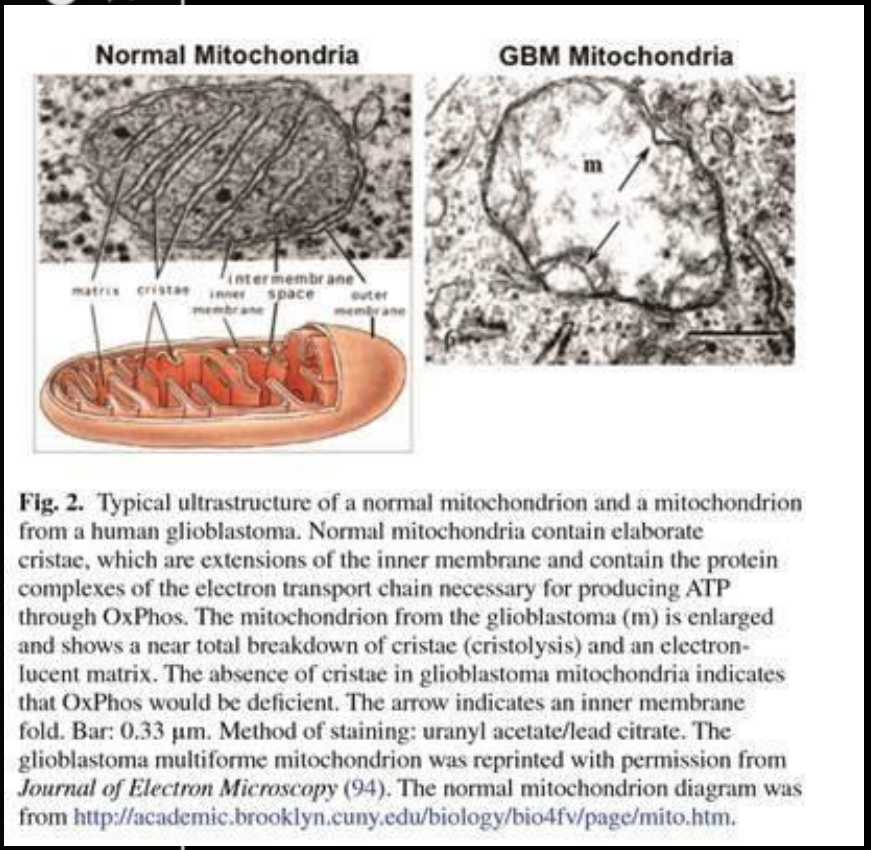


Fig. 2. Typical ultrastructure of a normal mitochondrion and a mitochondrion from a human glioblastoma. Normal mitochondria contain elaborate cristae, which are extensions of the inner membrane and contain the protein complexes of the electron transport chain necessary for producing ATP through OxPhos. The mitochondrion from the glioblastoma (m) is enlarged and shows a near total breakdown of cristae (cristolysis) and an electron-lucent matrix. The absence of cristae in glioblastoma mitochondria indicates that OxPhos would be deficient. The arrow indicates an inner membrane fold. Bar: 0.33 µm. Method of staining: uranyl acetate/lead citrate. The glioblastoma multiforme mitochondrion was reprinted with permission from *Journal of Electron Microscopy* (94). The normal mitochondrion diagram was from http://academic.brooklyn.cuny.edu/biology/bio4fv/page/mito.htm.

OXYMED

2015, HYPERBARIC OXYGEN IMPACTS THE CELLULAR LANDSCAPE

Harch *Medical Gas Research* (2015) 5:9
DOI 10.1186/s13618-015-0030-6

MEDICAL GAS RESEARCH

COMMENTARY Open Access

Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy

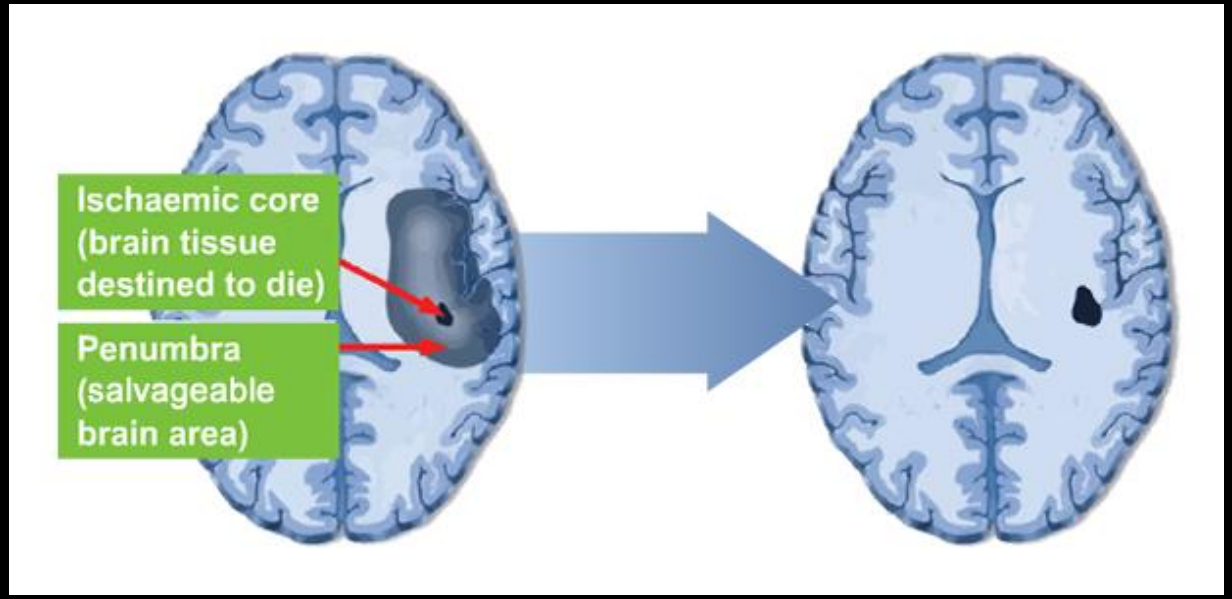
Hyperbaric Oxygen is breathing 100 per cent oxygen at pressures greater than ambient sea level (760 mmHg).

* Approximately 20 to 30 percent of the body's consumption of Oxygen occurs within three to five per cent of the body mass - the brain and spinal cord.

These structures are extremely sensitive to Oxygen deficiency and the use of HBO.

Penumbra State - in chronic injuries, the microenvironment is in a constant smoldering “cytokine storm” state. Pro-inflammatory cytokines are important in mobilizing the reparative and regenerative responses when ‘attacked’, but chronic over-expression leads to immune confusion and autoimmune degradation.

‘Over-expressions of pro-inflammatory cytokines can affect synaptic strength and synaptic plasticity, and excess contributes to maladaptive plasticity and chronic pain syndromes’.



OXYMED

2015, INJURY CASCADE – CHRONIC CYTOKINE STORM - MALADAPTIVE PLASTICITY

Degeneration, repair, and plasticity after SCI: A central role for cytokines.

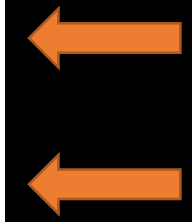
Michael Beattie, Adam Ferguson, and Jacqueline Bresnahan

Published Online: 1 Apr 2015 | **Abstract Number:** 210.2

Tools Share

Abstract

Spinal cord injury (SCI) induces a secondary injury process that releases pro-inflammatory cytokines, including TNFa from glial cells. The resulting neuroinflammation sends signals to the periphery to recruit immune cells that invade the lesion cite, causing additional inflammatory responses that can lead to glial and neuronal cell death. This acute innate response to injury is followed by compensatory anti-inflammatory signals that dampen the initial response. However, there remains a chronic 'smoldering' inflammation in the CNS that may continue to affect the spinal cord microenvironment. Pro-inflammatory cytokines can kill cells, but they are also important in mobilizing reparative and regenerative responses. Further, cytokines can affect synaptic strength and synaptic plasticity,and in excess can contribute to maladaptive plasticity, including chronic pain. This lecture will review some of the literature on the balance between degeneration and repair mediated by TNF, and present data from our group on attempts to modulate TNFa in the acute and chronic phases of SCI, and their effects on neuronal and glial survival, and on spinal cord adaptive and maladaptive plasticity. Although the situation is complex, it seems clear that optimizing pro-inflammatory cytokine production both in the CNS and in the periphery remains an important therapeutic target not only in the acute phase, but also in chronic SCI. The discovery and optimization of cytokine-directed therapies may also be aided by the use of multivariate approaches to the design and analysis of preclinical discovery platforms. Work reported here was supported by grants from the NIH (NINDS, NIA), the C.H.Neilsen Foundation, and the US Department of Defense.



OXYMED

WATERSHED - STEM CELL MOBILIZATION - 8 FOLD INCREASE & MOBILISATION

Am J Physiol Heart Circ Physiol. 2006 Apr;290(4):H1378-86. Epub 2005 Nov 18.

Stem cell mobilization by hyperbaric oxygen.

Thom SR[1], Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG.

Author information

Abstract

We hypothesized that exposure to hyperbaric oxygen (HBO(2)) would mobilize stem/progenitor cells from the bone marrow by a nitric oxide (*NO) -dependent mechanism. The population of CD34(+) cells in the peripheral circulation of humans doubled in response to a single exposure to 2.0 atmospheres absolute (ATA) O(2) for 2 h. Over a course of 20 treatments, circulating CD34(+) cells increased eightfold, although the overall circulating white cell count was not significantly increased. The number of colony-forming cells (CFCs) increased from 16 +/- 2 to 26 +/- 3 CFCs/100,000 monocytes plated. Elevations in CFCs were entirely due to the CD34(+) subpopulation, but increased cell growth only occurred in samples obtained immediately posttreatment. A high proportion of progeny cells express receptors for vascular endothelial growth factor-2 and for stromal-derived growth factor. In mice, HBO(2) increased circulating stem cell factor by 50%, increased the number of circulating cells expressing stem cell antigen-1 and CD34 by 3.4-fold, and doubled the number of CFCs. Bone marrow *NO concentration increased by 1,008 +/- 255 nM in association with HBO(2). Stem cell mobilization did not occur in knockout mice lacking genes for endothelial *NO synthase. Moreover, pretreatment of wild-type mice with a *NO synthase inhibitor prevented the HBO(2)-induced elevation in stem cell factor and circulating stem cells. We conclude that HBO(2) mobilizes stem/progenitor cells by stimulating *NO synthesis.

OXYMED

2019, HYPERBARIC ELEVATES BDNF/NT-3 GROWTH FACTORS

Tropomyosin receptor kinase B (**TrkB**),[5] also known as **tyrosine receptor kinase B**,[5] or **BDNF/NT-3 growth factors receptor.** TrkB is a receptor for brain-derived neurotrophic factor (BDNF).

Life Sci. 2019 Jul 15;229:187-199. doi: 10.1016/j.lfs.2019.05.029. Epub 2019 May 17.

Hyperbaric oxygen therapy reduces apoptosis and dendritic/synaptic degeneration via the BDNF/TrkB signaling pathways in SCI rats.

Ying X[1], Tu W[1], Li S[1], Wu Q[1], Chen X[1], Zhou Y[1], Hu J[1], Yang G[2], Jiang S[3].

Author information

1 Department of Physical Medicine and Rehabilitation, The Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China; Department of Intelligent Rehabilitation International (cross-strait) Alliance, Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China.

2 Department of Intelligent Rehabilitation International (cross-strait) Alliance, Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China.

3 Department of Physical Medicine and Rehabilitation, The Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China; Department of Intelligent Rehabilitation International (cross-strait) Alliance, Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China. Electronic address: jshwz@126.com.

Abstract

Spinal cord injury (SCI) is a serious neurological disease without efficacious drugs. Anti-apoptosis and suppressing dendritic/synaptic degeneration in the anterior horn are essential targets after SCI. Previous studies found that hyperbaric oxygen therapy (HBOT) significantly protected rats after SCI. However, its potential effects and mechanisms remain unknown. The BDNF/TrkB signaling pathways evidently contribute to the SCI recovery. Currently, we mainly investigate the potential effects and mechanism of HBOT on anti-apoptosis and ameliorating impaired dendrites, dendritic spines and synapses after SCI. Establish SCI model and randomly divide rats into 5 groups. After SCI, rats were subjected to HBOT. ANA-12 is the specific inhibitor of BDNF/TrkB signal pathway. Changes in neurological deficit, neuronal morphology, apoptosis, protein expression and dendrite/synapse were examined by Basso-Beattie-Bresnahan (BBB) locomotor rating scale, Hematoxylin-eosin (HE) and Nissl staining, TUNEL staining, RT-PCR, Western blot, immunofluorescence and Golgi-Cox staining. We found HBOT suppressed dendritic/synaptic degeneration and alleviated apoptosis, consistent with the increase of BDNF and TrkB expression and improved neurological recovery. In contrast to the positive effects of HBOT, inhibitor increased degeneration and apoptosis. Moreover, we observed that these HBOT-mediated protective effects were significantly inhibited by inhibitor, consistent with the lower expression of BDNF/TrkB and worse neurobehavioral state. These findings suggest that hyperbaric oxygen therapy ameliorates spinal cord injury-induced neurological impairment by anti-apoptosis and suppressing dendritic/synaptic degeneration via upregulating the BDNF/TrkB signaling pathways.

OXYMED

2015, HYPERBARIC ELEVATES HIPPOCAMPUS NESTIN, BRDU HI NEONATES

Int J Clin Exp Pathol. 2015 Feb 1;8(2):1752-9. eCollection 2015.

Hyperbaric oxygenation promotes neural stem cell proliferation and protects the learning and memory ability in neonatal hypoxic-ischemic brain damage.

Wei L[1], Wang J[2], Cao Y[3], Ren Q[2], Zhao L[2], Li X[4], Wang J[5].

Author information

1 Department of Neurology, Children's Medical Center, Qilu Hospital of Shandong University Jinan 250012, China ; Department of Pediatrics, Liaocheng People's Hospital Liaocheng 252000, China.

2 Department of Pediatrics, Liaocheng People's Hospital Liaocheng 252000, China.

3 Department of Neonatal, Affiliated Hospital of Zunyi Medical College Zunyi 563003, China.

4 Brain Science Research Institute, Shandong University Jinan 250012, China.

5 Department of Neurology, Children's Medical Center, Qilu Hospital of Shandong University, Brain Science Research Institute, Shandong University Jinan 250012, China.

Abstract

The aim of our study was to evaluate whether hyperbaric oxygenation (HBO) was an effective therapy for neonatal hypoxic ischemic brain damage (HIBD). Seven-day-old rat pups were divided into 3 groups: sham, hypoxia-ischemia (HI) control and HI-HBO group. HBO was administered for HI rats daily. The pathologic changes in brain tissues were observed by hematoxylin-eosin (H-E) staining. The immunohistochemical staining was applied to detect the Nestin and 5-bromo-2-deoxyuridine (BrdU) positive cells in hippocampal dentate gyrus region. The learning and memory function of rats was examined by Morris water maze. The HI rats showed obvious pathologic changes accompanied by levels decreasing and disorder arrangement of pyramidal cells, glial cells proliferation in postoperative, and nerve nuclei broken, while pathologic changes of rats in sham group was approximate to that in the HI + HBO group that was opposite to the HI group. Compared with the sham group, the Nestin and BrdU positive cells in HBO + HI group at different time points increased significantly ($P < 0.01$). Learning and memory function of rats in HI group was poor compared with the sham/HI + HBO group ($P < 0.01$), while that in HI + HBO group was approximate to that in sham group ($P > 0.05$). HBO treatment improved the learning and memory ability of the HI rats. HBO therapy may be effective for neonatal HIBD treatment.

OXYMED

2019, NORMOBARIC HYPEROXIA (42%), STEM CELLS AND CYTOKINE EXPRESSIONS

Med Gas Res. 2019 Jul-Sep;9(3):139-144. doi: 10.4103/2045-9912.266989.

Effect of intermittent hyperoxia on stem cell mobilization and cytokine expression.

MacLaughlin KJ[1], Barton GP[1], Braun RK[1], Eldridge MW[1].

Author information

1 Department of Pediatrics; John Rankin Laboratory of Pulmonary Medicine, University of Wisconsin, Madison, WI, USA.

Abstract

The best known form of oxygen therapy is hyperbaric oxygen (HBO) therapy, which increases both concentration and atmospheric pressure. HBO supports tissue regeneration and is indicated in an increasing number of pathologies. Less known but still showing some promising effects is normobaric oxygen (NBO) therapy, which provides some advantages over HBO including eliminating barotrauma risk, increased ease of administration and a significant cost reduction. However, still little is known about differences and similarities in treatment effects between HBO and NBO. Therefore we tested whether NBO induces a biological response comparable to HBO with a focus on stem progenitor cell mobilization and changes in serum cytokine concentration. We randomly assigned Sprague-Dawley rats into an NBO treatment group (n = 6), and a room air control group (n = 6). The NBO treatment group was exposed to 42% oxygen for 2 hours a day for 10 days. The room air group was concurrently kept at 20.9% oxygen. The frequency and number of stem progenitor cells in peripheral blood were analyzed by flow cytometry. Plasma cytokine expression was analyzed by cytokine array enzyme linked immunosorbent assay. All analyses were performed 24 hours after the final exposure to control for transient post treatment effects. The NBO treatment group showed an increase in circulating $CD133^+/CD45^+$ stem progenitor cell frequency and number compared to the room air control group. This rise was largely caused by $CD34^-$ stem progenitor cells ($CD133^+/CD34^-/CD45^+$) without changes in the $CD34^+$ population. The plasma cytokine levels tested were mostly unchanged with the exception of tumor necrosis factor-α which showed a decrease 24 hours after the last NBO exposure. These findings support our hypothesis that NBO induces a biological response similar to HBO, affecting serum stem progenitor cell populations and tumor necrosis factor-α concentration. The study was approved by Institutional Animal Care and Use Committee (IACUC) of the University of Wisconsin, Madison, WI, USA (approval No. M005439) on June 28, 2016.

OXYMED

2019, STEM CELL MIGRATION RELEASING ANTI INFLAMMTORY GENE EXPRESSIONS

Front Cell Neurosci. 2019 Aug 13;13:301. doi: 10.3389/fncel.2019.00301. eCollection 2019.

Advance of Stem Cell Treatment for Traumatic Brain Injury.

Zhou Y[1], Shao A[2], Xu W[2], Wu H[2], Deng Y[1].

Author information

1 Department of Surgical Oncology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China.
2 Department of Neurosurgery, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

Abstract

Traumatic brain injury (TBI) is an important cause of human mortality and morbidity, which can induce serious neurological damage. At present, clinical treatments for neurological dysfunction after TBI include hyperbaric oxygen, brain stimulation and behavioral therapy, but the therapeutic effect is not satisfactory. Recent studies have found that exogenous stem cells can migrate to damaged brain tissue, then participate in the repair of damaged brain tissue by further differentiation to replace damaged cells, while releasing anti-inflammatory factors and growth factors, thereby significantly improving neurological function. This article will mainly review the effects, deficiencies and related mechanisms of different types of stem cells in TBI.

OXYMED

2019, HYPERBARIC SPINAL CORD INJURY

Chin Med J (Engl). 2019 Mar 20;132(6):699-706. doi: 10.1097/CM9.0000000000000115.

Hyperbaric oxygen improves functional recovery of rats after spinal cord injury via activating stromal cell-derived factor-1/CXC chemokine receptor 4 axis and promoting brain-derived neurothrophic factor expression.

Meng XL[1], Hai Y[1], Zhang XN[1], Wang YS[1], Liu XH[2], Ma LL[2], Yue R[3], Xu G[1], Li Z[2].

Author information

1 Orthopedic Department, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China.
2 Hyperbaric Oxygen Department, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China.
3 Hyperbaric Oxygen Department, Xinjiang Uygur Autonomous Region People's Hospital, Urumqi, Xinjiang 830001, China.

Abstract

BACKGROUND: Spinal cord injury (SCI) is a worldwide medical concern. This study aimed to elucidate the mechanism underlying the protective effect of hyperbaric oxygen (HBO) against SCI-induced neurologic defects in rats via exploring the stromal cell-derived factor-1 (SDF-1)/CXC chemokine receptor 4 (CXCR4) axis and expression of brain-derived neurotrophic factor (BDNF).

METHODS: An acute SCI rat model was established in Sprague-Dawley rats using the Allen method. Sixty rats were divided into four groups (n=15 in each group): sham-operated, SCI, SCI treated with HBO (SCI+HBO), and SCI treated with both HBO and AMD3100 (an antagonist of CXCR4; SCI+HBO+AMD) groups. The rats were treated with HBO twice a day for 3 days and thereafter once a day after the surgery for up to 28 days. Following the surgery, neurologic assessments were performed with the Basso-Bettie-Bresnahan (BBB) scoring system on postoperative day (POD) 7, 14, 21, and 28. Spinal cord tissues were harvested to assess the expression of SDF-1, CXCR4, and BDNF at mRNA and protein levels, using quantitative real-time polymerase chain reaction, Western blot analysis, and histopathologic analysis.

RESULTS: HBO treatment recovered SCI-induced descent of BBB scores on POD 14, (1.25±0.75 vs. 1.03±0.66, P<0.05), 21 (5.27±0.89 vs. 2.56±1.24, P<0.05), and 28 (11.35±0.56 vs. 4.23±1.20, P<0.05) compared with the SCI group. Significant differences were found in the mRNA levels of SDF-1 (mRNA: day 21, SCI+HBO vs. SCI+HBO+AMD, 2.89±1.60 vs. 1.56±0.98, P<0.05), CXCR4 (mRNA: day 7, SCI+HBO vs. SCI, 2.99±1.60 vs.1.31±0.98, P<0.05; day 14, SCI+HBO vs. SCI+HBO+AMD, 4.18±1.60 vs. 0.80±0.34, P<0.05; day 21, SCI+HBO vs. SCI, 2.10±1.01 vs.1.15±0.03, P<0.05), and BDNF (mRNA: day 7, SCI+HBO vs. SCI, 3.04±0.41 vs. 2.75±0.31, P<0.05; day 14, SCI+HBO vs. SCI, 3.88±1.59 vs. 1.11±0.40, P<0.05), indicating the involvement of SDF-1/CXCR4 axis in the protective effect of HBO.

CONCLUSIONS: HBO might promote the recovery of neurologic function after SCI in rats via activating the SDF-1/CXCR4 axis and promoting BDNF expression.

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2019, HBOT INHIBITS GLIAL SCAR FORMATION

Am J Phys Med Rehabil. 2019 Oct;98(10):914-920. doi: 10.1097/PHM.0000000000001225.

Hyperbaric Oxygen Improves Functional Recovery of the Injured Spinal Cord by Inhibiting Inflammation and Glial Scar Formation.

Zhou Y[1], Dong Q, Pan Z, Song Y, Su P, Niu Y, Sun Y, Liu D.

Author information

1 From the Department of Orthopedics, The Second Affiliated Hospital of Soochow University, Suzhou, China (YZ, QD, Y. Song, PS, YN, Y. Sun, DL); The Experimental Center, The Second Affiliated Hospital of Soochow University, Suzhou, China (YZ); and Department of Radiology, People's Hospital of Changshan, Quzhou, China (ZP).

Abstract

BACKGROUND: Inflammation and glial scar formation determine the recovery process after spinal cord injury. Hyperbaric oxygen is used as a rehabilitation therapy for various clinical diseases, including spinal cord injury. However, the relationship between hyperbaric oxygen therapy and inflammation or glial scar is not fully understood.

OBJECTIVE: The aim of this study was to investigate the therapeutic effect and molecular mechanism of hyperbaric oxygen on spinal cord injury.

METHODS: A total of 54 developing female Sprague-Dawley rats were randomly divided into sham group, spinal cord injury group, and hyperbaric oxygen group, with 18 rats in each group. The model of spinal cord injury was established using Allen's method. Hyperbaric oxygen therapy was administered once a day until the rats were killed.

RESULTS: The results demonstrated inflammation and glial scar formation are involved in secondary spinal cord injury. After hyperbaric oxygen treatment, there was a notable improvement of the locomotor function in rats. Hyperbaric oxygen reduced the inflammatory reaction and glial scar formation by inhibiting inflammation-related factors iNOS and COX-2 and glial scar-related components GFAP and NG2. This process may be achieved by inhibiting AKT and NF-kB pathways.

CONCLUSIONS: Hyperbaric oxygen effectively promotes the recovery of spinal cord injury by inhibiting inflammation and glial scar formation.

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2017, HBOT PROTECTS INDUCED SCIATIC NEURONAL DEATH

BMC Neurol. 2017 Dec 16;17(1):220. doi: 10.1186/s12883-017-1004-1.

Neuroprotective effects of hyperbaric oxygen (HBO) therapy on neuronal death induced by sciatic nerve transection in rat.

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2 Molecular and Cell Biology Research Center, Department of Anatomy, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran. khalat90@yahoo.com.

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Abstract

BACKGROUND: Recent studies shows that hyperbaric oxygen (HBO) therapy exerts some protective effects against neural injuries. The purpose of this study was to determine the neuroprotective effects of HBO following sciatic nerve transection (SNT).

METHODS: Rats were randomly divided into five groups (n = 14 per group): Sham-operated (SH) group, SH + HBO group, SNT group, and SNT + pre- and SNT + post-HBO groups (100% oxygen at 2.0 atm absolute, 60 min/day for five consecutive days beginning on 1 day before and immediately after nerve transaction, respectively). Spinal cord segments of the sciatic nerve and related dorsal root ganglions (DRGs) were removed 4 weeks after nerve transection for biochemical assessment of malodialdehyde (MDA) levels in spinal cord, biochemical assessment of superoxide dismutase (SOD) and catalse (CAT) activities in spinal cord, immunohistochemistry of caspase-3, cyclooxigenase-2 (COX-2), S100beta (S100ß), and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) in spinal cord and DRG.

RESULTS: The results revealed that MDA levels were significantly decreased in the SNT + pre-HBO group, while SOD and CAT activities were significantly increased in SNT + pre- and SNT + post-HBO treated rats. Attenuated caspase-3 and COX-2 expression, and TUNEL reaction could be significantly detected in the HBO-treated rats after nerve transection. Also, HBO significantly increased S100ß expression.

CONCLUSIONS: Based on these results, we can conclude that pre- and post-HBO therapy had neuroprotective effects against sciatic nerve transection-induced degeneration.

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SHAI EFRATI – HBOT & ERECTILE DYSFUNCTION

Int J Impot Res. 2018 Nov;30(6):292-299. doi: 10.1038/s41443-018-0023-9. Epub 2018 May 18.

Hyperbaric oxygen can induce angiogenesis and recover erectile function.

Hadanny A[1,2,3], Lang E[4,5,6], Copel L[5,7], Meir O[4], Bechor Y[4], Fishlev G[4,5], Bergan J[4,5], Friedman M[4], Zisman A[5,6], Efrati S[4,5,8,9].

Author information

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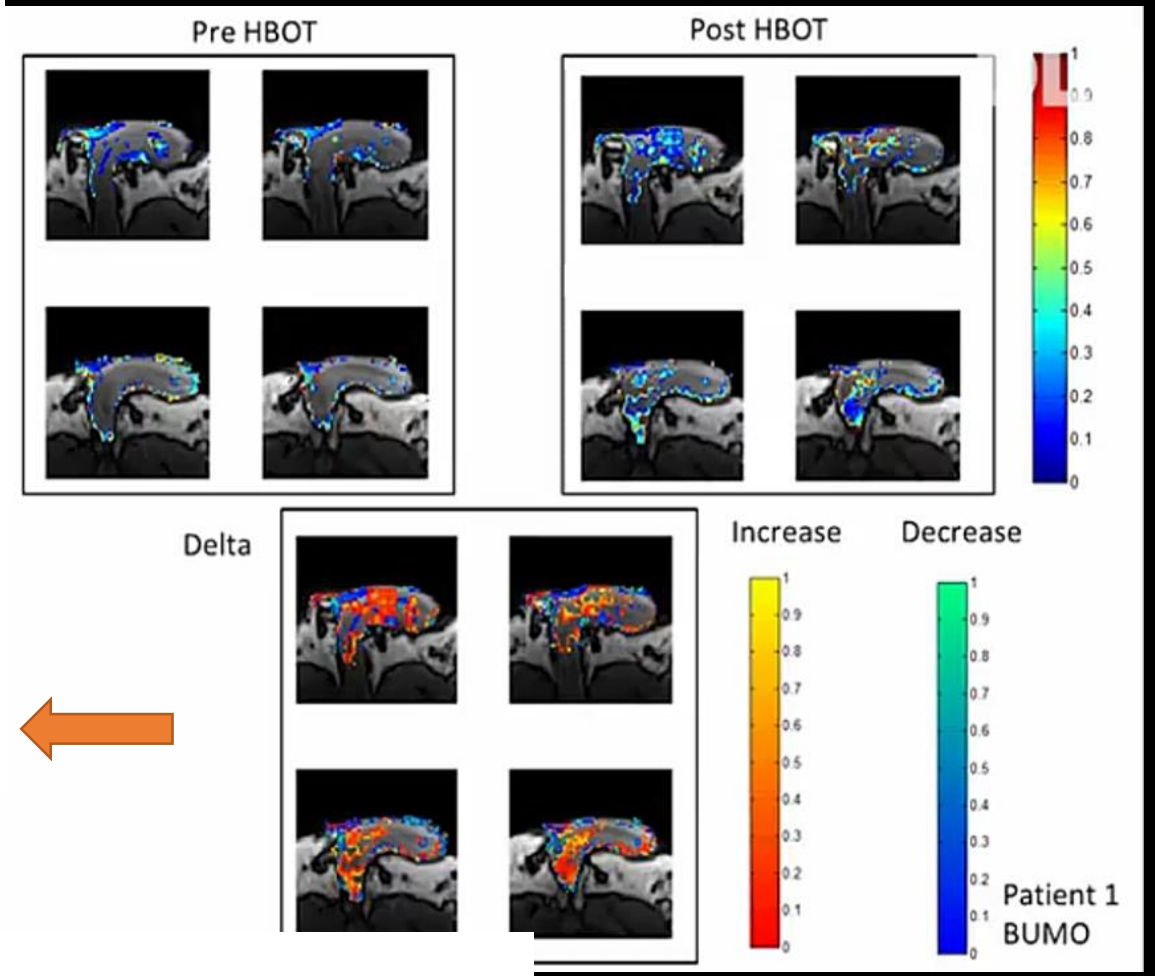
9 Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv, Israel.

Erratum in

Correction: Hyperbaric oxygen can induce angiogenesis and recover erectile function. [Int J Impot Res. 2018]

Abstract

Erectile dysfunction (ED) is caused by microvascular or macrovascular insufficiency in the majority of patients. Recent studies have shown that hyperbaric oxygen therapy (HBOT) can induce angiogenesis in different body organs. The effect of HBOT on the non-surgery-related ED has not been investigated yet. The aim of the current study was to evaluate the effects of HBOT on sexual function and penile vascular bed in non-surgical ED patients. A prospective analysis of patients suffering from chronic ED treated with 40 daily HBOT sessions. Clinical efficacy was assessed using the International Index of Erectile Function questionnaire (IIEF) and a global efficacy question (GEQ). The effect on the penile vascular bed was evaluated by perfusion MRI. Thirty men (mean age of 59.2 ± 1.4) suffering from ED for 4.2 ± 0.6 years completed the protocol. HBOT significantly improved all IIEF domains by 15-88% ($p < 0.01$). Erectile function improved by 88% ($p < 0.0001$) and 80% of the patients reported positive outcome according to the GEQ. Angiogenesis was indicated by perfusion MRI that showed a significant increase by 153.3 ± 43.2% of K-trans values in the corpous cavernous ($p < 0.0001$). HBOT can induce penile angiogenesis and improve erectile function in men suffering from EcD. HBOT reverses the basic common pathophysiology, atherosclerosis and decreased penile perfusion, responsible for most cases of ED.



J Urol. 2018 Sep;200(3):484. doi: 10.1016/j.juro.2018.05.109. Epub 2018 May 30.

Re: Improving Sperm Viability after Spinal Cord Injury Using Hyperbaric Therapy.

OXYMED

2018, HBOT AMELIORATED ACUTE SCI

Clin Biochem. 2018 Mar;53:1-7. doi: 10.1016/j.clinbiochem.2017.12.001. Epub 2017 Dec 5.

Hyperbaric oxygen ameliorated the lesion scope and nerve function in acute spinal cord injury patients: A retrospective study.

Tan JW[1], Zhang F[2], Liu HJ[1], Li Z[3].

⊕ Author information

Abstract

OBJECTIVE: This is a retrospective study to assess the therapeutic effect of hyperbaric oxygen (HBO) in early treatment of acute spinal cord injury (SCI) using magnetic resonance imaging (MRI) and electrophysiology in diagnosing.

METHODS: Forty acute SCI patients from Sun Yat-Sen Memorial Hospital who were assigned into HBO treatment were included during August 2013 to October 2014.The patients with adverse reactions or contraindications for HBO were assigned as controls. Both of two groups (HBO and Control) received medicine treatment with Urbason, GM-1 and mecobalamine after surgery. ASIA and the Frankel scores were used to evaluate the therapeutic effect of HBO at the 15th and 30th day after HBO treatment by using MRI and electrophysiology features.

RESULTS: Significant therapeutic effect of HBO treatment on acute SCI patients was observed compared with the control group ($P<0.05$). Comparison for ASIA and Frankel scores showed that motor and neurological functions were significantly improved in HBO group at day 15 and day 30 post treatment. MRI images showed that the grade III injury in HBO group was significant lower than the control group. In comparison with the control, the peak of somatosensory evoked potential (SEP) and motor evoked potential (MEP) amplitude increased, the latency was shortened, and the conduction velocity of sensory nerve (SCV) and motor nerve (MCV) was significantly increased in the HBO group ($P<0.05$).

CONCLUSIONS: HBO treatment has a great efficacy in acute SCI patients. HBO therapy at early stage of acute SCI is beneficiary to the recovery.

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2013, HYPERBARIC OXYGEN ELEVATES INTERLEUKIN 10

J Neurotrauma. 2013 Aug 1;30(15):1311-24. doi: 10.1089/neu.2012.2651. Epub 2013 Jul 18.

The therapeutic role of interleukin-10 after spinal cord injury.

Thompson CD[1], Zurko JC, Hanna BF, Hellenbrand DJ, Hanna A.

Author information

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Abstract

Spinal cord injury (SCI) is a devastating condition affecting 270,000 people in the United States. A potential treatment for decreasing the secondary inflammation, excitotoxic damage, and neuronal apoptosis associated with SCI, is the anti-inflammatory cytokine interleukin-10. The best characterized effects of IL-10 are anti-inflammatory-it downregulates pro-inflammatory species interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), tumor necrosis factor-α, interferon-γ, matrix metalloproteinase-9, nitric oxide synthase, myeloperoxidase, and reactive oxygen species. Pro-apoptotic factors cytochrome c, caspase 3, and Bax are downregulated by IL-10, whereas anti-apoptotic factors B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X, B-cell lymphoma-extra large (Bcl-xl) are upregulated by IL-10. IL-10 also provides trophic support to neurons through the IL-10 receptor. Increased tissue sparing, functional recovery, and neuroprotection are seen with an immediate post-SCI systemic administration of IL-10. Treatment of SCI with IL-10 has been used successfully in combination with Schwann cell and olfactory glial cell grafts, as well as methylprednisolone. Minocycline, tetramethylpyrazine, and hyperbaric oxygen treatment all increase IL-10 levels in a SCI models and result in increased tissue sparing and functional recovery. A chronic systemic administration of IL-10 does not appear to be beneficial to SCI recovery and causes increased susceptibility to septicemia, pneumonia, and peripheral neuropathy. However, a localized upregulation of IL-10 has been shown to be beneficial and can be achieved by herpes simplex virus gene therapy, injection of poliovirus replicons, or surgical placement of a slow-release compound. IL-10 shows promise as a treatment for SCI, although research on local IL-10 delivery timeline and dosage needs to be expanded.

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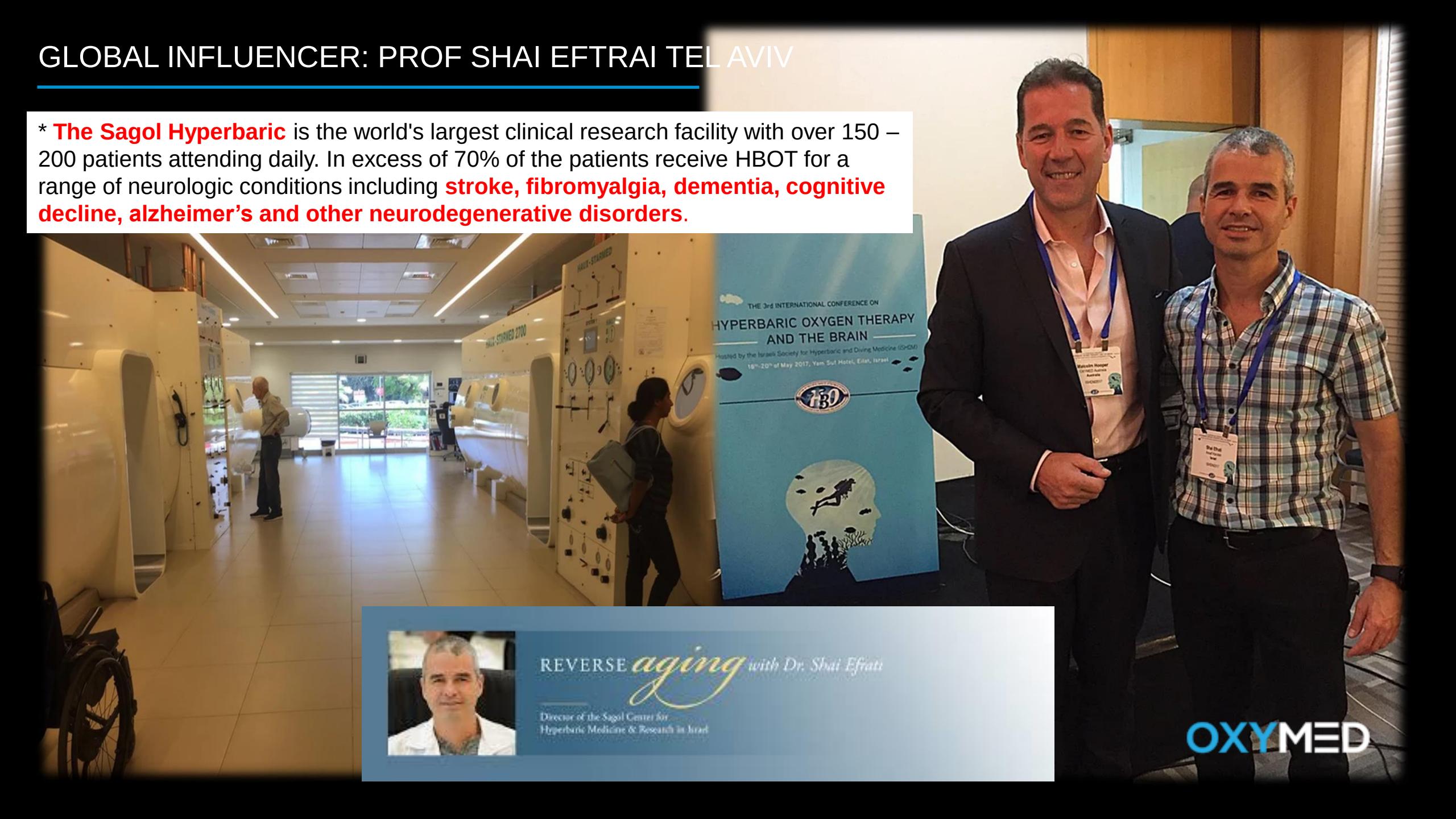
GLOBAL INFLUENCER: PROF SHAI EFTRAI TEL AVIV

* **The Sagol Hyperbaric** is the world's largest clinical research facility with over 150 – 200 patients attending daily. In excess of 70% of the patients receive HBOT for a range of neurologic conditions including **stroke, fibromyalgia, dementia, cognitive decline, alzheimer's and other neurodegenerative disorders**.



PROF SHAI EFRATI – IN EXCESS 34 PUBLICATIONS

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SHAI EFTRAI

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2013, NEUROVASCULAR PENUMBRA

OPEN ACCESS Freely available online

PLOS ONE

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

Shai Efrati[1,2,3]*, Gregori Fishlev[1], Yair Bechor[1], Olga Volkov[3,4], Jacob Bergan[1], Kostantin Kliakhandler[5], Izhak Kamiager[3,6], Nachum Gal[1], Mony Friedman[1], Eshel Ben-Jacob[2,5,7], Haim Golan[3,4]

1 The Institute of Hyperbaric Medicine, Assaf Harofeh Medical Center, Zerifin, Israel, **2** Research and Development Unit, Assaf Harofeh Medical Center, Zerifin, Israel, **3** Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel, **4** Nuclear Medicine Institute, Assaf Harofeh Medical Center, Zerifin, Israel, **5** School of Physics and Astronomy, The Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv, Israel, **6** Neurology Department, Assaf Harofeh Medical Center, Zerifin, Israel, **7** Center for Theoretical Biological Physics, Rice University, Houston, Texas, United States of America

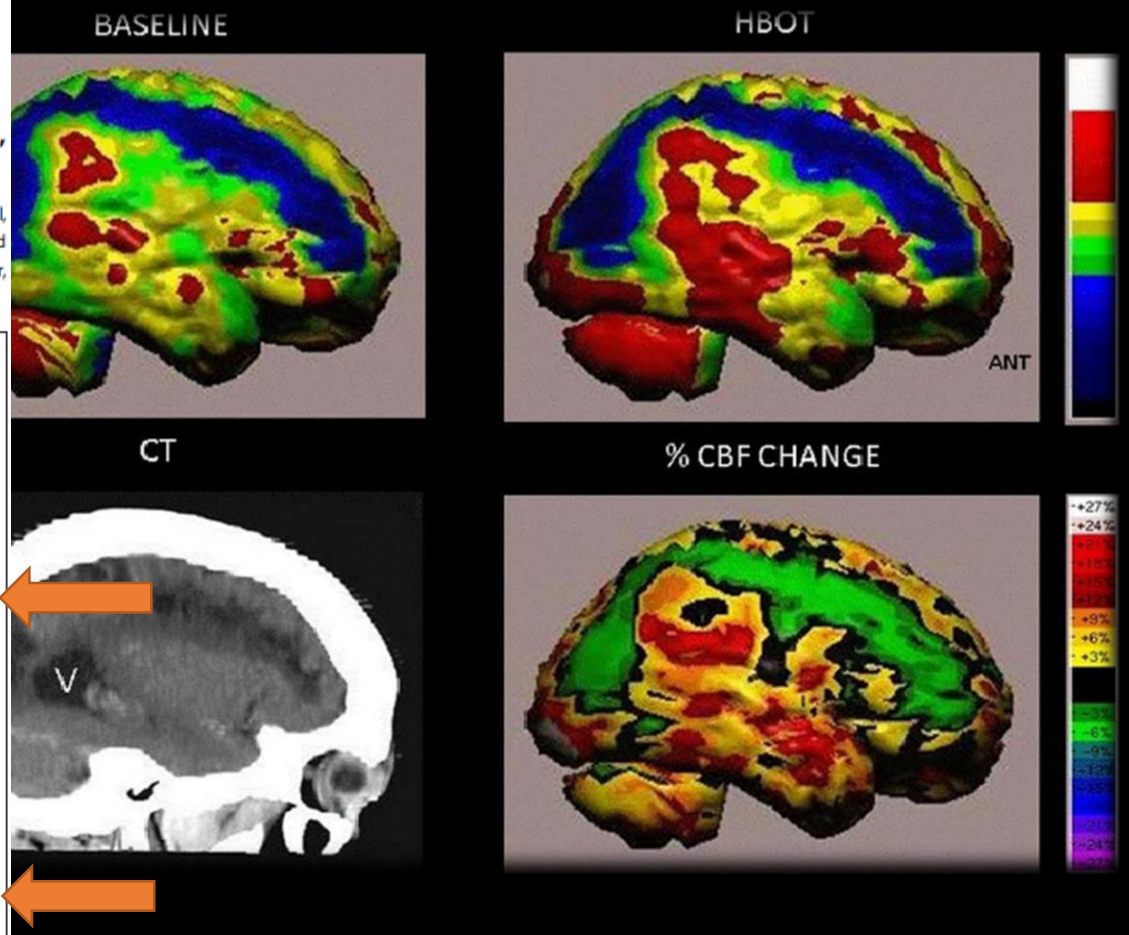
Abstract

Background: Recovery after stroke correlates with non-active (stunned) brain regions, which may persist for years. The current study aimed to evaluate whether increasing the level of dissolved oxygen by Hyperbaric Oxygen Therapy (HBOT) could activate neuroplasticity in patients with chronic neurologic deficiencies due to stroke.

Methods and Findings: A prospective, randomized, controlled trial including 74 patients (15 were excluded). All participants suffered a stroke 6–36 months prior to inclusion and had at least one motor dysfunction. After inclusion, patients were randomly assigned to "treated" or "cross" groups. Brain activity was assessed by SPECT imaging; neurologic functions were evaluated by NIHSS, ADL, and life quality. Patients in the treated group were evaluated twice: at baseline and after 40 HBOT sessions. Patients in the cross group were evaluated three times: at baseline, after a 2-month control period of no treatment, and after subsequent 2-months of 40 HBOT sessions. HBOT protocol: Two months of 40 sessions (5 days/week), 90 minutes each, 100% oxygen at 2 ATA. We found that the neurological functions and life quality of all patients in both groups were significantly improved following the HBOT sessions while no improvement was found during the control period of the patients in the cross group. Results of SPECT imaging were well correlated with clinical improvement. Elevated brain activity was detected mostly in regions of live cells (as confirmed by CT) with low activity (based on SPECT) – regions of noticeable discrepancy between anatomy and physiology.

Conclusions: The results indicate that HBOT can lead to significant neurological improvements in post stroke patients even at chronic late stages. The observed clinical improvements imply that neuroplasticity can still be activated long after damage onset in regions where there is a brain SPECT/CT (anatomy/physiology) mismatch.

Trial Registration: ClinicalTrials.gov NCT00715897



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NEUROPROTECTION MECHANISMS OF HBOT

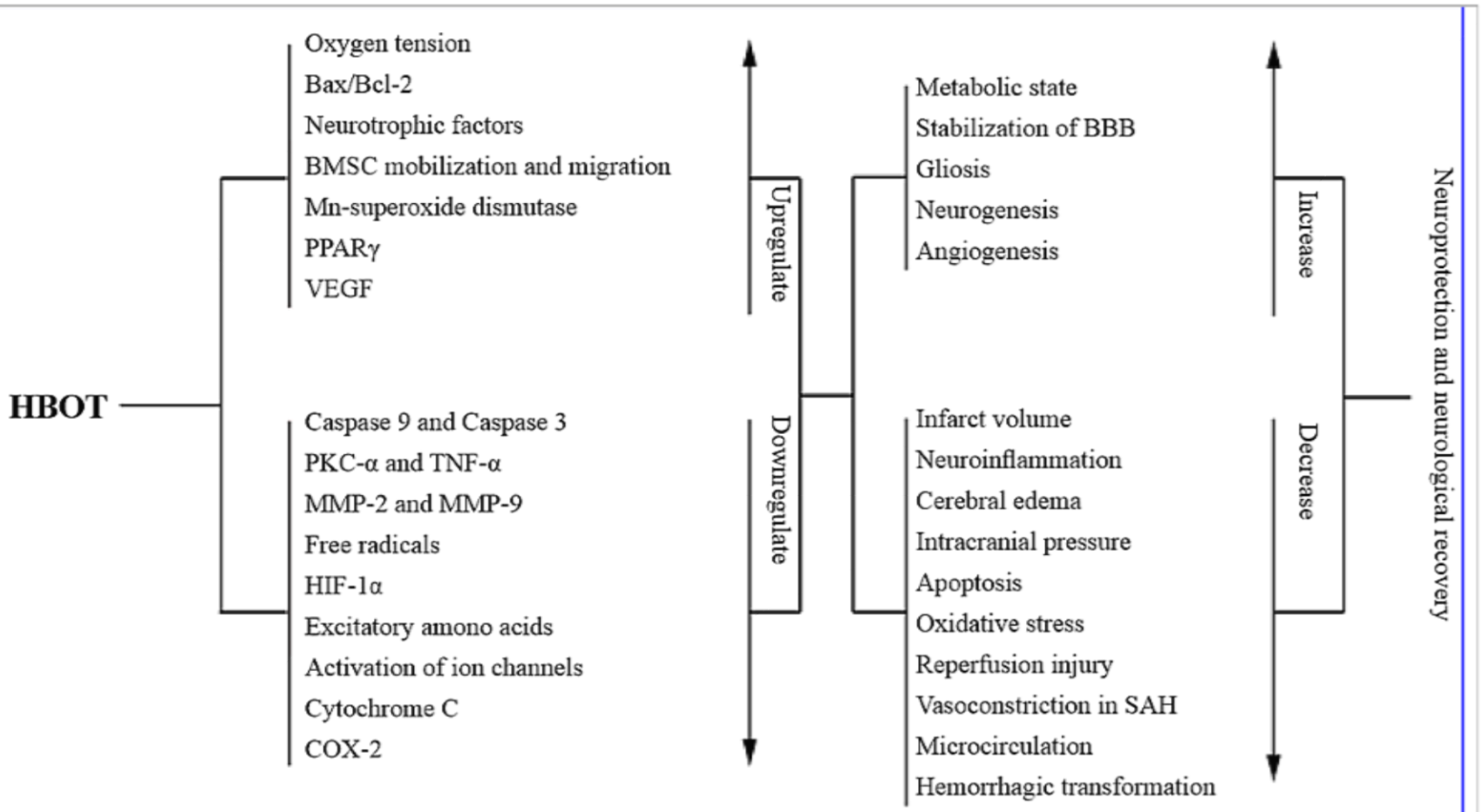
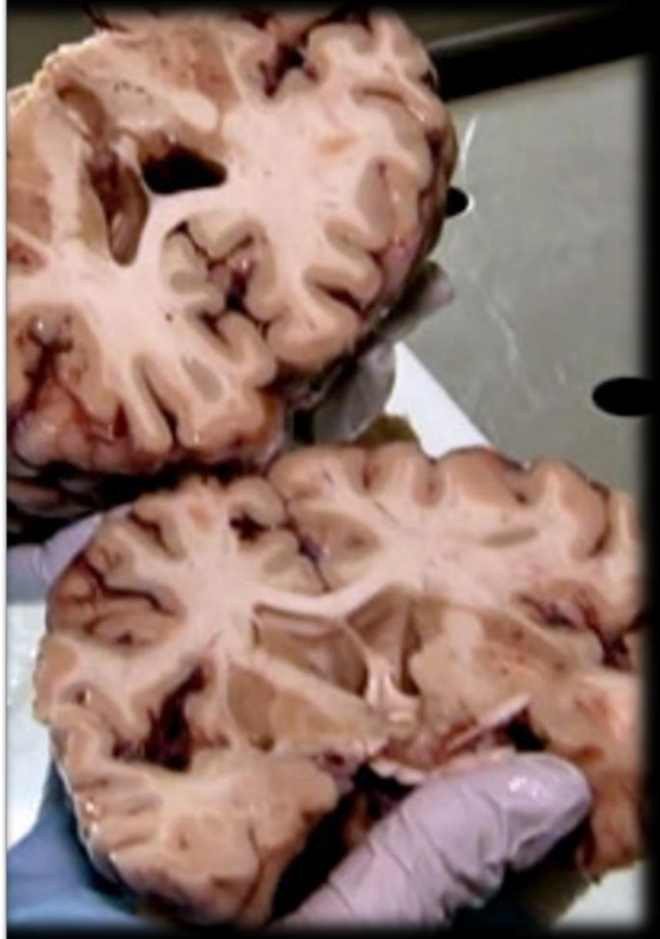


Figure 1: Possible mechanisms of hyperbaric oxygen therapy (HBOT) in stroke treatment.
Note: BMSC: Bone marrow stem cell; PPARγ: peroxisome proliferator activated receptor-γ; VEGF: vascular endothelial growth factor; PKC-α: phospho-protein kinase C-alpha; TNF-α: tumor necrosis factor-alpha; MMP: matrix metalloproteinases; HIF-1α: hypoxia-inducible factor-1α; COX-2: cyclooxygenase-2; BBB: blood-brain barrier; SAH: subarachnoid hemorrhage.



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MECHANISMS OF HBOT IN BRAIN INJURY

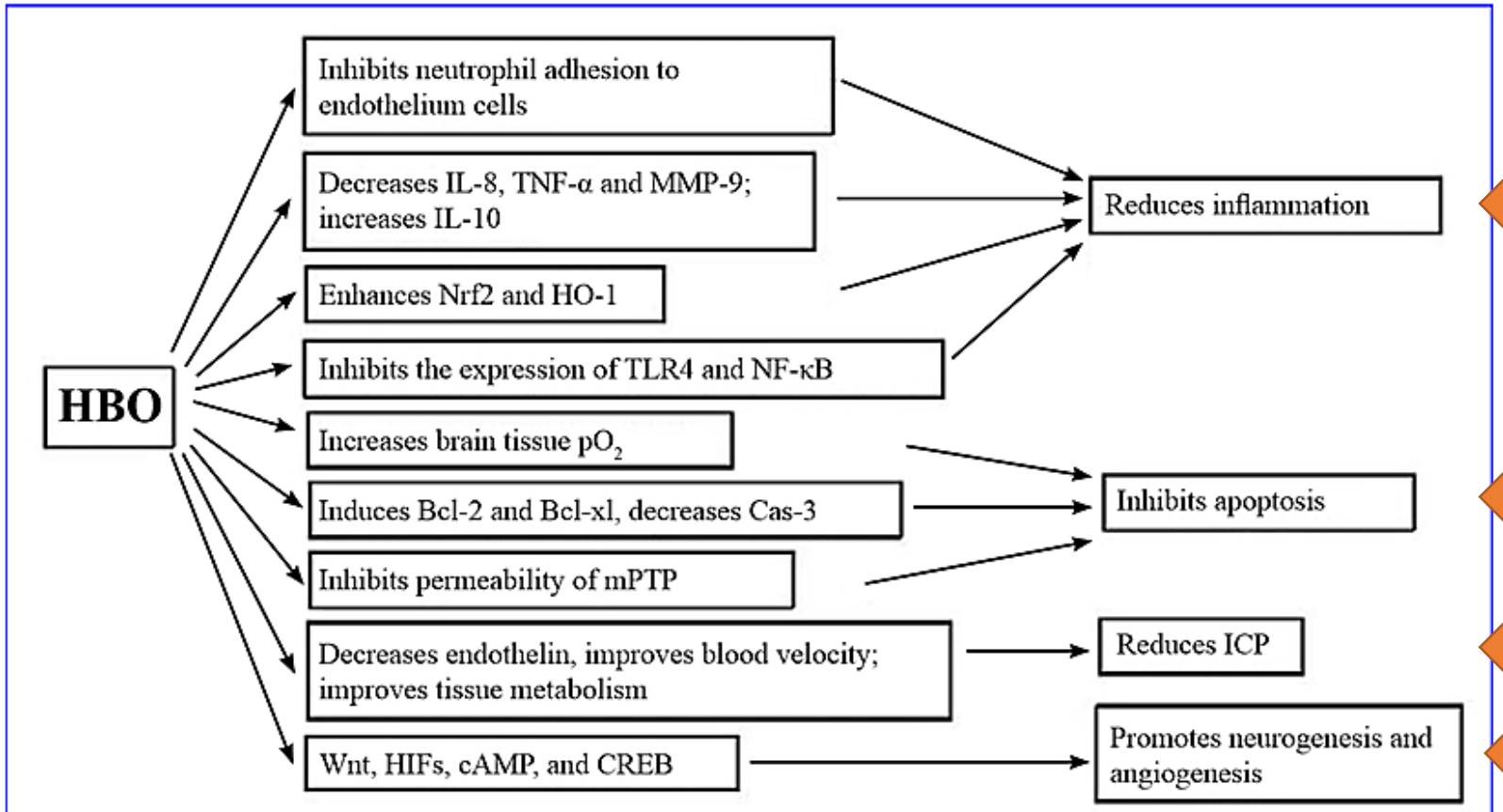
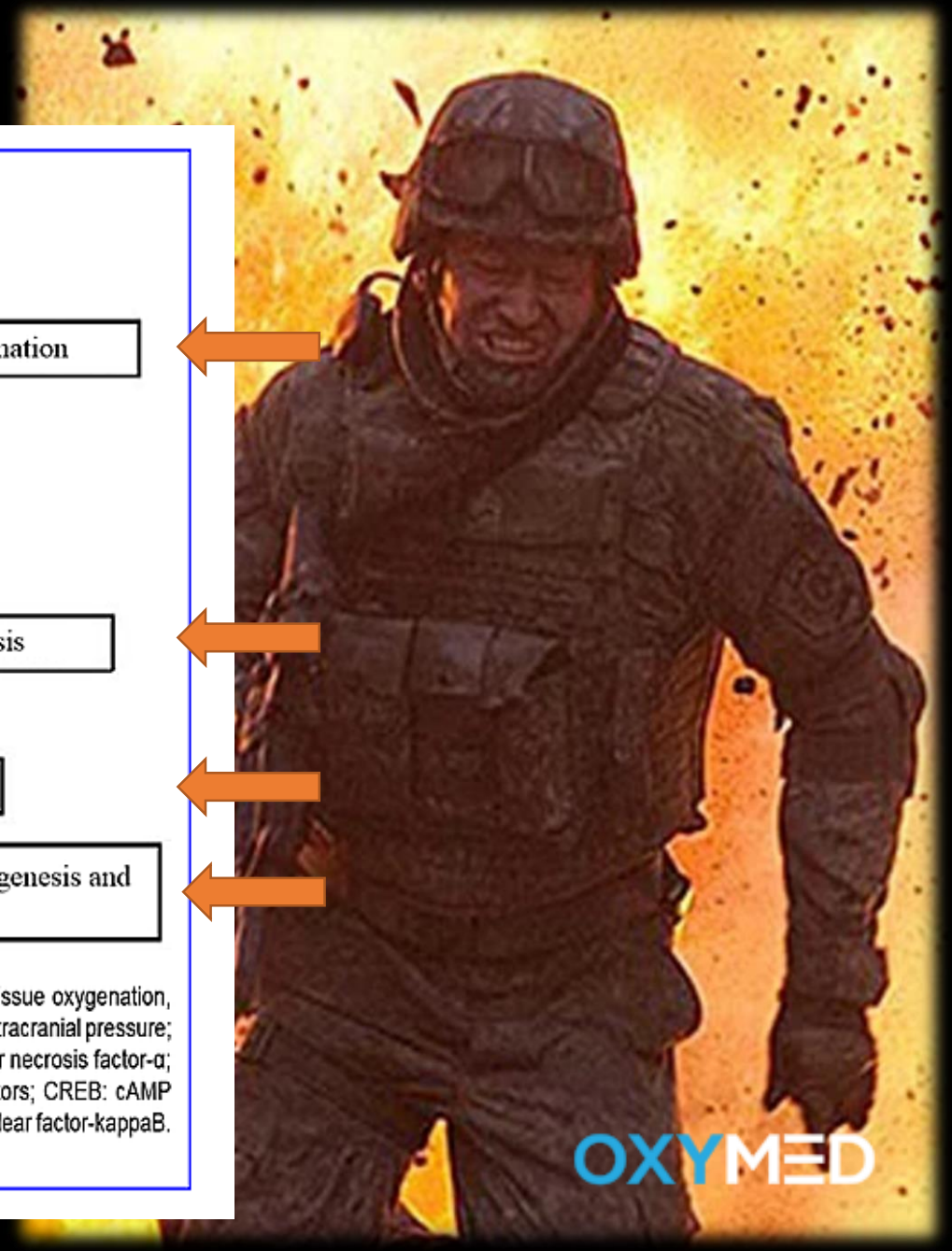


Figure 1: Potential mechanisms of HBO therapy.

Note: Many of the pathways work parallel, or together, to induce neuroprotection in the brain. These mechanisms include: increasing tissue oxygenation, reducing inflammation, inhibiting apoptosis, reducing ICP, and promoting neurogenesis and angiogenesis. HBO: Hyperbaric oxygen; ICP: intracranial pressure; CBF: cerebral blood flow; CSF: cerebrospinal fluid; pO_2: partial pressure of oxygen; IL-8: interleukin-8; IL-10: interleukin-10; TNF-α: tumor necrosis factor-α; MMP-9: matrix metalloproteinase-9; mPTP: mitochondrial permeability transition pore; Cas-3: caspase-3; HIFs: hypoxia-inducible factors; CREB: cAMP response element-binding; Nrf2: nuclear factor (erythroid-derived 2)-like 2; HO-1: heme oxygenase-1; TLR4: Toll-like receptor 4; NF-κB: nuclear factor-kappaB.



1966 - TRAUMATIC BRAIN INJURY

Table 1: Experimental studies of HBOT in TBI

HBO paradigm	Effects	Reference
2 ATA for 4 hours	Reduce CSF pressure	Coe and Hayes, 1966
3 ATA for 45 minutes	Reduce brain edema and decrease mortality	Dunn and Lawson, 1966
2 ATA for 4 hours	Decrease ICP and CBF	Miller et al., 1970
2.8 ATA for 45 minutes for two sessions	Decrease apoptosis	Palzur et al., 2004
2.8 ATA for 45 minutes for two sessions	Decreased apoptosis and preserved mitochondrial membrane properties	Palzur et al., 2008
2.8 ATA for 45 minutes for two sessions	Reduced inflammation and the expression of matrix metalloproteinase-9	Vlodavsky et al., 2006
2.0 ATA for 1 hour	Increased interleukin-10, reduced lesion volume and cerebral edema, and improved neurological status	Chen et al., 2014
3 ATA hourly for 3 or 5 days	Multiple HBO treatment reduced apoptosis and neurological deficits	Daugherty et al., 2004
1.5/2.5 ATA for 1 hour	Increased brain tissue pO_2	Contreras et al., 1988; Brkic et al., 2012
2 ATA for 90 minutes daily for 4 days	Increased the overall cerebral glucose utilization	Niklas et al., 2004
2.0 ATA for 60 minutes daily for 3 days	Inhibited inflammation and gliosis, and stimulated both angiogenesis and neurogenesis	Lin et al., 2012
2.5 ATA for 60 minutes daily for 10 days	Promoted axonal sprouting and synapse remodeling, and improved recovery of motor functions	Harch et al., 2007
1.5 ATA for 90 minutes twice daily for 40 days	Increased hippocampus vascular density and improved cognitive function	Hardy et al., 2007

Note: HBOT: Hyperbaric oxygen therapy; TBI: traumatic brain injury; HBO: hyperbaric oxygen; ICP: intracranial pressure; CBF: cerebral blood flow; CSF: cerebrospinal fluid; pO_2: partial pressure of oxygen. 1 Atmosphere absolute (ATA) = 101.3 kPa.

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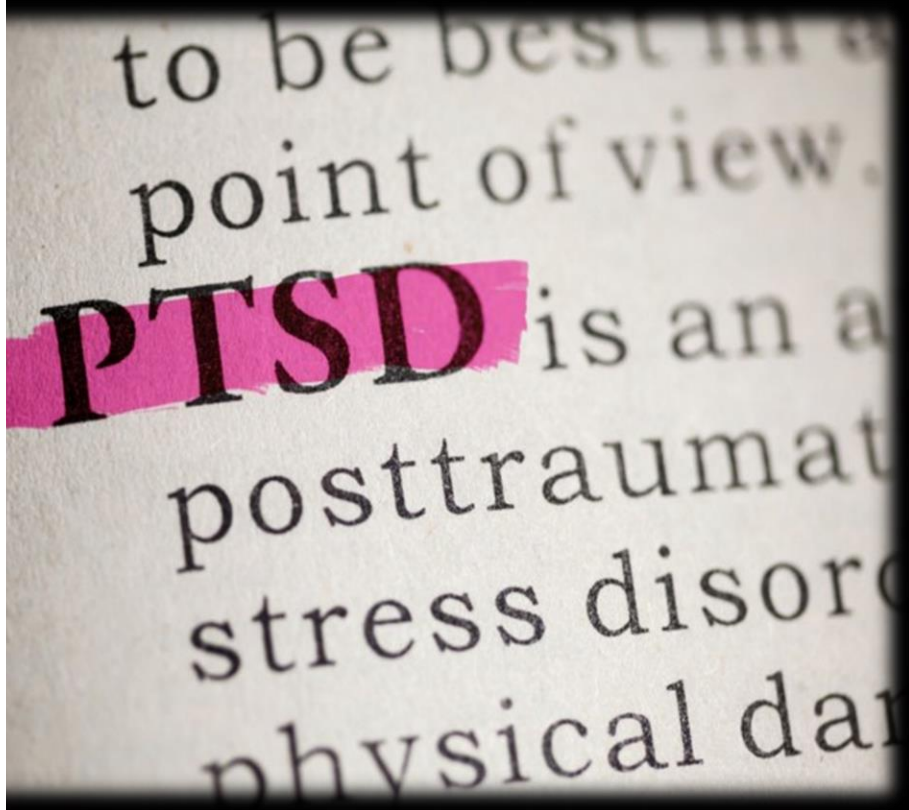
PTSD, CONCUSSION, TBI

Table 2: Clinical studies of HBOT in TBI patients

HBO paradigm	TBI type	Effects	Reference
2.0 ATA	Acute TBI	Affected ICP and CBF	Hayakawa et al., 1971; Sukoff and Ragatz, 1982
1.5–1.75 ATA for 1 hour daily for total 188 treatments with breaks	Closed head injury	Improved grey matter metabolic activity	Neubauer et al., 1994
1.5 ATA for 35–40 minutes	Brain lesion	Improved glucose metabolism	Holbach et al., 1977
1.5 ATA for 1–2 hours daily for 3–10 days	Severe TBI	Reduced mortality and improve outcome	Lv et al., 2011; Prakash et al., 2012; Rockswold et al., 2013
1.25 to 2.5 ATA, twice a week to 12 times a week	Chronic TBI	Improved CBF	Golden et al., 2002
1.25 to 2.5 ATA, twice a week to 12 times a week	Chronic TBI	Ameliorated the neuropsychological disorders	Golden et al., 2002, 2006
2 ATA for 1 hour daily for 20 days or 60 days	Chronic TBI	Improved outcome	Holbach et al., 1974
1.5 ATA for 1 hour, twice a day on weekdays for 1 or 2 months	Post-concussion syndrome	Improved CBF and alleviated post-concussive symptoms	Harch et al., 2009, 2012; Boussi-Gross et al., 2013
2.5 ATA	Head injury coma	Promoted consciousness recover	Artru et al., 1976
1.5 ATA for 1 hour daily until the patient was awake	Closed-head trauma	Did not improve outcome	Rockswold et al., 1992
2.5 ATA for 40–60 minutes daily for 10 days, 4 sessions with intervals	Severe TBI	Improved outcome, reduced ICP, decreased the mortality and morbidity	Ren et al., 2001a; Mao et al., 2010
2.5 ATA for 1 hour daily for 10 days	Craniocerebral injury	Did not improve outcome	Xie et al., 2007
1.5 or 2.0 ATA for 1 hour daily for 40 treatments in 10 weeks	Post-concussion syndrome	Did not improve outcome	Wolf et al., 2012b; Cifu et al., 2014a, b; Miller et al., 2015

Note: HBOT: Hyperbaric oxygen therapy; TBI: traumatic brain injury; HBO: hyperbaric oxygen; ICP: intracranial pressure; CBF: cerebral blood flow; CSF: cerebrospinal fluid. 1 Atmosphere absolute (ATA) = 101.3 kPa.



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HOUSE OF REPRESENTATIVES - SEPTEMBER 2019

H. R. 4370

To amend title 38, United States Code, to direct the Secretary of Veterans Affairs to furnish hyperbaric oxygen therapy to veterans with traumatic brain injury or post-traumatic stress disorder.

IN THE HOUSE OF REPRESENTATIVES
Mr. BIGGS introduced the following bill; which was referred to the Committee

on September 18, 2019

A study of veterans of the US armed forces with mild traumatic brain injury (TBI) or persistent post-concussion syndrome (PPCS), with or without post-traumatic stress disorder (PTSD), has found **significant improvements in persistent post-concussion syndrome and PTSD symptoms, neurological exam, memory, intelligence quotient, attention, cognition, depression, anxiety, quality of life, and brain blood flow following hyperbaric oxygen therapy (HBOT).**

* Compared to controls, the patients' brain SPECT scans were significantly abnormal before treatment and became statistically indistinguishable from controls in 75% of abnormal areas after treatment.

HYPERBARIC GENE SIGNALING

HYPERBARIC OXYGEN ‘EPIGENETIC CELLULAR THERAPY’

HBOT effects Traumatic Brain Injury: Oxygen, Pressure & Gene Therapy (Harch 2015)

During hyperbaric therapy **- physicians are playing a symphony with patients’ gene expression**, the music of which is determined by the **various pressures and different amounts of hyperoxia** to which the patient is exposed.

* Tissue growth requires replication of DNA. **The oxygen component of HBOT is a DNA signaling agent**.

* A single HBOT, at the pressure used for diabetic foot wounds and radiation wounds **up or downregulated the expression of 8,101 (nearly 50%) of the known 19-20,000 protein-coding genes in the human genome**.

* Further work showed **clusters of neuronal genes** are affected by **‘different pressures’** and **‘different amounts of hyperoxia’**.

* Upregulated genes are primarily **growth and repair hormones and anti-inflammatory genes**.

* Downregulated genes are the **pro-inflammatory and apoptotic genes**.

* HBO **expands the therapeutic window** reducing continuing neurovascular deterioration. HBO upregulates the patient's own **target specific Stem Cells** with an **8-fold or 800 percent increase in circulating CD34+**.

* HBO enhances **Mitochondrial respiration**.

*** HBO proliferates Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), Interleukin-3 (IL3), Interleukin-4 (IL4), Interleukin-10 (IL10), Interleukin-13 (IL13), Interleukin-21 (IL21), Brain Derived Neural Growth Factors (BDNF, GDNF), Vascular Growth Factors (VEGF), TGFβ1 Signalling, IGF1.**

* HBO reduces **Telomere degeneration**.

* HBO down regulates toxic **intra and extra cellular inflammatory Cytokines** (IL1, 2, 6, 7, 8, 17), Tumour Necrosis Factor Alpha (TNFα), GlycA, S100B.

* HBO **inhibits opportunistic infections** (MRSA, viral, bacterial, parasitic), cell sepsis and more.

PARADIGM SHIFT

Tony Robbins ‘Unleash the POWER within’
Ephesians 3 vs 20

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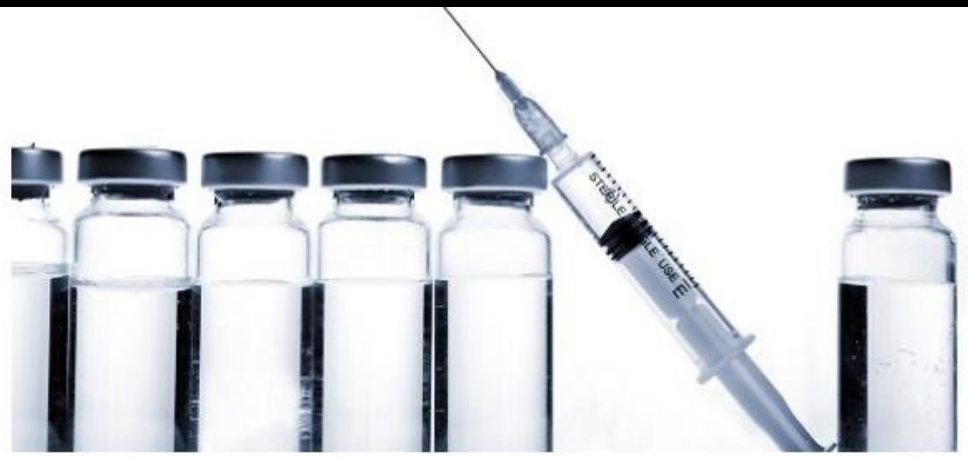
CURRENT MODEL – ‘DAYS OF OUR LIVES’ REHABILITATION

BOTOX – NUMBER 1 FOR ASSISTING SPASTICITY



Allergan gets FDA okay for paediatric Botox use

Phil Taylor

October 25, 2019

The FDA has approved Allergan's Botox to treat lower-limb spasticity in children, further extending the use of the drug – widely used as a wrinkle treatment – in therapeutic indications.

The US regulator has given the botulinum toxin-based drug a green light for all forms of lower-limb spasticity – increased muscle contraction causing stiffness that can interfere with movement – with one exception: when it is caused by cerebral palsy.

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2019, FDA APPROVAL BROADENS THE USE OF BOTOX AND FUNDING

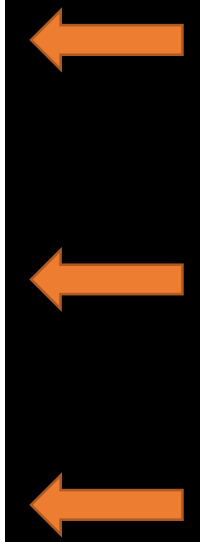
The latest approval comes on the back of data from a 12-week, phase 3 study involving more than 300 children aged 2 to 17 years, which showed that treatment with Botox made patients more likely to meet active goals such as improvements in walking, as well as having other benefits on pain, spasm, and the need to wear braces on their legs.

"Lower limb spasticity can impact many aspects of a child's life and have a drastic influence on their overall development and quality of life," said Allergan's head of R&D David Nicholson.

"This milestone will continue to support and advance care for children and their caregivers who may be struggling with lower limb spasticity," he added.

Allergan has progressively extended the number of approved therapeutic indications for Botox since its launch for blepharospasm and strabismus in 1989, with the latest taking the tally to date to 11.

The extension of Botox's use is also good news for AbbVie, which is in the process of acquiring Allergan in a $63 billion deal.



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CONSUMER PRODUCT INFORMATION

AUSTRALIAN PRODUCT INFORMATION – BOTOX® (BOTULINUM TOXIN, TYPE A) POWDER FOR INJECTION

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BOTOX® (botulinum toxin type A) purified neurotoxin complex is indicated for the following therapeutic indications:

- treatment of overactive bladder with symptoms of urinary incontinence, urgency and frequency, in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication
- treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication
- prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)
- treatment of strabismus in patients twelve years and over
- treatment of blepharospasm associated with dystonia, including benign blepharospasm and VIIth nerve disorders (specifically hemifacial spasm) in patients twelve years and over
- treatment of cervical dystonia (spasmodic torticollis)
- treatment of focal spasticity of the upper and lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients two years and older
- treatment of severe primary hyperhidrosis of the axillae
- treatment of focal spasticity in adults
- treatment of spasmodic dysphonia.

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MECHANISM OF ACTION – CLEAVING TO SNAP-25, SYNAPTIC REGRESSION

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Therapeutic class: neuromuscular blocking agent.

Mechanism of action

Clostridium botulinum type A neurotoxin blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals by cleaving SNAP-25, a protein integral to the docking and release of acetylcholine from vesicles located within the nerve terminals.

After injection, there is an initial high-affinity binding of toxin to specific cell surface receptors on cholinergic nerve terminals. Bound toxin is then internalised by endocytosis, and the catalytic light chain is translocated across the vesicular membrane into the cytosol where it cleaves SNAP-25. Progressive inhibition of acetylcholine release follows and clinical signs usually manifest within 2-3 days. In sensory neurons, BOTOX® inhibits the release of sensory neurotransmitters (e.g., Substance P, CGRP) and inhibits the delivery of receptors, such as TRPV1, to the cell surface. BOTOX® may also prevent and/or reverse sensitisation in some nociceptive sensory neurons.

Recovery after intramuscular injection takes place normally within 12 weeks. Preclinical studies have demonstrated that, new sprouts from the original preterminal axons allow for a temporary reconnection of the neuron with the endplates. These sprouts are only partially effective and subsequently regress while the original nerve terminal at the primary neuromuscular junction becomes functional again. The relevance of these preclinical

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BOTOX PROPERTIES

5.2 PHARMACOKINETIC PROPERTIES

Classical absorption, distribution, biotransformation and elimination studies on the active substance have not been performed due to the nature of this product.

Distribution

Distribution in rats was studied following injection of ^{125}I-botulinum neurotoxin A complex into the gastrocnemius muscle. Radioactivity associated with the toxin complex was mostly retained at the injection site, declining with a half-life of approximately 10 hours. Radioactivity detected in other locations (plasma, muscle, thyroid, skin) was mainly associated with probable breakdown products, indicating minimal systemic exposure to toxin.

Metabolism

The toxin is probably metabolised by proteases and the molecular components cycled through normal metabolic pathways.

Excretion

Within 24 hours of dosing, 60% of the radioactivity was excreted in the urine.

Use in lactation

There is no information on whether BOTOX® is excreted in human milk.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX® injection. BOTOX® is not structurally related to any known carcinogens.

6.2 INCOMPATIBILITIES

Incompatibility studies were not assessed as part of the registration of BOTOX®. BOTOX® should therefore not be mixed with other medicinal products.

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USA ALLEGRAN - WARNING

Allergan

SAFETY DATA SHEET

Revision Date 02-Oct-2018 **Version** 13

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

Product identifier
Product Name Neurotoxin from Organism (Clostridium botulinum) Lyophilized Drug Product

Other means of identification
Product Code FP-66
Synonyms Botox

Recommended use of the chemical and restrictions on use
Recommended Use Acetylcholine release inhibitor and Neuromuscular blocking agent for OAB, Prophylaxis of headaches in adults with chronic migraine, spasticity in adults, cervical dystonia in adults, blepharospasm associated with dystonia, strabismus

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Chemical Name	Germ cell mutagenicity	Carcinogenicity	Reproductive toxicity	Effects on or via lactation
Botulinum toxin type A	Not mutagenic in the standard battery of tests.	Studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX® and BOTOX® Cosmetic. The product is not structurally related to any known carcinogens. The clinical experience with BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex (100 Units) since 1980 has provided no evidence of carcinogenicity. In addition, in vitro and in vivo mutagenicity and genotoxicity studies showed no carcinogenic potential.	In fertility studies of BOTOX (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the maximum recommended human dose of 400 Units on a body weight basis (Units/kg).	It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when this drug is administered to nursing mothers.

Note to physicians

WARNING: DISTANT SPREAD OF TOXIN EFFECT. The effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration.

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‘POST MARKETING’ - SAFETY WARNING

Spread of toxin effect

Post-marketing safety data from BOTOX® and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin, have been reported hours to weeks after injection, and may include muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing and respiratory depression. The risk of symptoms is probably greatest in children treated for spasticity, but these symptoms can also occur in patients who have underlying conditions and co-morbidities that would predispose them to these symptoms including adults treated for spasticity and other conditions and are treated with high doses. Swallowing and breathing difficulties can be life threatening and there have been reports of death. Advise patients or caregivers to seek immediate medical attention if any of these symptoms occur.

Pre-existing neuromuscular disorders

Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) should only receive BOTOX® with extreme caution. Patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of

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‘CLINICALLY SIGNIFICANT SYSTEMIC EFFECTS’

BOTOX®. Published medical literature has reported rare cases of administration of botulinum toxin to patients with known or unrecognised neuromuscular junction disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube. When exposed to very high doses, patients with neurologic disorders, e.g. paediatric cerebral palsy or adult spasticity may also be at increased risk of clinically significant systemic effects.

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2019, COCHRANE – CEREBRAL PALSY

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

Botulinum toxin type A in the treatment of lower limb spasticity in children with cerebral palsy

Quality of the evidence

We considered the quality of the evidence as very low for the comparison BoNT-A versus usual care or physiotherapy; moderate for the comparison BoNT-A versus placebo; moderate and low for the comparison BoNT-A versus plaster casts; and very low for the comparison BoNT-A versus splints.

Conclusion

There is limited evidence that, compared to placebo or regular care, BoNT-A improves walking, joint motion, satisfaction with the outcome of treatment, and muscle spasticity in children with CP. The rate of side effects with BoNT-A was similar to placebo. BoNT-A was no better than plaster casts in any of our analyses, but was better than splints at improving range of motion and spasticity.

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2019, COCHARNE – MIGRAINE

BMJ Open. 2019 Jul 16;9(7):e027953. doi: 10.1136/bmjopen-2018-027953.

Cochrane systematic review and meta-analysis of botulinum toxin for the prevention of migraine.

Herd CP[1], Tomlinson CL[2], Rick C[3], Scotton WJ[4], Edwards J[5], Ives NJ[2], Clarke CE[6], Sinclair AJ[4].

Author information

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4 University of Birmingham, Institute of Metabolism and Systems Research, Birmingham, UK.
5 Sandwell and West Birmingham Hospitals NHS Trust, Department of Neurology, Birmingham, Birmingham, UK.
6 University of Birmingham, Neurology, Birmingham, UK.

Abstract

OBJECTIVES: To assess the effects of botulinum toxin for prevention of migraine in adults.

DESIGN: Systematic review and meta-analysis.

DATA SOURCES: CENTRAL, MEDLINE, Embase and trial registries.

ELIGIBILITY CRITERIA: We included randomised controlled trials (RCTs) of botulinum toxin compared with placebo, active treatment or clinically relevant different dose for adults with chronic or episodic migraine, with or without the additional diagnosis of medication overuse headache.

DATA EXTRACTION AND SYNTHESIS: Cochrane methods were used to review double-blind RCTs. Twelve week post-treatment time-point data was analysed.

RESULTS: Twenty-eight trials (n=4190) were included. Trial quality was mixed. Botulinum toxin treatment resulted in reduced frequency of -2.0 migraine days/month (95% CI -2.8 to -1.1, n=1384) in chronic migraineurs compared with placebo. An improvement was seen in migraine severity, measured on a numerical rating scale 0 to 10 with 10 being maximal pain, of -2.70 cm (95% CI -3.31 to -2.09, n=75) and -4.9 cm (95% CI -6.56 to -3.24, n=32) for chronic and episodic migraine respectively. Botulinum toxin had a relative risk of treatment related adverse events twice that of placebo, but a reduced risk compared with active comparators (relative risk 0.76, 95% CI 0.59 to 0.98) and a low withdrawal rate (3%). Although individual trials reported non-inferiority to oral treatments, insufficient data were available for meta-analysis of effectiveness outcomes.

CONCLUSIONS: In chronic migraine, botulinum toxin reduces migraine frequency by 2 days/month and has a favourable safety profile. Inclusion of medication overuse headache does not preclude its effectiveness. Evidence to support or refute efficacy in episodic migraine was not identified.

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2018, ADVERSE EVENTS - 22% OF INJECTIONS IN CEREBRAL PALSY CHILDREN

Dev Med Child Neurol. 2018 May;60(5):498-504. doi: 10.1111/dmcn.13686. Epub 2018 Feb 16.

Severity of cerebral palsy and likelihood of adverse events after botulinum toxin A injections.

Swinney CM[1], Bau K[2], Burton KLO[2], O'Flaherty SJ[3], Bear NL[4], Paget SP[2].

Author information

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2 The Children's Hospital at Westmead, Westmead, NSW, Australia.
3 Sydney Children's Hospital, Randwick, NSW, Australia.
4 Child and Adolescent Health Services, Perth, WA, Australia.

Abstract

AIM: To determine the incidence of common adverse events after botulinum toxin A (BoNT-A) injections in children with cerebral palsy (CP) and to identify whether the severity of CP influences the incidence of adverse events.

METHOD: This was an observational study of patients attending a BoNT-A clinic at a tertiary paediatric hospital (2010-2014). Data examined included procedural adverse events at the time of injection and at follow-up. Systemic adverse events were defined as lower respiratory tract illnesses, generalized weakness, dysphagia, and death. Severity of CP was categorized by the Gross Motor Function Classification System (GMFCS). The relationships between GMFCS and adverse events were analysed using negative binomial regression models.

RESULTS: In total, 591 children underwent 2219 injection episodes. Adverse events were reported during the procedure (130 [6%] injection episodes) and at follow-up (492 [22%] injection episodes). There were significantly increased rates of systemic adverse events in injection episodes involving children in GMFCS level IV (incidence rate ratio [IRR] 3.92 [95% confidence interval] 1.45-10.57]) and GMFCS level V (IRR 7.37 [95% confidence interval 2.90-18.73]; p<0.001).

INTERPRETATION: Adverse events after BoNT-A injections are common but mostly mild and self-limiting. Children in GMFCS levels IV and V are at increased risk of systemic adverse events. The relationship between CP severity and BoNT-A adverse events is complex and further research is required to better understand this relationship.

WHAT THIS PAPER ADDS: Adverse events reported at the time of botulinum toxin A injection occurred in 6% of injection episodes. Adverse events were reported at follow-up in 22% of injection episodes. Children in Gross Motor Function Classification System (GMFCS) levels IV and V have increased rates of systemic adverse events. Children in GMFCS levels IV and V report less local weakness and pain.

Comment in

Botulinum toxin: did the black box warning change how we treat children with cerebral palsy? [Dev Med Child Neurol. 2018]

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Type A botulinum neurotoxin complex proteins differentially modulate host response of neuronal cells

Lei Wang [a,*], Yi Sun [a], Weiping Yang [a], Paul Lindo [a], Bal Ram Singh [a,b]

[a] Prime Bio Inc., Dartmouth, MA 02747, USA
[b] Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, Dartmouth, MA 02747, USA

A B S T R A C T

Type A Botulinum neurotoxin (BoNT/A), the most potent poison known to mankind, is produced by Clostridium botulinum type A as a complex with neurotoxin-associated proteins (NAPs). Currently BoNT/A in purified and complex forms are both available in therapeutic and cosmetic applications to treat neuromuscular disorders. Whereas Xeomin® (incobotulinumtoxin A, Merz Pharmaceuticals, Germany) is free from complexing proteins, Botox® (onabotulinumtoxin A, Allergan, USA) contains NAPs, which by themselves have no known role in the intracellular biochemical process involved in the blockade of neurotransmitter release. Since the fate and possible interactions of NAPs with patient tissues after intramuscular injection are not known, it was the aim of this study to evaluate the binding of BoNT/A and/or the respective NAPs to cells derived from neuronal and non-neuronal human tissues, and to further explore neuronal cell responses to different components of BoNT/A. BoNT/A alone, the complete BoNT/A complex, and the NAPs alone, all bind to neuronal SH-SY5Y cells. The BoNT/A complex and NAPs additionally bind to RMS13 skeletal muscle cells, TIB-152 lymphoblasts, Detroit 551 fibroblasts besides the SH-SY5Y cells. However, no binding to these non-neuronal cells was observed with pure BoNT/A. Although BoNT/A, both in its purified and complex forms, bind to SH-SY5Y, the intracellular responses of the SH-SY5Y cells to these BoNT/A components are not clearly understood. Examination of inflammatory cytokine released from SH-SY5Y cells revealed that BoNT/A did not increase the release of inflammatory cytokines, whereas exposure to NAPs significantly increased release of IL-6, and MCP-1, and exposure to BoNT/A complex significantly increased release of IL-6, MCP-1, IL-8, TNF-α, and RANTES vs. control, suggesting that different components of BoNT/A complex induce significantly differential host response in human neuronal cells. Results suggest that host response to different compositions of BoNT/A based therapeutics may play important role in local and systemic symptoms in patients.

BoNT/A vs **BoNT/A COMPLEX NAP**

* BOTOX (ALLEGRAN) contains NAPs

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BOTOX (ALLERGAN) CONTAINS NAPS (NEUROTOXIN ASSOCIATED PROTEINS)

Type A botulinum neurotoxin complex proteins differentially modulate host response of neuronal cells

Lei Wang [a,*], Yi Sun [a], Weiping Yang [a], Paul Lindo [a], Bal Ram Singh [a,b]

[a] Prime Bio Inc., Dartmouth, MA 02747, USA
[b] Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, Dartmouth, MA 02747, USA

Over five million patients are being treated with botulinum neurotoxins globally (Singh et al., 2010), and because of the safety concerns of this being the most toxic sub-stance known to mankind, the United States Food and Drug Administration (US FDA) has designated all botulinum neurotoxin based drugs for black box label (Kuehn, 2009).

* There have been reports of side effects such as cognition issues and flu-like symptoms from BoNT-based therapeutics (Alam et al., 2002; Costa et al., 2005; Cote et al., 2005),with little knowledge of their causes.

* **Botox (Allergan)** contains **NAPs** (neurotoxin-associated proteins)

Flu-like symptoms after BoNT/A application may also be the result of inflammation resulting from the cytokine inflammatory mediators (**cytokine release syndrome**) released in response to some components in the BoNT/A NAP complexing protein.

Examination of inflammatory cytokine released from SH-SY5Y cells revealed that BoNT/A did not increase the release of inflammatory cytokines, where as exposure to NAPs significantly increased release of IL-6, and MCP-1, and exposure to BoNT/A complex significantly increased release of IL-6, MCP-1, IL-8, TNF-a, and RANTES vs. control.

* BoNT/A NAP complex induce significantly differential host response in human neuronal cells and may play important role in local and systemic symptoms in patients

US $7.5B BY 2026 - BOTOX (ALLERGAN)

Botulinum Toxin Market Size Worth Around US$7.5 Bn by 2026

Acumen Research and Consulting, a global provider of market research studies, in a recently published report titled "Botulinum Toxin Market Report 2019 - 2026"

Email | Print Friendly | Share

June 18, 2019 10:00 ET | **Source:** Acumen Research and Consulting

LOS ANGELES, June 18, 2019 (GLOBE NEWSWIRE) -- The global **botulinum toxin market** is estimated to grow at CAGR above 8 % over the forecast time frame 2019 to 2026 and reach the market value around USD 7.5 billion by 2026.

Botox maker Allergan to be sold for $90 billion

Drew Armstrong

Jun 26, 2019 — 12.31am

New York | AbbVie has agreed to pay $63 billion ($90 billion) for rival drugmaker Allergan, the latest huge merger in a pharmaceutical sector rapidly being reshaped by deals.

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CONTEMPORAY REHABILITATION – ALLERGAN (MAJOR SPONSORS)

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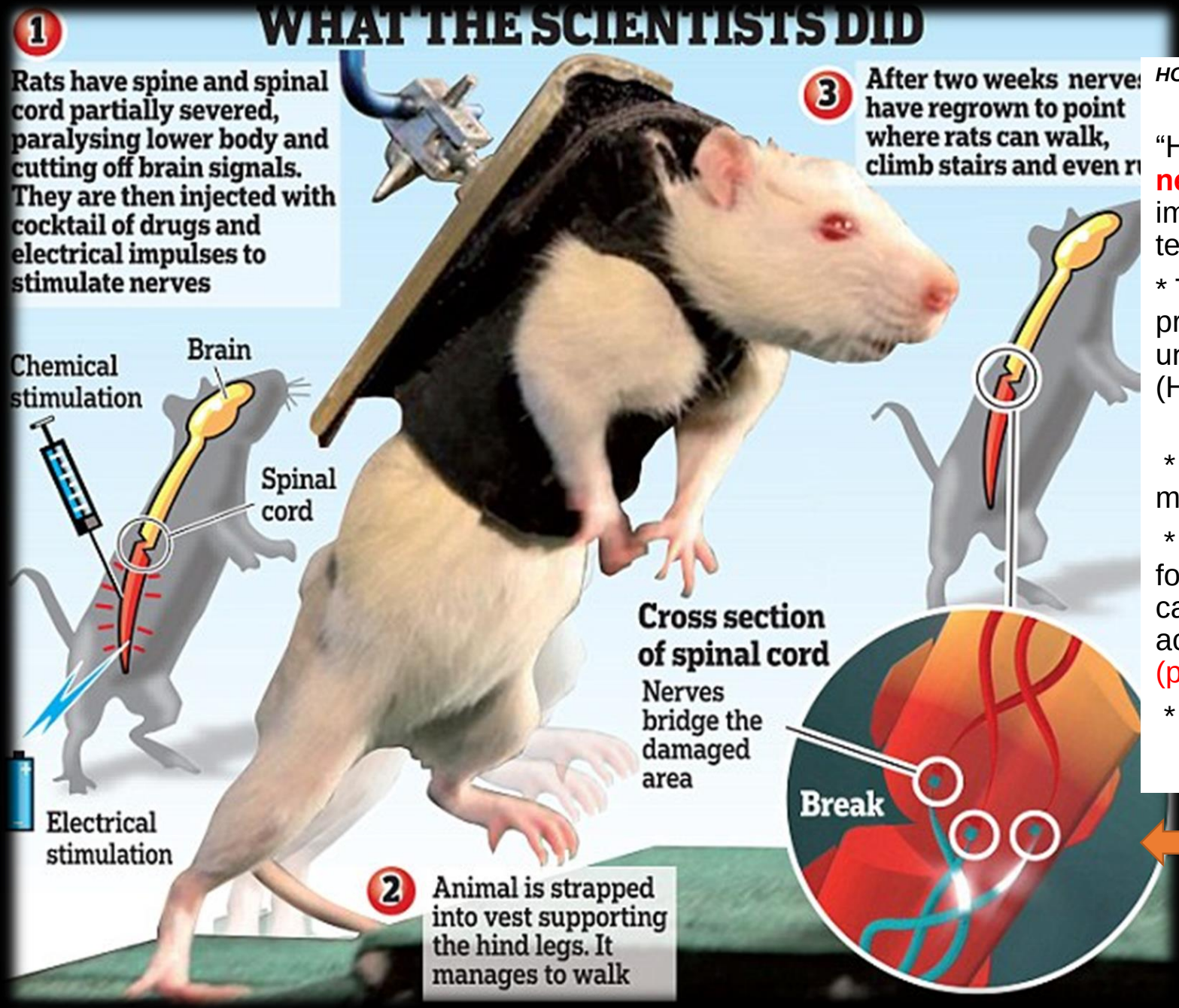
2008, DO WHEEL CHAIRS INHIBIT RECOVERY

MALADAPTIVE PLASTICITY

National Neurotrauma Society Symposium in Orlando, Florida

* NewScientist Aug 2008 - INJURED rats strapped to tiny "wheelchairs" that restrict their movements recovered less limb function and coordination than those left to fend for themselves. This might mean that people with a spinal cord injury would recover better if they were encouraged to use their limbs sooner after injury and relied less on wheelchairs.



HOOPER 2005

"Hyperbaric Oxygen Therapy creates a **'fertile neurovascular platform'** for emerging stem cell, immunotherapies and nanotechnology techniques.

* The impact and success of these and future procedures are dependent on the integrity of the underlying supporting neurovascular bed." (Hooper 2005).

* HBO acts as a 'catalyst' promoting immune modulation

* HBO results in increased blood flow by fostering the formation of existing and new capillary dynamics (neovascularization) activating damaged and dormant nerve cells (penumbra state)

* HBO accelerates neuroplasticity

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NANOPARTICLE BIOSCAFFOLDING

Regeneration strategies after the adult mammalian central nervous system injury—biomaterials

Yudan Gao, Zhaoyang Yang ✉, Xiaoguang Li ✉

Regenerative Biomaterials, Volume 3, Issue 2, 1 June 2016, Pages 115–122,

Mater Sci Eng C Mater Biol Appl. 2017 Feb 1;71:1122-1134. doi: 10.1016/j.msec.2016.11.100. Epub 2016 Nov 26.

Investigation of cell adhesion in chitosan membranes for peripheral nerve regeneration.

Proc Natl Acad Sci U S A. 2018 Jun 12;115(24):E5595-E5604. doi: 10.1073/pnas.1804735115. Epub 2018 May 29.

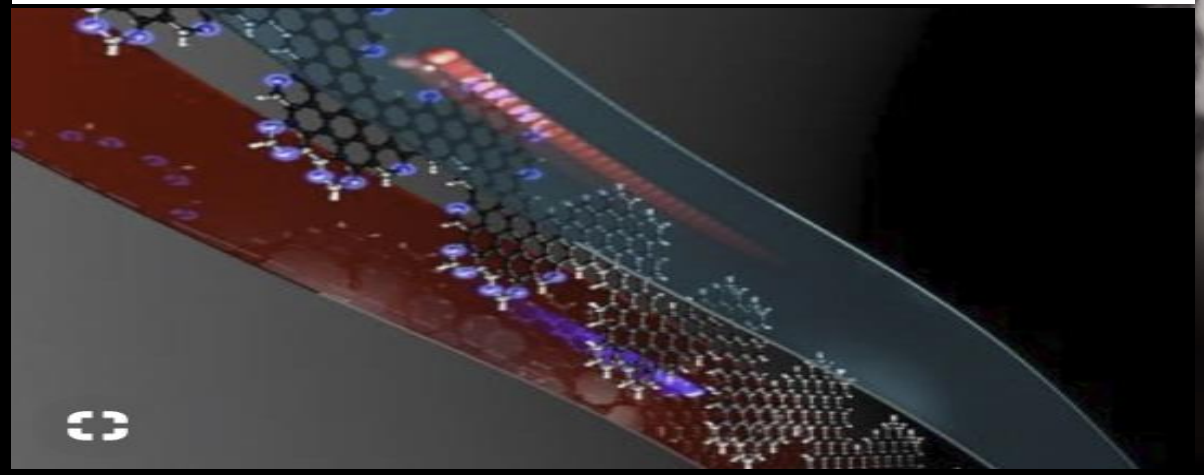
NT3-chitosan enables de novo regeneration and functional recovery in monkeys after spinal cord injury.

Biomaterials. 2017 Sep;138:91-107. doi: 10.1016/j.biomaterials.2017.05.024. Epub 2017 May 19.

Physical chitosan microhydrogels as scaffolds for spinal cord injury restoration and axon regeneration.

Neural Regen Res. 2018 Jul;13(7):1231-1240. doi: 10.4103/1673-5374.235061.

A partition-type tubular scaffold loaded with PDGF-releasing microspheres for spinal cord repair facilitates the directional migration and growth of cells.



FUNCTIONAL REHABILITATION

BODY WEIGHT SUPPORT TREADMILL TRAINING

* Two or more physical therapists manually move the patient's legs in a walking pattern. However, the labour-intensive, strenuous nature and variability of the manual method can limit the frequency, quality and duration of the therapy.

ROBOTIC EXOSKELETON ASSISTIVE TECHNOLOGIES

* The patient is suspended in a harness over a treadmill and the exoskeleton frame of the robot, attached to the outside of the legs, moves the legs in a natural walking pattern.

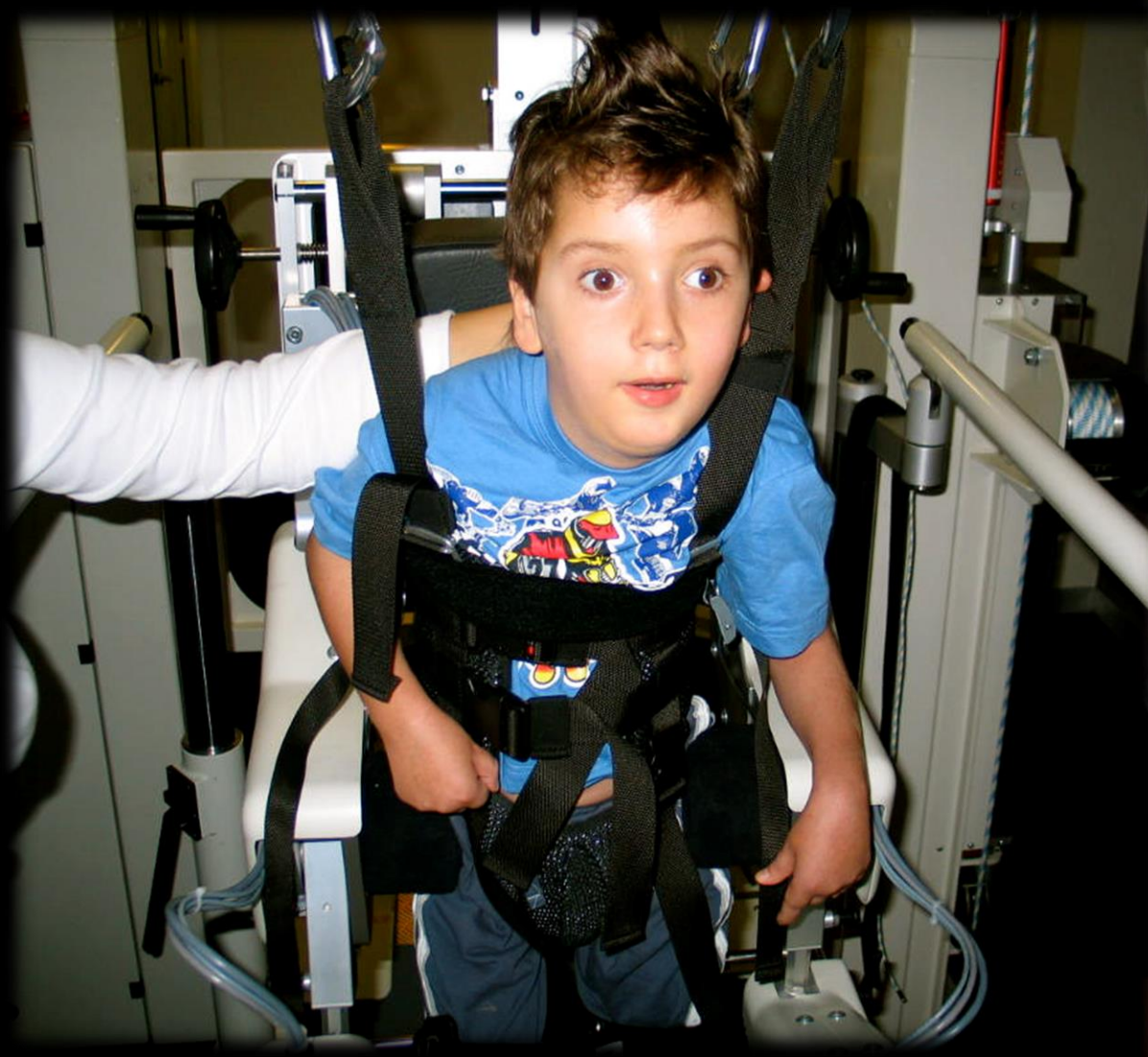
* Neuroplasticity mechanisms work on the basis that by controlling the repetitive walking pattern we can help the brain and spinal cord work together to re-route signals that were interrupted by injury or illness.

* Robotics assisted walking helps to strengthen muscles and improve circulation.

* The robotic device does the heavy work - pattern and pace are consistent and the exercise can be sustained over longer training time.

* Typically patients undertake 3-5 sessions per week for 30-60 minutes durations over 8-12 weeks initially.

ROBOTICS PROMOTES ACTIVITY BASED REORGANISATION



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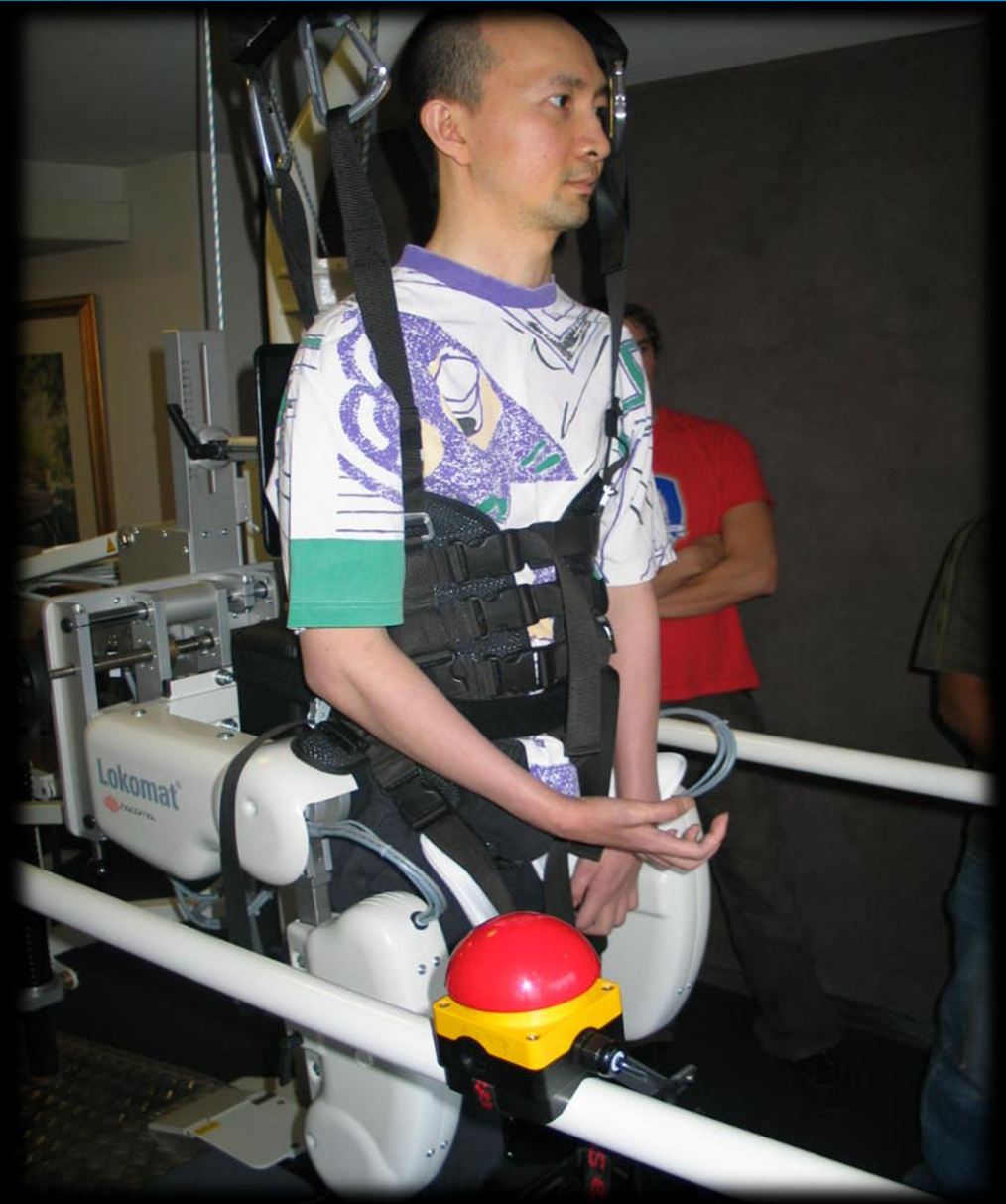
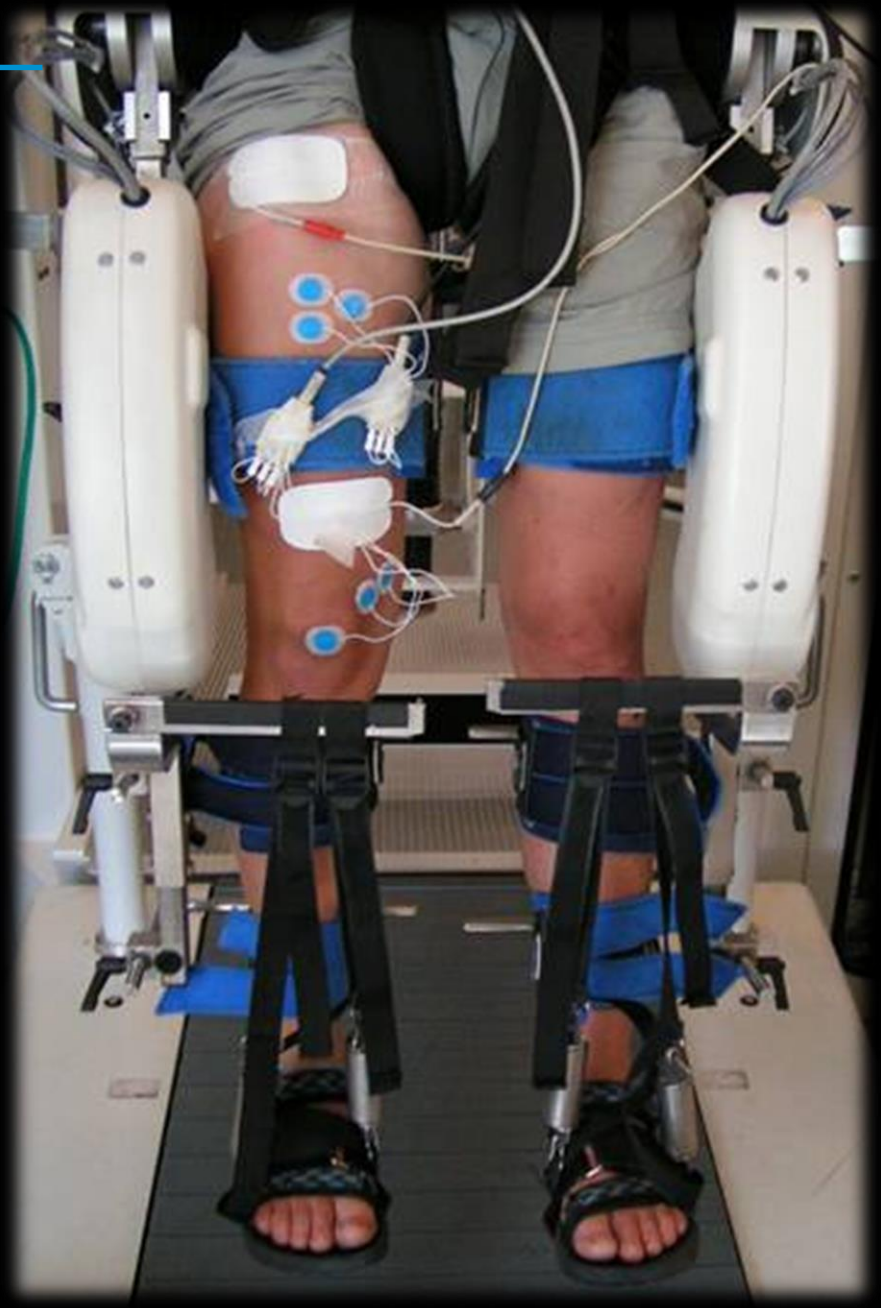
EXOSKELETON NEURAL PRIMING





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CLONUS VS PERONEAL NERVE SWING PHASE STIMULATION

Front Neurosci. 2018 Jun 1;12:374. doi: 10.3389/fnins.2018.00374. eCollection 2018.

Supplemental Stimulation Improves Swing Phase Kinematics During Exoskeleton Assisted Gait of SCI Subjects With Severe Muscle Spasticity.

Ekelem A[1], Goldfarb M[1].

Author information

Abstract

Spasticity is a common comorbidity associated with spinal cord injury (SCI). Robotic exoskeletons have recently emerged to facilitate legged mobility in people with motor complete SCI. Involuntary muscle activity attributed to spasticity, however, can prevent such individuals from using an exoskeleton. Specifically, although most exoskeleton technologies can accommodate low to moderate spasticity, the presence of moderate to severe spasticity can significantly impair gait kinematics when using an exoskeleton. In an effort to potentially enable individuals with moderate to severe spasticity to use exoskeletons more effectively, this study investigates the use of common peroneal stimulation in conjunction with exoskeleton gait assistance. The electrical stimulation is timed with the exoskeleton swing phase, and is intended to acutely suppress extensor spasticity through recruitment of the flexion withdrawal reflex (i.e., while the stimulation is activated) to enable improved exoskeletal walking. In order to examine the potential efficacy of this approach, two SCI subjects with severe extensor spasticity (i.e., modified Ashworth ratings of three to four) walked in an exoskeleton with and without supplemental stimulation while knee and hip motion was measured during swing phase. Stimulation was alternated on and off every ten steps to eliminate transient therapeutic effects, enabling the acute effects of stimulation to be isolated. These experiments indicated that common peroneal stimulation on average increased peak hip flexion during the swing phase of walking by 21.1° (236%) and peak knee flexion by 14.4° (56%). Additionally, use of the stimulation decreased the swing phase RMS motor current by 228 mA (15%) at the hip motors and 734 mA (38%) at the knee motors, indicating improved kinematics were achieved with reduced effort from the exoskeleton. Walking with the exoskeleton did not have a significant effect on modified Ashworth scores, indicating the common peroneal stimulation has only acute effects on suppressing extensor tone and aiding flexion. This preliminary data indicates that such supplemental stimulation may be used to improve the quality of movement provided by exoskeletons for persons with severe extensor spasticity in the lower limb.

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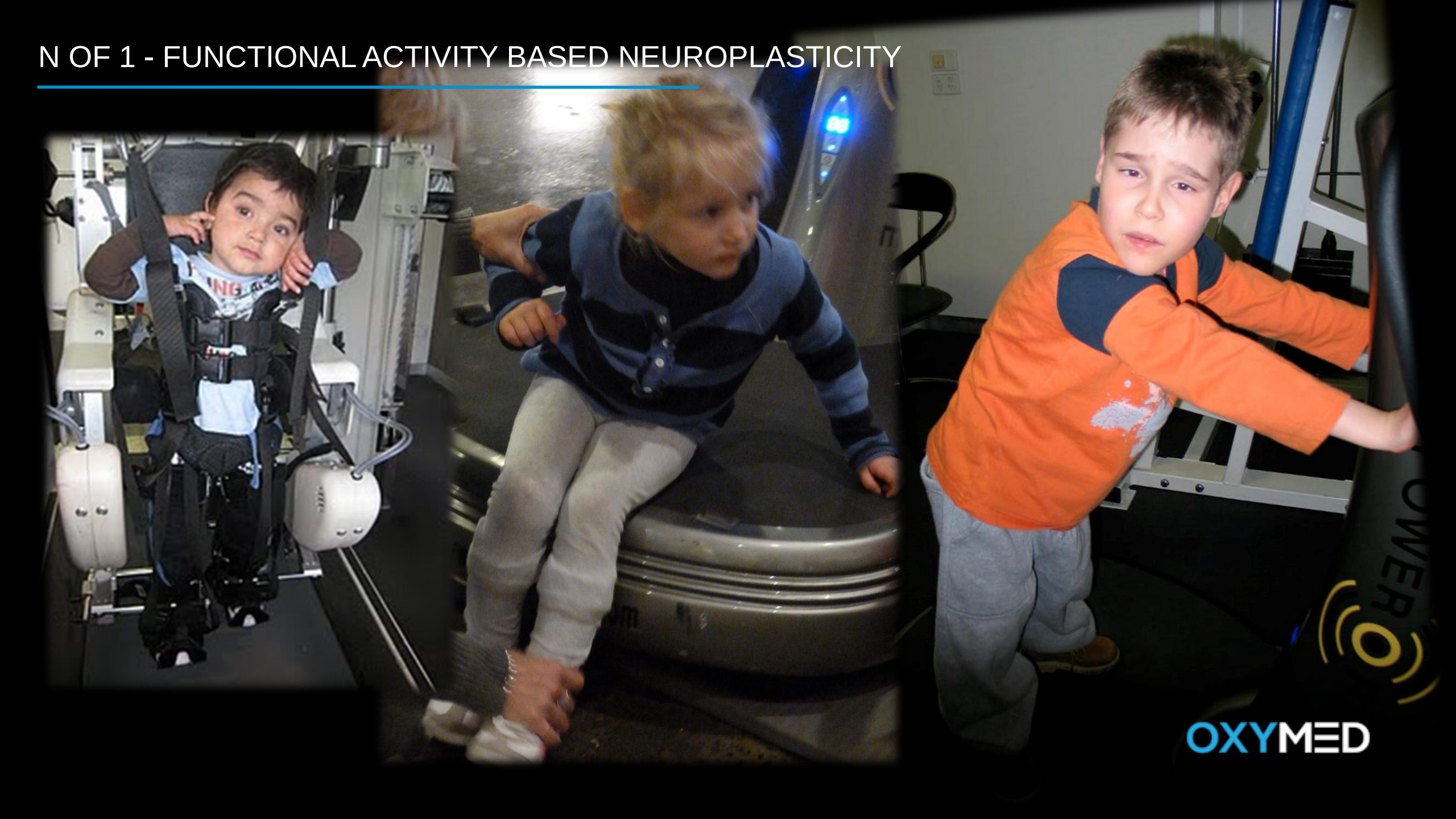
N OF 1 - FUNCTIONAL ACTIVITY BASED NEUROPLASTICITY



EMERGING NEURORECOVERY GYMNASIUMS

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SPASTICITY VS WHOLE BODY VIBRATION

Clin Rehabil. 2017 Jan;31(1):23-33. doi: 10.1177/0269215515621117. Epub 2016 Jul 11.

Effects of whole body vibration on muscle spasticity for people with central nervous system disorders: a systematic review.

Huang M[1], Liao LR[1,2], Pang MY[1].

Author information

Abstract

OBJECTIVES: To examine the effects of whole-body vibration on spasticity among people with central nervous system disorders.

METHODS: Electronic searches were conducted using CINAHL, Cochrane Library, MEDLINE, Physiotherapy Evidence Database, PubMed, PsycINFO, SPORTDiscus and Scopus to identify randomized controlled trials that investigated the effect of whole-body vibration on spasticity among people with central nervous system disorders (last search in August 2015). The methodological quality and level of evidence were rated using the PEDro scale and guidelines set by the Oxford Centre for Evidence-Based Medicine.

RESULTS: Nine trials with totally 266 subjects (three in cerebral palsy, one in multiple sclerosis, one in spinocerebellar ataxia, and four in stroke) fulfilled all selection criteria. One study was level 1b (PEDro$\geqslant$6 and sample size>50) and eight were level 2b (PEDro<6 or sample size $\leqslant$50). All three cerebral palsy trials (level 2b) reported some beneficial effects of whole-body vibration on reducing leg muscle spasticity. Otherwise, the results revealed no consistent benefits on spasticity in other neurological conditions studied. There is little evidence that change in spasticity was related to change in functional performance. The optimal protocol could not be identified. Many reviewed studies were limited by weak methodological and reporting quality. Adverse events were minor and rare.

CONCLUSION: Whole-body vibration may be useful in reducing leg muscle spasticity in cerebral palsy but this needs to be verified by future high quality trials. There is insufficient evidence to support or refute the notion that whole-body vibration can reduce spasticity in stroke, spinocerebellar ataxia or multiple sclerosis.

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WBV CEREBRAL PALSY VS JOINT POSITION, BALANCE, JOINT SENSE

Physiother Can. 2016;68(2):99-105.

Effects of Three Weeks of Whole-Body Vibration Training on Joint-Position Sense, Balance, and Gait in Children with Cerebral Palsy: A Randomized Controlled Study.

Ko MS[1], Sim YJ[2], Kim DH[3], Jeon HS[4].

Author information

Abstract in **English**, French

Purpose : To observe the effects of whole-body vibration (WBV) training in conjunction with conventional physical therapy (PT) on joint-position sense (JPS), balance, and gait in children with cerebral palsy (CP). ***Methods:*** In this randomized controlled study, 24 children with CP were randomly selected either to continue their conventional PT or to receive WBV in conjunction with their conventional PT programme. Exposure to the intervention was intermittent (3 min WBV, 3 min rest) for 20 minutes, twice weekly for 3 weeks. JPS, balance, and gait were evaluated before and after treatment. ***Results:*** Ankle JPS was improved after 3 weeks of WBV training (p=0.014). Participants in the WBV group showed greater improvements in speed ($F_{1,21}$=5.221, p=0.035) and step width ($F_{1,21}$=4.487, p=0.039) than participants in the conventional PT group. ***Conclusion:*** Three weeks of WBV training was effective in improving ankle JPS and gait variables in children with

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WBV VS BONE DENSITY, MUSCLE MASS

Sci Rep. 2016 Mar 3;6:22518. doi: 10.1038/srep22518.

Effects of whole-body vibration training on physical function, bone and muscle mass in adolescents and young adults with cerebral palsy.

Gusso S[1], Munns CF[2], Colle P[1], Derraik JG[1], Biggs JB[1], Cutfield WS[1], Hofman PL[1].

Author information

Abstract

We performed a clinical trial on the effects of whole-body vibration training (WBVT) on muscle function and bone health of adolescents and young adults with cerebral palsy. Forty participants (11.3-20.8 years) with mild to moderate cerebral palsy (GMFCS II-III) underwent 20-week WBVT on a vibration plate for 9 minutes/day 4 times/week at 20 Hz (without controls). Assessments included 6-minute walk test, whole-body DXA, lower leg pQCT scans, and muscle function (force plate). Twenty weeks of WBVT were associated with increased lean mass in the total body (+770 g; p = 0.0003), trunk (+410 g; p = 0.004), and lower limbs (+240 g; p = 0.012). Bone mineral content increased in total body (+48 g; p = 0.0001), lumbar spine (+2.7 g; p = 0.0003), and lower limbs (+13 g; p < 0.0001). Similarly, bone mineral density increased in total body (+0.008 g/cm(2); p = 0.013), lumbar spine (+0.014 g/cm(2); p = 0.003), and lower limbs (+0.023 g/cm(2); p < 0.0001). Participants reduced the time taken to perform the chair test, and improved the distance walked in the 6-minute walk test by 11% and 35% for those with GMFCS II and III, respectively. WBVT was associated with increases in muscle mass and bone mass and density, and improved mobility of adolescents and young adults with cerebral palsy.

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WBV STROKE VS SITTING, BALANCE, TRUNK CONTROL

Top Stroke Rehabil. 2017 Mar 23:1-6. doi: 10.1080/10749357.2017.1305655. [Epub ahead of print]

The effect of a whole-body vibration therapy on the sitting balance of subacute stroke patients: a randomized controlled trial.

Lee JH[1], Kim SB[1], Lee KW[1], Lee SJ[1], Park H[2], Kim DW[1].

Author information

Abstract

BACKGROUND: The use of a whole-body vibration (WBV) therapy has recently been applied and investigated as a rehabilitation method for subacute stroke patients.

OBJECTIVE: To evaluate the effects of a WBV therapy on recovery of balance in subacute stroke patients who were unable to gain sitting balance.

METHODS: The conventional rehabilitation group (CG) received conventional physical therapy, including sitting balance training by a physical therapist, for 30 min a one session, for twice a day for five days a week for two weeks. The whole-body vibration group (VG) received one session of conventional physical therapy, and received WBV therapy instead of conventional physical therapy for 30 min a day for five days a week for two weeks.

RESULTS: There were 15 patients in the CG and 15 patients in the VG who completed the two-week therapy. After the two-week therapy, both groups showed functional improvement. Patients in the VG improved functional ambulation categories, Berg balance scale, trunk impairment scale scores. But, no statistically significant correlations between the therapeutic methods and outcomes were observed in either group.

CONCLUSION: Our results suggest that WBV therapy led to improvement of the recovery in balance recovery for subacute stroke patients. Because the WBV therapy was as effective as conventional physical therapy, we can consider a WBV therapy as a clinical method to improve the sitting balance of subacute stoke patients.

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CONTRACTURES, SPASTICITY – MUSCLE SATELLITE STEM CELLS

J Orthop Res. 2015 Jul;33(7):1039-45. doi: 10.1002/jor.22860. Epub 2015 Apr 10.

Reduced satellite cell number in situ in muscular contractures from children with cerebral palsy.

Dayanidhi S[1,2], Dykstra PB[1], Lyubasyuk V[1], McKay BR[3], Chambers HG[1,4], Lieber RL[1,2,5].

Children with cerebral palsy suffer **impaired muscular growth and contractures**.

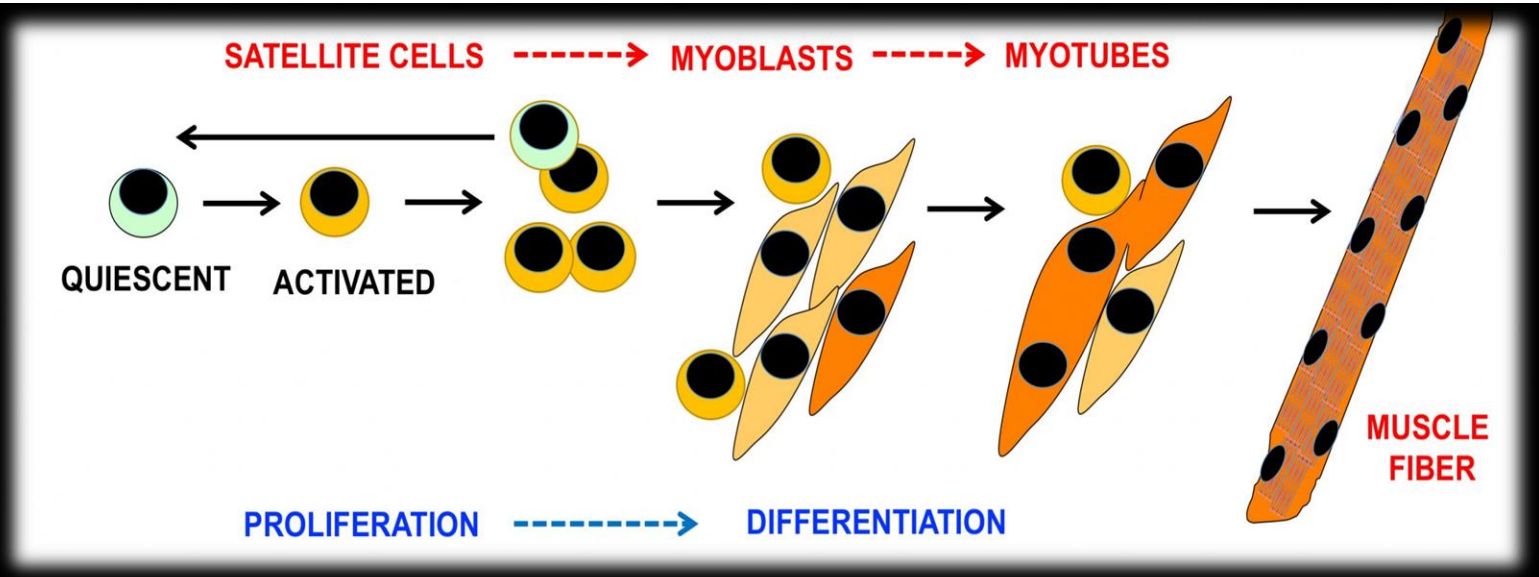
Satellite cells are muscle stem cells critical for **post-natal growth, regeneration and repair** of skeletal muscles.

Conclusion:

Loss of satellite stem cells results in **increase in collagen deposition causing muscle stiffness** - a result of non-use.

* Children with spastic CP have a **reduced number of satellite stem cells**.

Reduced satellite stem cells results in impaired muscle growth and a decreased responsiveness of CP muscle to exercise.



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HBOT INCREASES MUSCLE SATELLITE CELL DIFFERENTIATION

J Appl Physiol (1985). 2014 Jan 15;116(2):149-55. doi: 10.1152/japplphysiol.00235.2013. Epub 2013 Dec 12.

Enhancement of satellite cell differentiation and functional recovery in injured skeletal muscle by hyperbaric oxygen treatment.

Horie M[1], Enomoto M, Shimoda M, Okawa A, Miyakawa S, Yagishita K.

Abstract:

The use of hyperbaric oxygen (HBO) treatments by elite athletes to accelerate recovery from muscle injuries has become increasingly popular.

Study: Rats were placed in an animal chamber with 100% oxygen under 2.5 atmospheres absolute for 2 h/day, 5 days/wk. for 2 wk.

Results:

* **The cross-sectional areas and maximum force-producing capacity** of the regenerating muscle fibers were increased by HBO treatment after injury.

* The mRNA expression of MyoD, myogenin, and IGF-1 increased significantly in the HBO group at 3 and 5 days after injury. The number of Pax7(+)/MyoD(+), Pax7(-)/MyoD(+), and Pax7(+)/BrdU(+) positive nuclei was increased by HBO treatment.

Conclusion:

* HBO treatment **accelerated satellite cell proliferation and myofiber maturation** in rat muscle.

* HBO treatment **accelerates healing and functional recovery** after muscle injury.

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SPECT HYPOPERFUSION CEREBRAL PALSY

Int J Clin Exp Med. 2015 Jan 15;8(1):1101-7. eCollection 2015.

99mTc-ECD brain perfusion SPECT imaging for the assessment of brain perfusion in cerebral palsy (CP) patients with evaluation of the effect of hyperbaric oxygen therapy.

Asl MT[1], Yousefi F[2], Nemati R[2], Assadi M[3].

11 CP patients were enrolled in this study, of which 4 patients underwent oxygen therapy.

Before oxygen therapy and at the end of **40 sessions of oxygen treatment**, SPECT was performed, and the results were compared.

STUDY:

11 CP patients; 7 females and 4 males age range of 5-27 years.

SPECT studies - all the patients showed perfusion impairments.

* The region most significantly involved was **frontal lobe (54.54%), followed by temporal lobe (27.27%), occipital lobe (18.18%), visual cortex (18.18%), basal ganglia (9.09%), parietal lobe (9.09%), and the cerebellum (9.09%).**

* **Frontal-lobe hypoperfusion** was seen in all types of cerebral palsy.

CONCLUSION:

Study demonstrated decreased cerebral perfusion in CP patients.

Two out of 4 patients (2 males and 2 females) who underwent oxygen therapy revealed brain perfusion improvement. **HBOT improved cerebral perfusion**.

Larger study is required to strengthen a link this approach may have some value.

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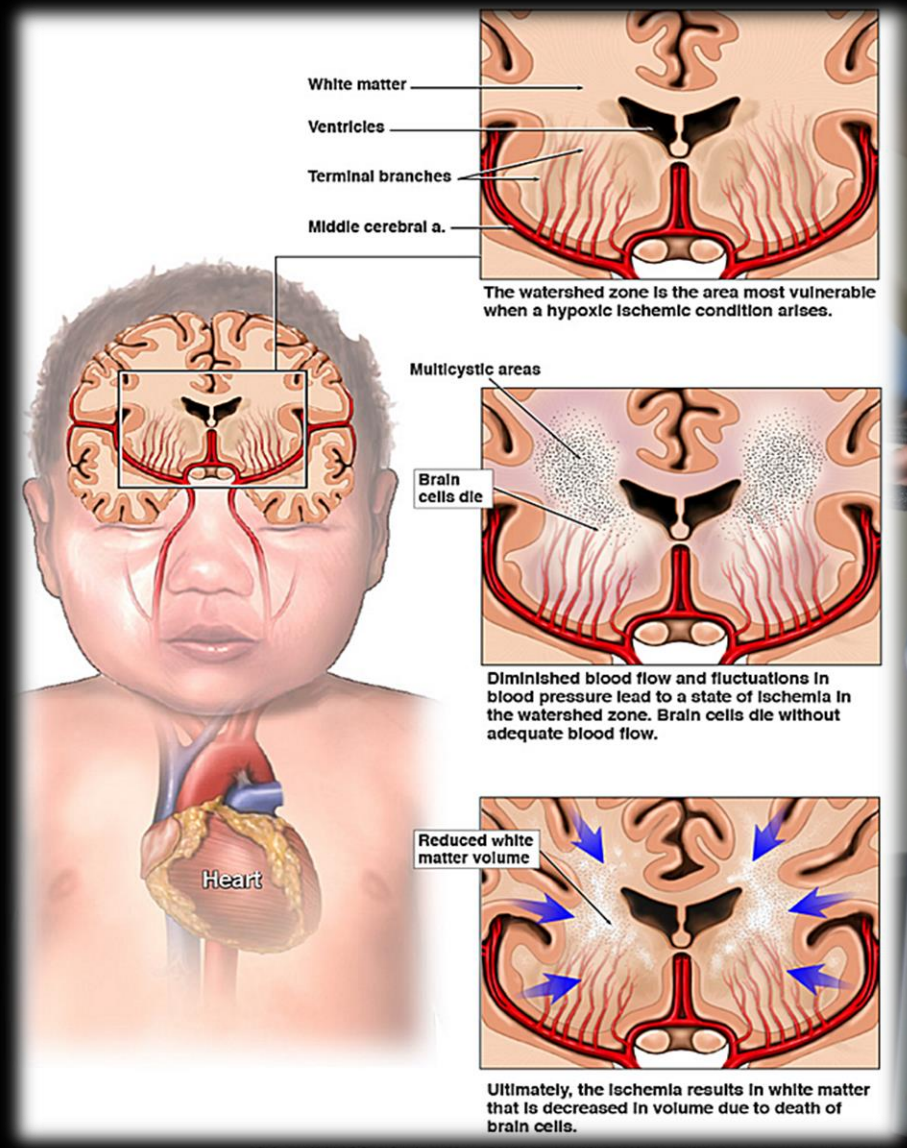
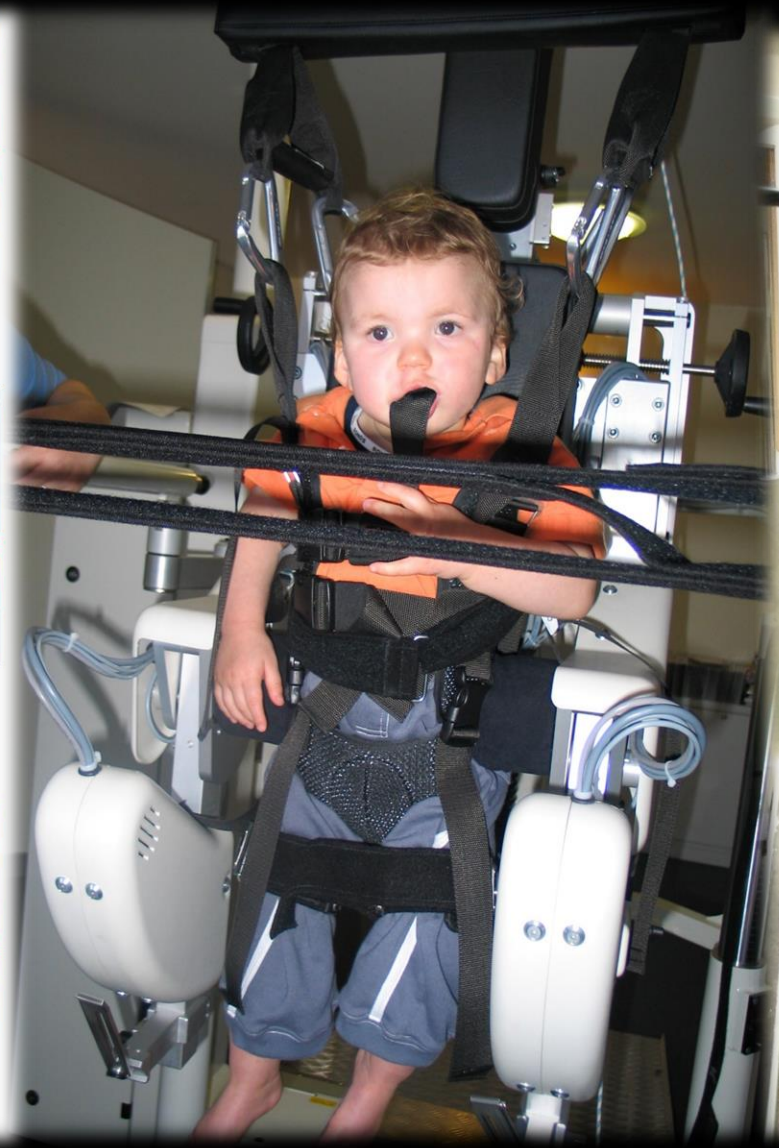
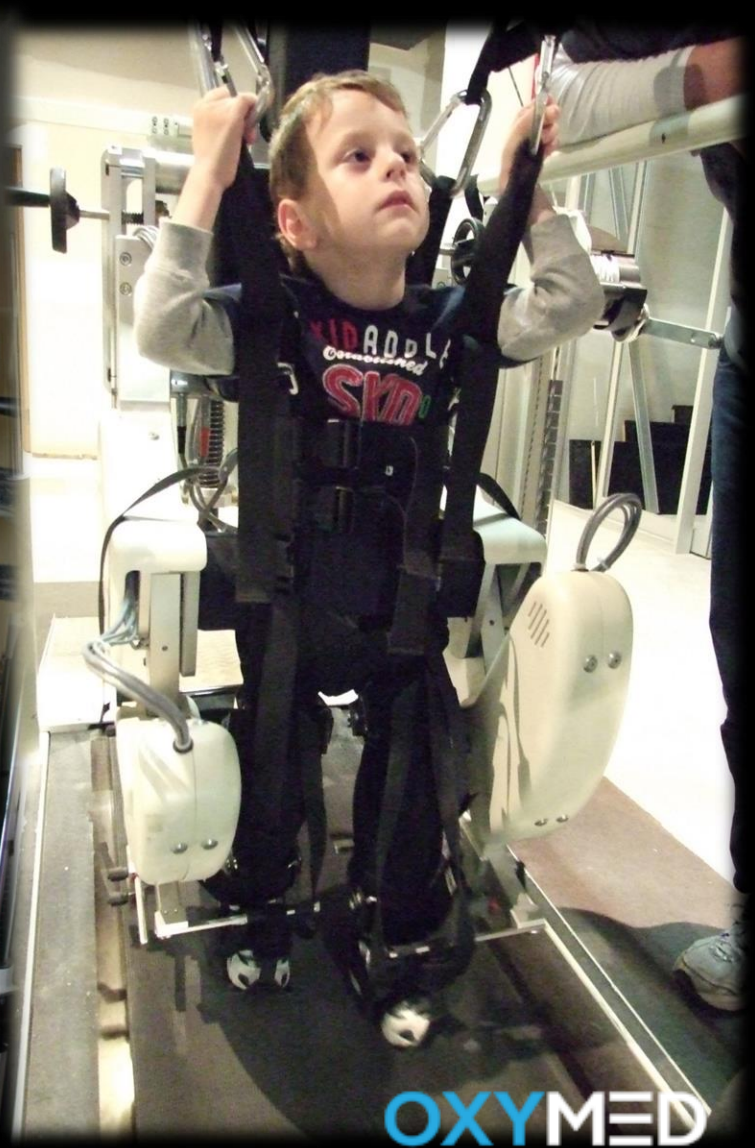
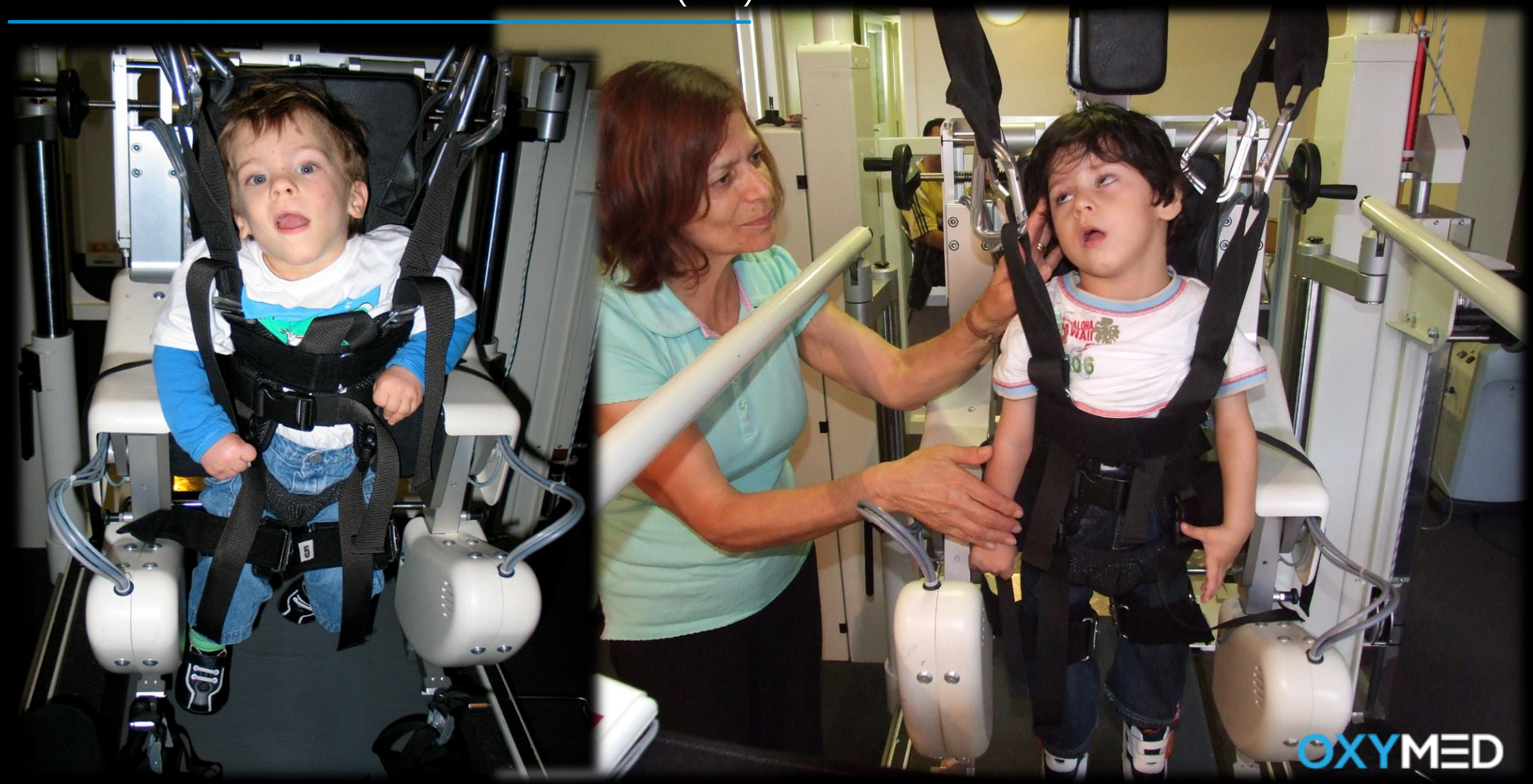
PERIVENTRICULAR LEUKOMALACIA (PVL)







HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE)



MALADAPTIVE PLASTICITY – HYPOXIC ACQUIRED NON USE

LOKOMAT – AUSTRALIAN EXPERIENCE

LOKOMAT Australian Experience: Robotically Gait Assisted Body Weight Support Treadmill Training (BWSTT) – Lokomat Gait Training.

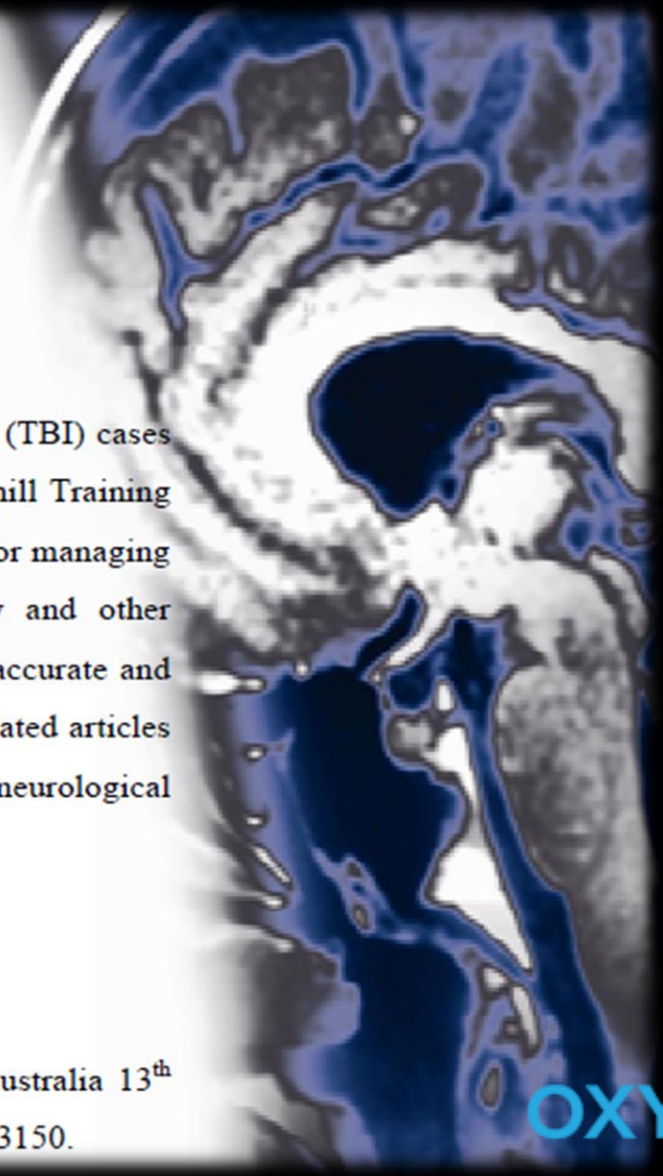
Is it an effective and financially feasible treatment?

HyperMED NeuroRecovery Centre – Melbourne, Australia. M. R. Hooper, T. Chamacham 2008.

Abstract: Growing number of adult and pediatric spinal cord injury (SCI) and traumatic brain injury (TBI) cases each year indicates an increasing need for treatment modalities, like Body Weight-Supported Treadmill Training (BWSTT) to assist functional recovery. In addition to treatment of SCI cases, BWSTT has been used for managing other various neurological diseases such as stroke and multiple sclerosis (MS), cerebral palsy and other neurodegenerative states. Robotically Gait Assisted BWSTT (Lokomat) has been shown to be more accurate and financially feasible, compared to the other BWSTT modalities. In this article, we intend to review related articles and evidence to explain the medical and financial feasibility of using this treatment modality for neurological diseases.

Keywords: locomotion, exoskeleton, locomotor training, bodyweight support, robotics

Corresponding author: Malcolm R. Hooper Director Rehabilitation HyperMED NeuroRecovery Australia 13th floor 15 Collins St Melbourne 3001. Email info@hypermed.com.au T: +61 3 9650 3136 F: +61 3 9650 3150.



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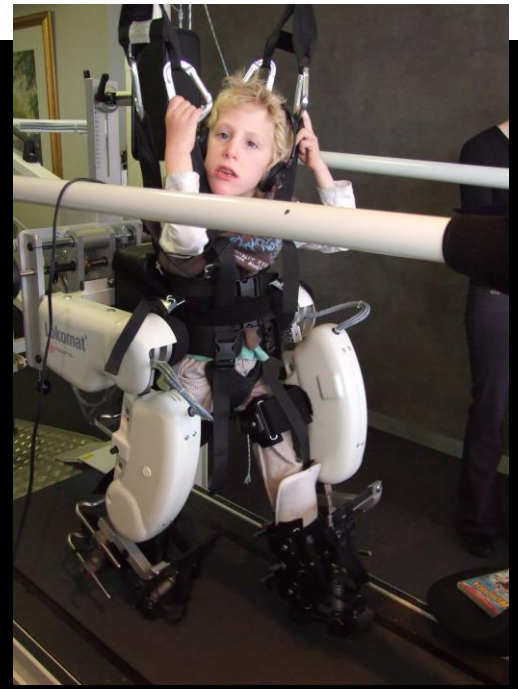
ACQUIRED GAIT DYSFUNCTION

Children with cerebral palsy have an acquired dysfunction which their central nervous system function deems normal. This is evident when CP children undertake an intensive Lokomat Gait Training protocol. Many of these children demonstrate a 'normal gait' whilst on the Lokomat which raises question of acquired neural pathways and motor function wrongly developed and reinforced over time. When these same children come off the Lokomat they immediately return back to the acquired gait. Intensity and repetition enables the CP child to generate a new functionality which resembles a 'normal gait'. It is a frequent finding to observe the bewilderment of both parents and CP child when the child sees themselves 'walking normal' on the Lokomat. Visualization whilst on the Lokomat is an important paradigm shift for not only the CP child and parent but also the therapist.



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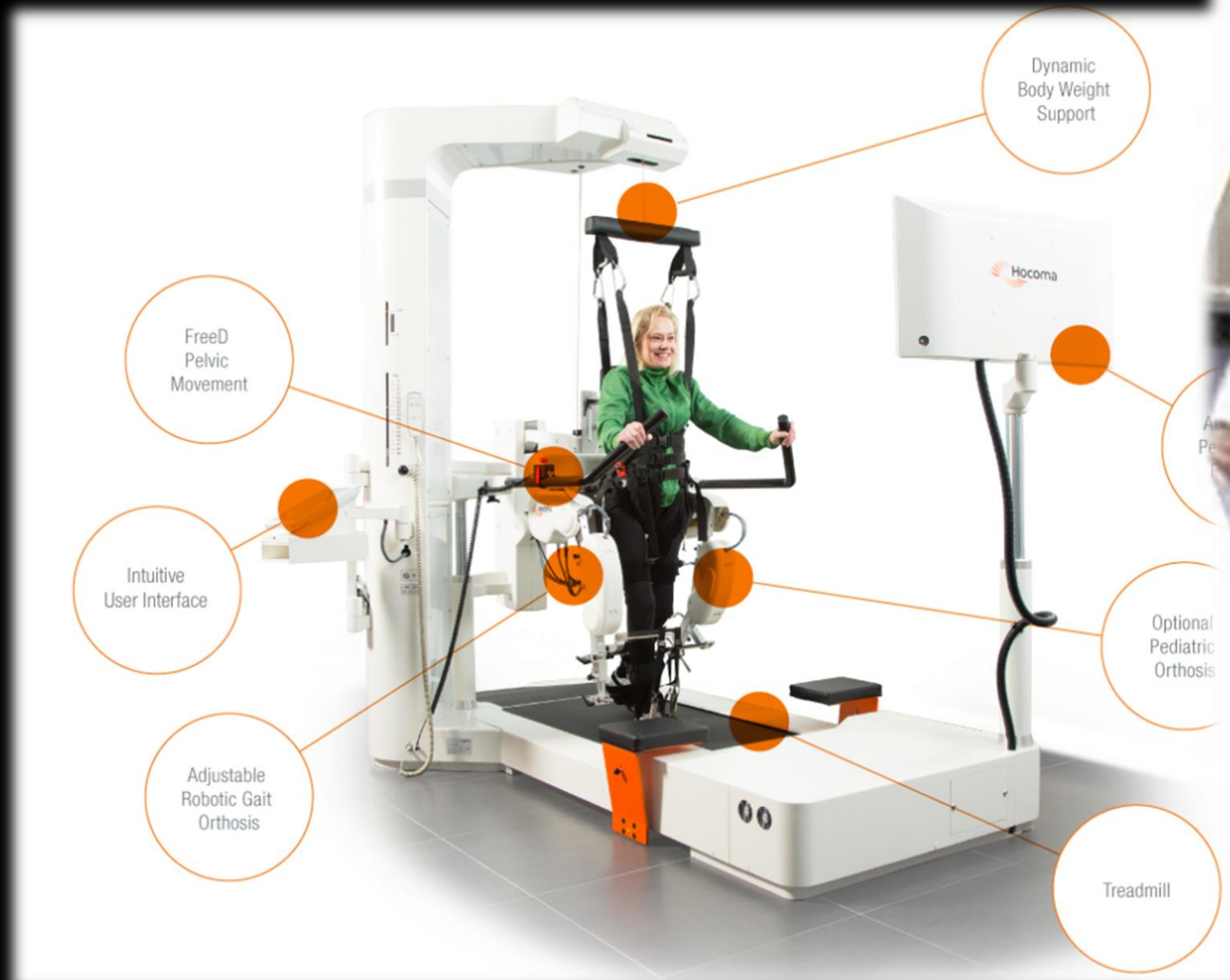
ROBOTIC SETUP - PURPOSEFUL INTENTION



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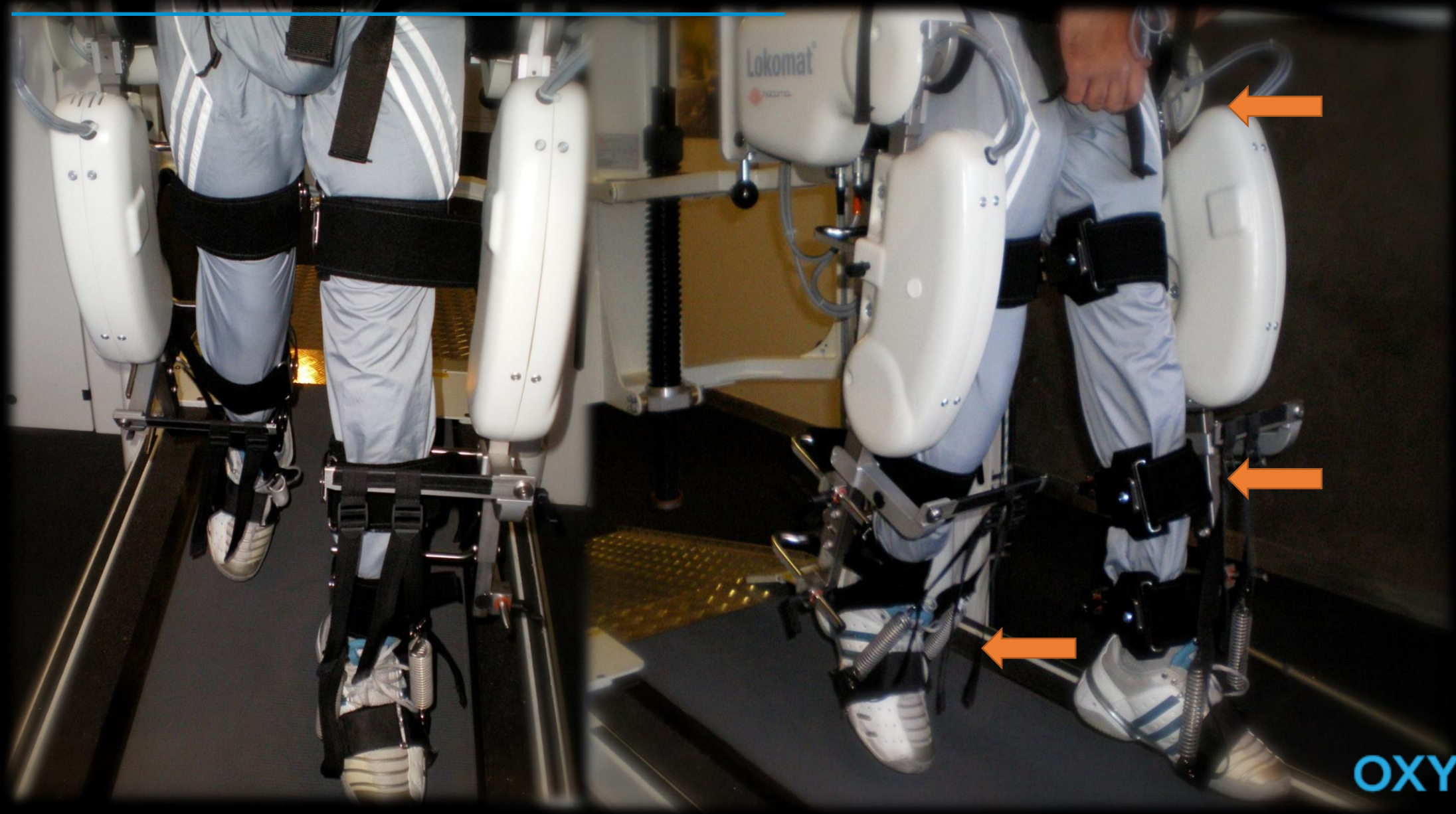
MATCHING THE PATIENT – MAN AND MACHINE



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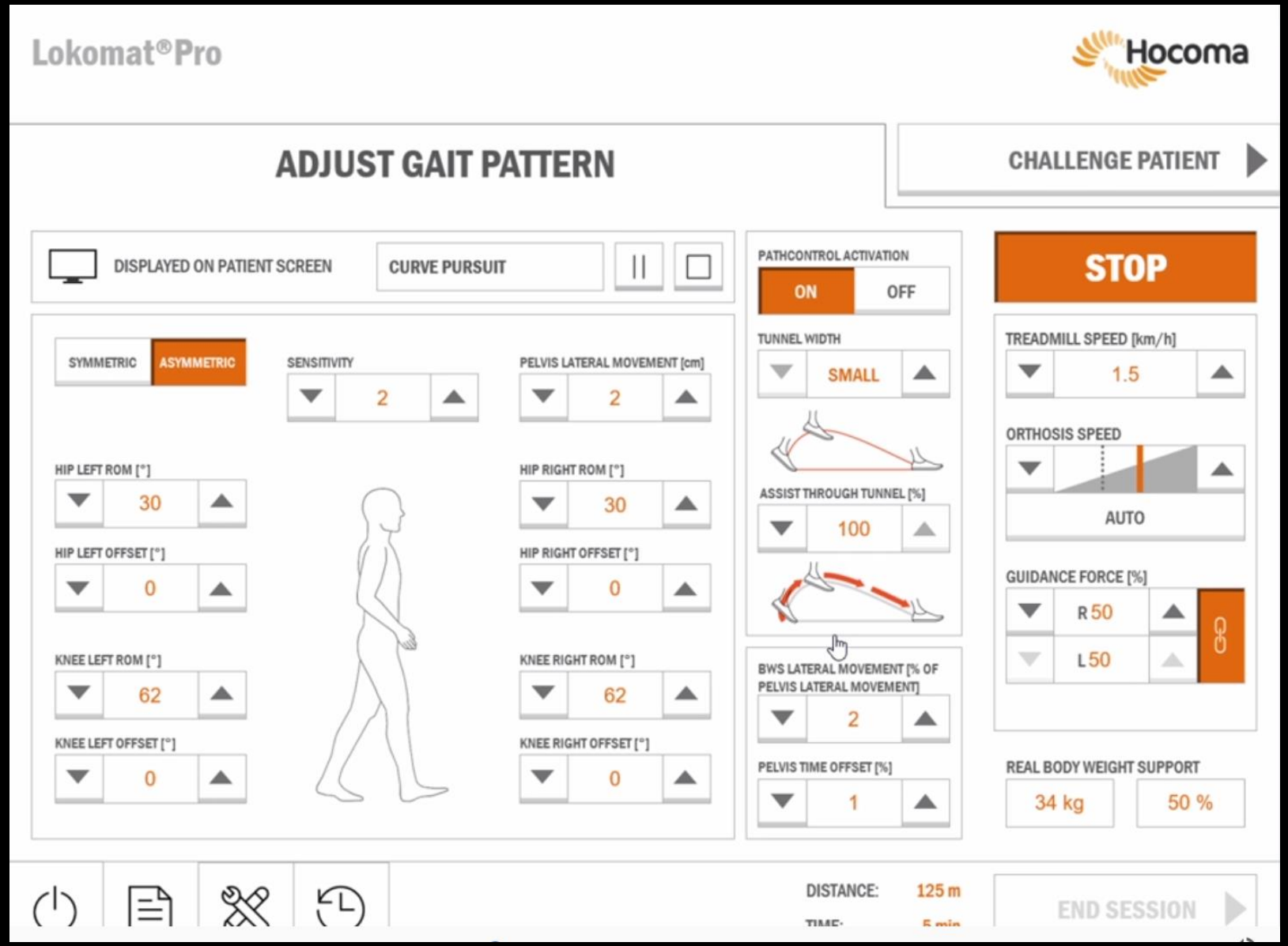
LOKOMAT SEGMENTAL SETTINGS



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UNIQUE PATIENT CHALLENGE PROGRAMS

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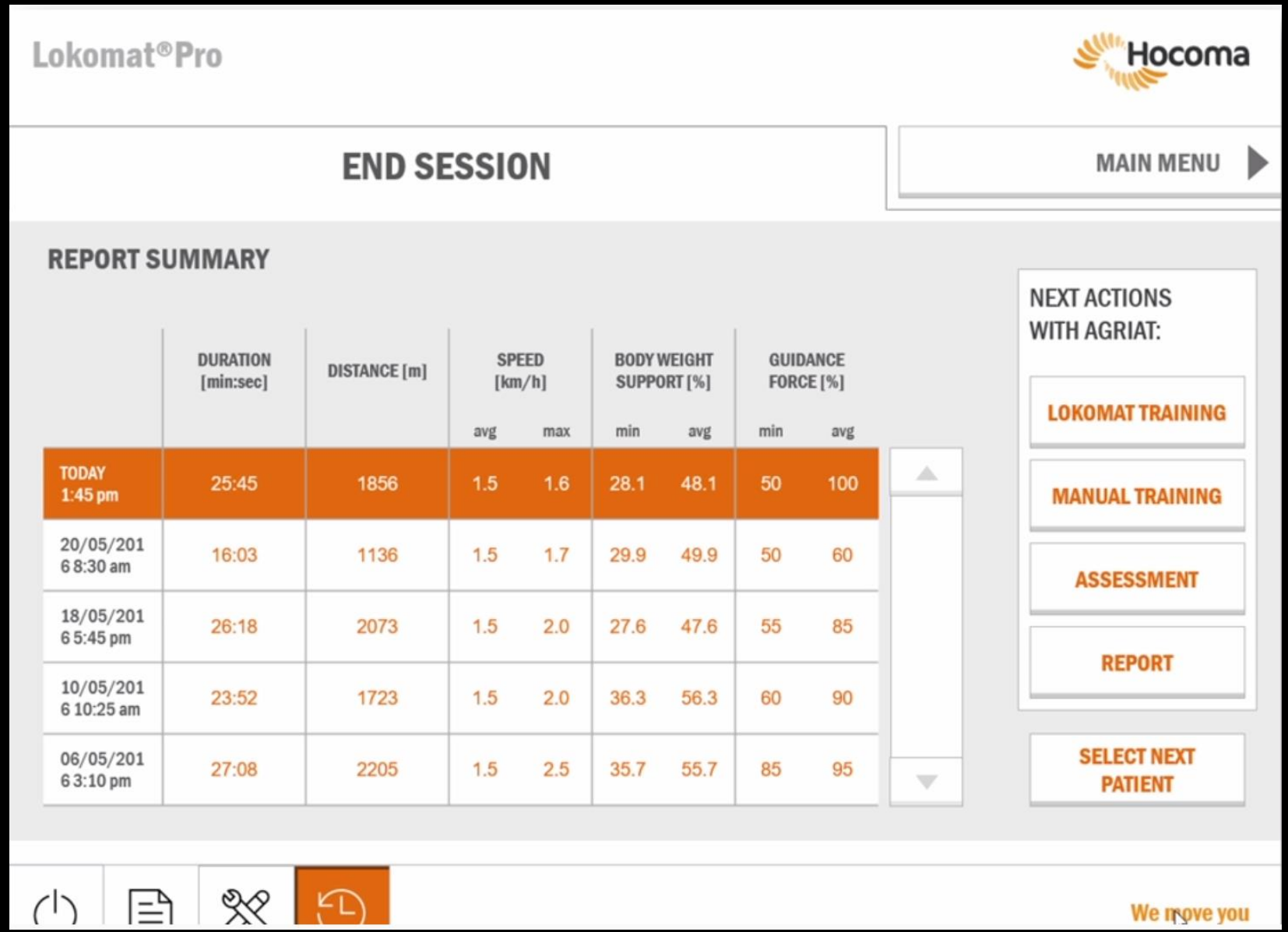
CUSTOMISED TRACKING



	DURATION [min:sec]	DISTANCE [m]	SPEED [km/h]		BODY WEIGHT SUPPORT [%]		GUIDANCE FORCE [%]	
			avg	max	min	avg	min	avg
TODAY 1:45 pm	25:45	1856	1.5	1.6	28.1	48.1	50	100
20/05/2016 8:30 am	16:03	1136	1.5	1.7	29.9	49.9	50	60
18/05/2016 5:45 pm	26:18	2073	1.5	2.0	27.6	47.6	55	85
10/05/2016 10:25 am	23:52	1723	1.5	2.0	36.3	56.3	60	90
06/05/2016 3:10 pm	27:08	2205	1.5	2.5	35.7	55.7	85	95

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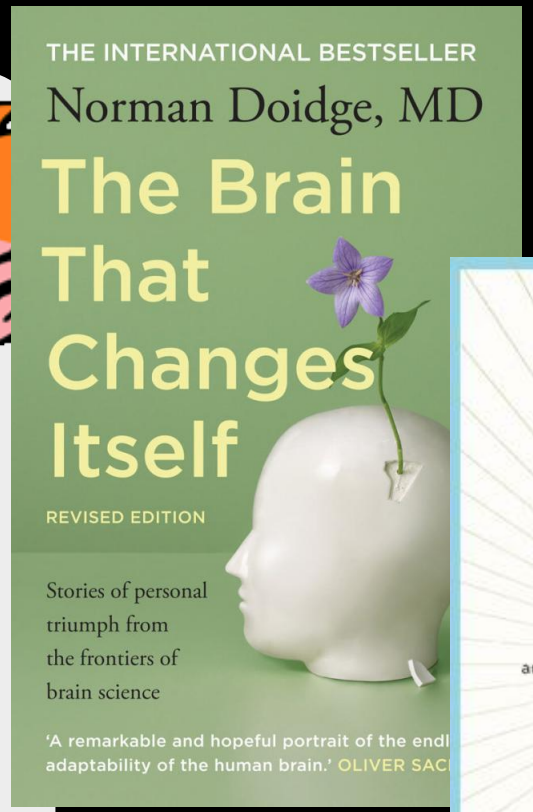
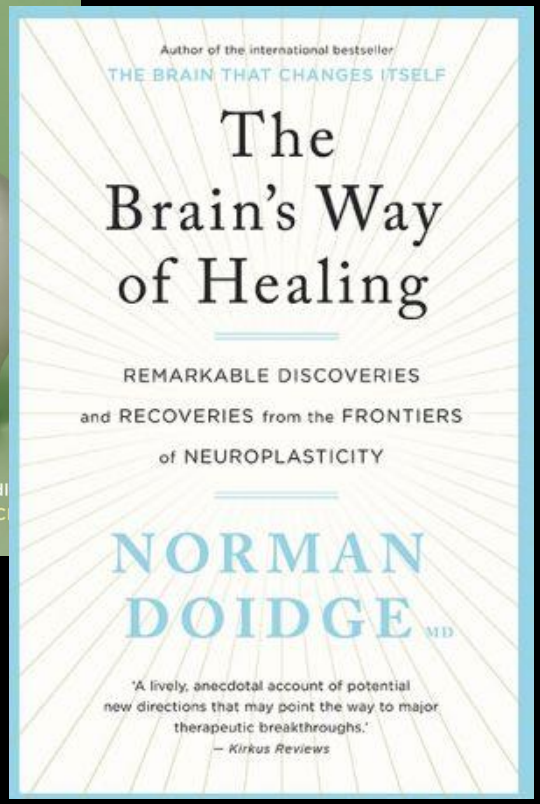
PRACTISE MAKES PERFECT





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CONNECTIVITY – EFFORT PLUS INSPIRATION

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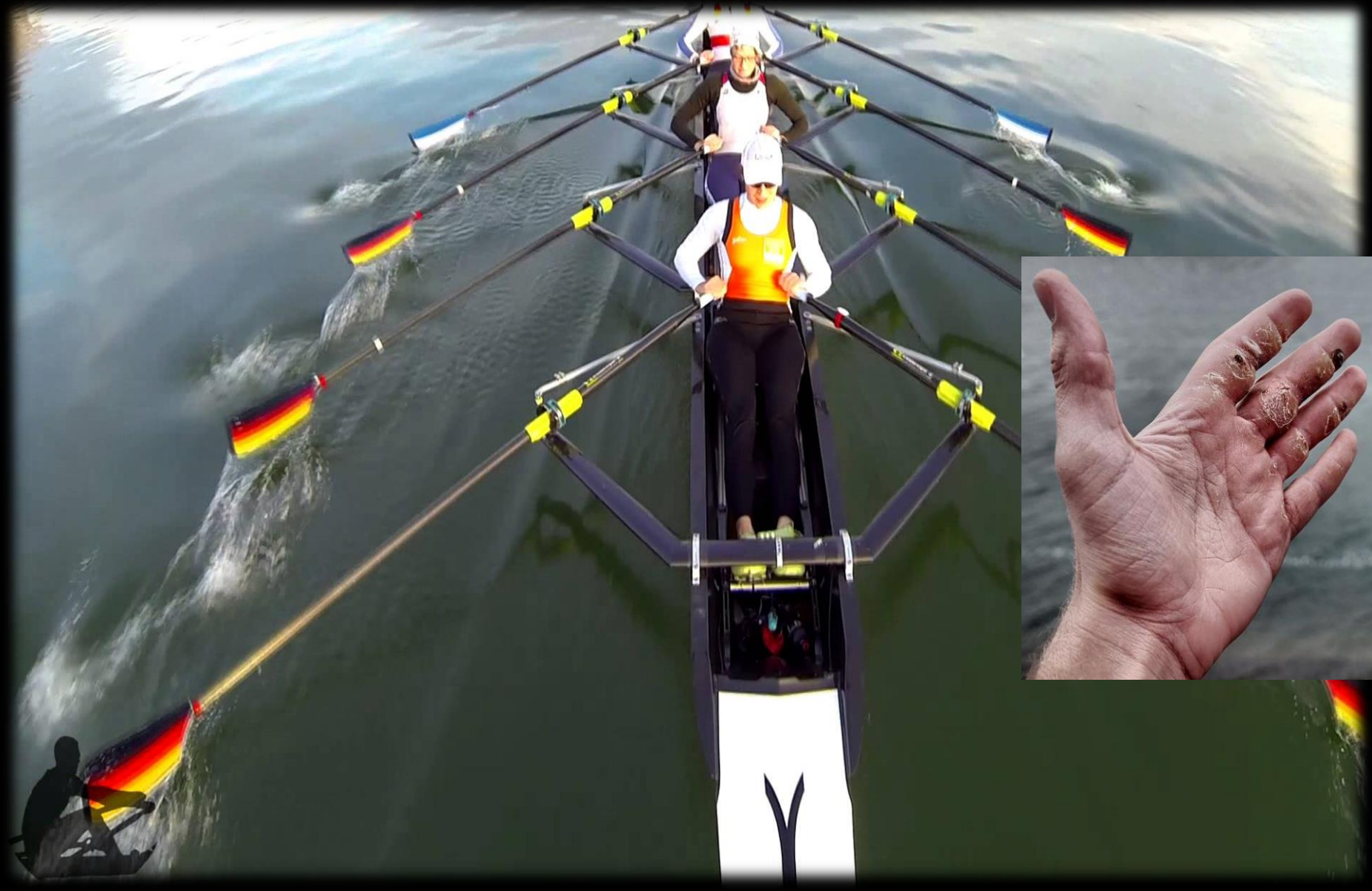
NEUROPLASTICITY RECRUITMENT WITH PURPOSE



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ACTIVITY BASED REHABILITATION

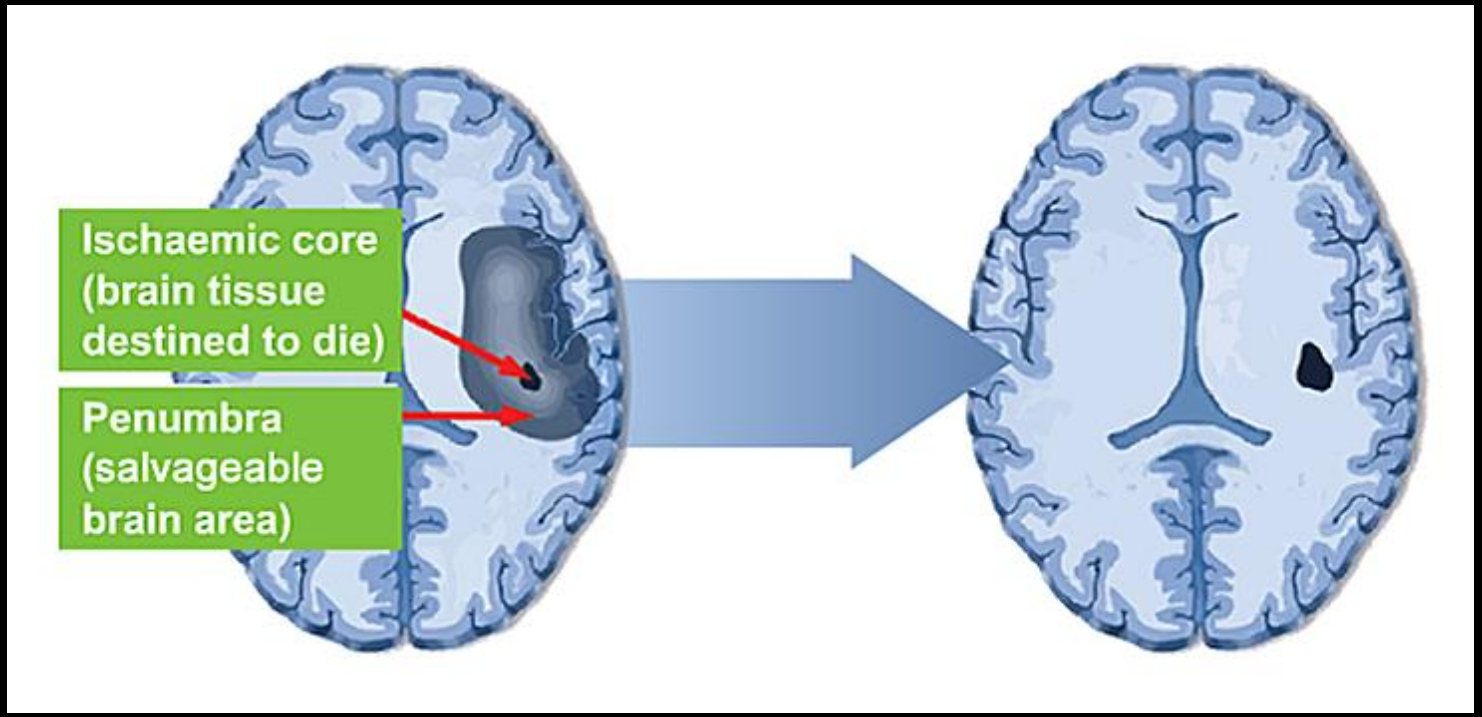
THREE KEY PRINCIPLES OF MOTOR LEARNING

* **Practice -** more functional learning will occur with more accurate practice.

* **Specificity -** the best way to improve performance of a motor task is to execute that specific motor task repeated many times.

* **Effort** - individuals need to maintain a high degree of focus, participation and involvement to facilitate motor learning – not watching “days of our lives” and taking another ‘generic’ tablet.

These principles are critical to promoting activity-dependent plasticity – altering the excitation patterns of neural pathways by activating those pathways. Plasticity occurs in neural pathways that are both active and inactive



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2009, ACTIVITY STIMULATES PLASTICITY & NEUROGENESIS

Dev Disabil Res Rev. 2009;15(2):112-6. doi: 10.1002/ddrr.61.

Activity-based restorative therapies: concepts and applications in spinal cord injury-related neurorehabilitation.

Sadowsky CL[1], McDonald JW.

The field of neurorehabilitation is changing. After years of evidence the old, deep rooted rehabilitative principles of compensation and adaptation are slowly starting to change.

* The adult injured central nervous system is capable of reorganization allowing for significant improvement following injury.

* Reorganization and plasticity occurs: cortical, subcortical, spinal cord, and in the peripheral nervous system.

The repair process is referred to as synaptic plasticity and occurs in pre-existing connections peripheral and central) resulting in sprouting and formation of new connections.

* “Neuroplasticity” refers to the remyelination and new cell birth correcting, restoring, and replacing the damaged nerve cells.

* Neurogenesis reported in adult brain: hippocampus and olfactory system.

* Physical activity stimulates neurogenesis - proliferation of neuronal stem cells.

* Activity reverses decline in neurogenesis associated with aging.

* Exercise activates neighbouring axons and proliferates precursor cells.

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2016, NEURAL PLASTICITY LIFE LONG PROCESS

Cell Mol Life Sci. 2016 Mar;73(5):975-83. doi: 10.1007/s00018-015-2102-0. Epub 2015 Dec 8.

Physical exercise, neuroplasticity, spatial learning and memory.

Cassilhas RC[1,2], Tufik S[3], de Mello MT[4].

NEURONAL PLASTICITY OCCURS THROUGHOUT LIFE

* The hippocampus dentate gyrus is a 'highly plastic region' able to generate new neurons, and can **double or triple in size after physical exercise**.

* Physical exercise induces **hippocampal plasticity** – neurogenesis, cell proliferation and dendritic branching.

*** Brain Derived Neurotrophic Factor** (BDNF) is one of the major modulators of the CNS and brain plasticity. In 1995, Neeper et al. demonstrated that physical exercise **enhanced BDNF gene expression in the hippocampus**.

NEUROTROPHIC FACTORS UP-REGULATED BY PHYSICAL EXERCISE

* **Nerve Growth Factor** (NGF), **Vascular Endothelial Growth Factor** (VEGF), **Fibroblast Growth Factor 2** (FGF-2), **BDNF** and **Insulin Growth Factors** (IGFs).

* **Insulin Growth Factor** (IgF1) - promotes growth, differentiation and cellular survival.

* IgF1 is **upregulated in the hippocampus.** IgF1 has **neurotrophic effects in the CNS** and involved in differentiation, proliferation, synaptic plasticity and neurogenesis. IgF1 is increased in **neurogenesis & cognitive function**.

*** Physical exercise and task specific activity requiring hippocampus-dependent memory expressed** higher circulating levels of IgF1 and BDNF in the hippocampus, cerebellum and spinal cord.

OXYMED

2016, ANGIOGENESIS, LEARNING, MEMORY

Cell Mol Life Sci. 2016 Mar;73(5):975-83. doi: 10.1007/s00018-015-2102-0. Epub 2015 Dec 8.

Physical exercise, neuroplasticity, spatial learning and memory.

Cassilhas RC[1,2], Tufik S[3], de Mello MT[4].

* Physical exercise, similarly to injury, is a compelling stimulant of new vessels (angiogenesis) and endothelial cell proliferation - VEGF.

* **Neurogenesis and plasticity** appear to be mediated by IGF-1, BDNF and VEGF.
* **Resistance training** and aerobic exercise upregulates IGF-1, BDNF and VEGF in the hippocampus and peripheral circulation.

* Using arterial spin labeling MRI in humans, an increase in the was verified in **elderly individuals** exposed to 4 months of aerobic exercise increased cortical hippocampal flow.

* Cerebral blood volume (CBV) in the DG was also increased in young subjects after 3 months of aerobic training.
* Cognitive improvements were also associated with aerobic training and increased cerebral blood volume.

* Physical conditioning **increased the number of small blood vessels** in elderly individuals indicating angiogenesis.
* In contrast **sedentary individuals** displayed increased numbers of vessel tortuosity in both brain hemispheres.

OXYMED

2015, ROBOTIC-R (RESISTANCE) VS OVER GROUND WALKING

JRRD Volume 52, Number 1, 2015
Pages 113–130

Training with robot-applied resistance in people with motor-incomplete spinal cord injury: Pilot study

Tania Lam, PhD;[1–2*] Katherine Pauhl, MSc;[1–2] Amanda Ferguson, BScPT;[3] Raza N. Malik, BKin;[1–2] Andrei Krassioukov, MD, PhD;[2,4–5] Janice J. Eng, PhD[2,5–6]
[1]School of Kinesiology and [2]International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, British Columbia, Canada; [3]NeuroMotion Physical Therapy, Vancouver, British Columbia, Canada; [4]Department of Medicine, Division of Physical Medicine and Rehabilitation, University of British Columbia, Vancouver, British Columbia, Canada; [5]GF Strong Rehabilitation Centre, Vancouver, British Columbia, Canada [6]Department of Physical Therapy, University of British Columbia, Vancouver, British Columbia, Canada

Journal Rehabilitation Research & Development 2015:
Almost half of all people with incomplete spinal cord injury (SCI) have some voluntary motor function below the level of injury. People with motor-incomplete SCI can recover basic walking with **intensive, task-specific gait training**.

* ***'Scientific evidence suggests'*** that ***'BWSTT is not better than overground gait training'*** in SCI or other neurologic disorders.

There was debate as to whether the overground training used in this clinical trial was reflective of a realistic 'conventional therapy' ie BWSTT vs living with disability.

* The results were consistent – intensive practice and task-oriented gait retraining (whether it is provided by BWSTT or overground practice) can result in **improved walking outcomes**.

* **A major shift and focus** is now on the potential efficacy of **Robotic-applied resistance** (Robotic-R) training on functional ambulation, overground walking with chronic m-iSCI and other neurologic disorders.

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2015, ROBOTIC-R (RESISTANCE), VARIABILITY & NOISE

* Task-specific locomotor training **adopting alterations in the movement can mediate 'feedback-error learning'.**

* **Feedback-error learning** during walking can be used to elicit locomotor adaptations.

* Short-term adaptation to **robot-applied resistance against hip flexion** demonstrates a **longer stride length that persists overground** immediately after walking against resistance.

* Diminished hip, knee and ankle flexion observed during swing phase, compromising foot clearance height – **toe stabbing**.

* Improvements in overground walking speed and distance but also in skilled walking tasks, obstacle crossing and stair climbing, as well as the kinematic quality of the gait pattern.

* Variability during practice is seen as a key feature for facilitating learning - repeated (and varied) opportunities to experience errors and solve motor problems.

* **Variability and 'Noise'** during training helps to **reinforce convergent synaptic connections** from central and sensory inputs to the locomotor circuitry. (Learning not to fall).

* Robotic applied 'resistance' would also have required greater engagement during training to avoid toe drag and stumbling.

* Greater **cognitive engagement** during training elicited greater involvement of cortical regions associated with gait adjustments of motor output during swing.

* Indeed, it has been shown that **corticospinal excitability** is tuned according to the level of cognitive engagement during gait training and resistance.

OXYMED

2016, ROBOTIC ACCURACY AND REPETITION

A patient-specific muscle force estimation model for the potential use of human-inspired swing-assist rehabilitation robots

Ye Ma ✉, Shengquan Xie & Yanxin Zhang

Pages 948-964 | Received 13 Feb 2016, Accepted 27 Mar 2016, Published online: 22 Apr 2016

GAIT REHABILITATION ROBOTS, WHICH ARE PRECISE

* **Swing-phase deviations** are related to quadriceps spasticity, hip flexion weakness, ankle dorsiflexion weakness or spasticity, hamstring contracture, spasticity and quadriceps weakness, which will lead to inadequate knee joint flexion and extension as well as excessive knee joint flexion and extension.

* Clinical evidence shows that **"task-oriented" repetitive intensive movement swing-phase training** improved walking speeds, endurance and performance on functional tasks for individuals with neurologic gait disability.

* Gait rehabilitation robots, which are **precise**, rehabilitation effectiveness with **high accuracy**, could yield better training outcomes than traditional physiotherapists.

* Optimal control strategy should comprise **task-specificity, repeatability, intensity and optimal physical and mental engagement**.

* **Robotic swing-assistance task-specific, intensive and non-fatigue training, can improve the locomotion ability of the incomplete SCI patient and other neurologic gait dysfunction**.

OXYMED

OXYGEN & CARDIORESPIRATORY LOAD LOWER WITH ROBOTICS

Neurorehabil Neural Repair. 2018 Dec;32(12):1043-1054. doi: 10.1177/1545968318810810. Epub 2018 Nov 12.

Physiological Responses and Perceived Exertion During Robot-Assisted and Body Weight-Supported Gait After Stroke.

Lefeber N[1], De Keersmaecker E[1], Henderix S[2], Michielsen M[2], Kerckhofs E[1], Swinnen E[1].

Author information

1 1 Rehabilitation Research-Neurological Rehabilitation Group, Vrije Universiteit Brussel, Brussels, Belgium.

2 2 Jessa Hospitals, Herk-de-Stad, Belgium.

Abstract

INTRODUCTION: Physiological responses are rarely considered during walking after stroke and if considered, only during a short period (3-6 minutes). The aims of this study were to examine physiological responses during 30-minute robot-assisted and body weight-supported treadmill and overground walking and compare intensities with exercise guidelines.

METHODS: A total of 14 ambulatory stroke survivors (age: 61 ± 9 years; time after stroke: 2.8 ± 2.8 months) participated in 3 separate randomized walking trials. Patients walked overground, on a treadmill, and in the Lokomat (60% robotic guidance) for 30 minutes at matched speeds (2.0 ± 0.5 km/h) and matched levels of body weight support (BWS; 41% ± 16%). Breath-by-breath gas analysis, heart rate, and perceived exertion were assessed continuously.

RESULTS: Net oxygen consumption, net carbon dioxide production, net heart rate, and net minute ventilation were about half as high during robot-assisted gait as during body weight-supported treadmill and overground walking ($P < .05$). Net minute ventilation, net breathing frequency, and net perceived exertion significantly increased between 6 and 30 minutes (respectively, 1.8 L/min, 2 breaths/min, and 3.8 units). During Lokomat walking, exercise intensity was significantly below exercise recommendations; during body weight-supported overground and treadmill walking, minimum thresholds were reached (except for percentage of heart rate reserve during treadmill walking).

CONCLUSION: In ambulatory stroke survivors, the oxygen and cardiorespiratory demand during robot-assisted gait at constant workload are considerably lower than during overground and treadmill walking at matched speeds and levels of body weight support. Future studies should examine how robotic devices can be Future studies should examine how robotic devices can be exploited to induce aerobic exercise.

OXYMED

ROBOTIC NEUROLOGIC ASSISTANCE

Dev Neurorehabil. 2016 Dec;19(6):410-415. Epub 2015 Apr 2.

Robot-assisted gait training might be beneficial for more severely affected children with cerebral palsy.

van Hedel HJ[1,2,3], Meyer-Heim A[1,2,3], Rüsch-Bohtz C[1,2].

Eur J Paediatr Neurol. 2017 May;21(3):557-564. doi: 10.1016/j.ejpn.2017.01.012. Epub 2017 Feb 2.

Robotic-assisted gait training improves walking abilities in diplegic children with cerebral palsy.

Wallard L[1], Dietrich G[2], Kerlirzin Y[2], Bredin J[3].

Sci Rep. 2017 Oct 18;7(1):13512. doi: 10.1038/s41598-017-13554-2.

The Effects of Exoskeleton Assisted Knee Extension on Lower-Extremity Gait Kinematics, Kinetics, and Muscle Activity in Children with Cerebral Palsy.

Restor Neurol Neurosci. 2017;35(5):527-536. doi: 10.3233/RNN-170745.

Robotic-assisted gait training combined with transcranial direct current stimulation in chronic stroke patients: A pilot double-blind, randomized controlled trial.

Arch Phys Med Rehabil. 2018 Jul 25. pii: S0003-9993(18)30448-9. doi: 10.1016/j.apmr.2018.06.020. [Epub ahead of print]

Effects of Electromechanical Exoskeleton-assisted Gait Training on Walking Ability of Stroke Patients: A Randomized Controlled Trial.

J Clin Neurosci. 2018 Feb;48:11-17. doi: 10.1016/j.jocn.2017.10.048. Epub 2017 Dec 6.

What does best evidence tell us about robotic gait rehabilitation in stroke patients: A systematic review and meta-analysis.

Int J Neurosci. 2017 Nov;127(11):996-1004. doi: 10.1080/00207454.2017.1288623. Epub 2017 Feb 13.

Robotic-assisted gait training in Parkinson's disease: a three-month follow-up randomized clinical trial.

OXYMED

OPTIMAL REHABILITATION

Journal of Motor Behavior, Vol. 47, No. 1, 2015

REVIEW ARTICLE

Science-Based Neurorehabilitation: Recommendations for Neurorehabilitation From Basic Science

Jens Bo Nielsen[1], Maria Willerslev-Olsen[1], Lasse Christiansen[1], Jesper Lundbye-Jensen[1], Jakob Lorentzen[2]

[1]Department of Neuroscience and Pharmacology and Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark. [2]Helene Elsass Center, Charlottenlund, Copenhagen, Denmark.

Optimal rehabilitation should involve :

* Robotic assisted devices combined with overground walking
* Active (patient) participation and engagement
* Training involving many repetitions, but continues to challenge the skill
* Resistance training
* Feedback error learning – changing and challenging environment
* Motivation and reward
* Intensive training and practice over a long time
* Combination training - overground training activities

"Learn to walk by learning not to fall"

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ROBOTIC VIRTUAL REALITY

NEW ERA - ROBOTIC EXOSUITS

OXYMED

WEARABLE EXOSUITS

Gait Posture. 2018 Jun 26. pii: S0966-6362(18)30881-6. doi: 10.1016/j.gaitpost.2018.06.124. [Epub ahead of print]

O 089 - A soft robotic exosuit assisting the paretic ankle in patients post-stroke: Effect on muscle activation during overground walking.

Sloot L[1], Bae J[2], Baker L[2], O'Donnell K[2], Menard N[2], Porciuncula F[2], Choe D[2], Ellis T[3], Awad L[3], Walsh C[3].

Author information

Abstract

This study compared overground walking with and without exosuit assistance in post-stroke patients. Exosuit-assisted walking was found to improve paretic propulsion and ground clearance during swing, two common gait deviations in stroke patients. No changes in leg muscle activity was found, motivating further study of the exosuit as a tool for gait training during stroke rehabilitation.

IEEE Trans Neural Syst Rehabil Eng. 2018 May;26(5):1011-1016. doi: 10.1109/TNSRE.2018.2817647.

Effect of the Synchronization-Based Control of a Wearable Robot Having a Non-Exoskeletal Structure on the Hemiplegic Gait of Stroke Patients.

J Neuroeng Rehabil. 2017 Nov 28;14(1):123. doi: 10.1186/s12984-017-0333-z.

Gait performance and foot pressure distribution during wearable robot-assisted gait in elderly adults.

JAMA. 2017 Sep 12;318(10):898. doi: 10.1001/jama.2017.13165.

Lightweight Exosuit Could Help Patients Walk After Stroke.

IEEE Int Conf Rehabil Robot. 2017 Jul;2017:1646-1653. doi: 10.1109/ICORR.2017.8009484.

Design of a lightweight, tethered, torque-controlled knee exoskeleton.

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PASSIVE ASSISTIVE EXOSKELETONS - AMBULATORY

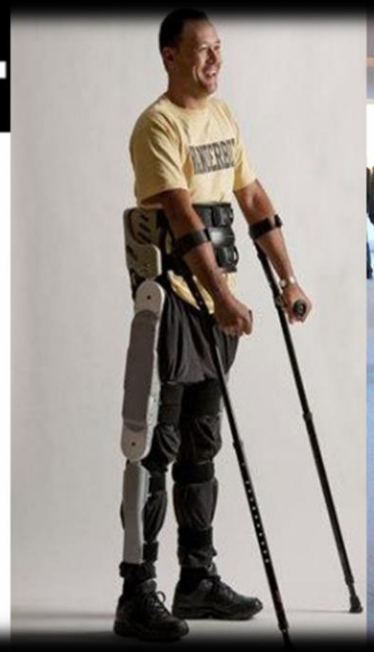
OXYMED

PASSIVE ASSISTIVE EXOSKELETONS - REWALK TEL-AVIV (2006)

OXYMED

VARIABLE ASSIST EXOSKELETONS

* Today and emerging - new powered gait orthosis featuring programmable “variable assist” movements in the hip and knee joints enabling independent training and neurorehabilitation in a clinical environment and at home.



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OVER GROUND WALKING EXOSKELTONS VS LOKOMAT

J Neuroeng Rehabil. 2018 Nov 20;15(1):109. doi: 10.1186/s12984-018-0453-0.

Overground walking with a robotic exoskeleton elicits trunk muscle activity in people with high-thoracic motor-complete spinal cord injury.

Alamro RA[1,2,3], Chisholm AE[1,2], Williams AMM[1,2], Carpenter MG[2], Lam T[4,5].

Author information

1 School of Kinesiology, University of British Columbia, Vancouver, Canada.
2 International Collaboration on Repair Discoveries (ICORD), Blusson Spinal Cord Centre, 818 West 10th Ave, Vancouver, BC, V5Z 1M9, Canada.
3 Current address: Rehabilitation Hospital, King Fahad Medical City, Riyadh, Saudi Arabia.
4 School of Kinesiology, University of British Columbia, Vancouver, Canada. tania.lam@ubc.ca.
5 International Collaboration on Repair Discoveries (ICORD), Blusson Spinal Cord Centre, 818 West 10th Ave, Vancouver, BC, V5Z 1M9, Canada. tania.lam@ubc.ca.

Abstract

BACKGROUND: The trunk muscles are critical for postural control. Recent neurophysiological studies have revealed sparing of trunk muscle function in individuals with spinal cord injury (SCI) classified with thoracic or cervical motor-complete injuries. These findings raise the possibility for recruiting and retraining this spared trunk function through rehabilitation. Robotic gait training devices may provide a means to promote trunk muscle activation. Thus, the objective of this study was to characterize and compare the activation of the trunk muscles during walking with two robotic gait training devices (Ekso and Lokomat) in people with high thoracic motor-complete SCI.

METHODS: Participants with chronic motor-complete paraplegia performed 3 speed-matched walking conditions: Lokomat-assisted walking, Ekso-assisted walking overground, and Ekso-assisted walking on a treadmill. Surface electromyography (EMG) signals were recorded bilaterally from the rectus abdominis (RA), external oblique (EO), and erector spinae (ES) muscles.

RESULTS: Greater recruitment of trunk muscle EMG was elicited with Ekso-assisted walking compared to the Lokomat. Similar levels of trunk EMG activation were observed between Ekso overground and Ekso on the treadmill, indicating that differences between Ekso and Lokomat could not be attributed to the use of a hand-held gait aid. The level of trunk EMG activation during Lokomat walking was not different than that recorded during quiescent supine lying.

CONCLUSIONS: Ekso-assisted walking elicits greater activation of trunk muscles compared to Lokomat-assisted walking, even after controlling for the use of hand-held assistive devices. The requirement of the Ekso for lateral weight-shifting in order to activate each step could lead to better postural muscle activation.

OXYMED

J Neuroeng Rehabil. 2018 Apr 6;15(1):30. doi: 10.1186/s12984-018-0366-y.

Advanced Robotic Therapy Integrated Centers (ARTIC): an international collaboration facilitating the application of rehabilitation technologies.

van Hedel HJA[1], Severini G[2,3], Scarton A[2], O'Brien A[2], Reed T[4], Gaebler-Spira D[5], Egan T[5], Meyer-Heim A[6], Graser J[6], Chua K[7], Zutter D[8], Schweinfurther R[8], Möller JC[8], Paredes LP[8], Esquenazi A[9], Berweck S[10], Schroeder S[11], Warken B[11], Chan A[12], Devers A[12], Petioky J[13], Paik NJ[14], Kim WS[14], Bonato P[2], Boninger M[15], ARTIC network.

Collaborators (36)

Author information

1 Rehabilitation Center for Children and Adolescents, University Children's Hospital Zurich, Mühlebergstrasse 104, CH-8910, Affoltern am Albis, Switzerland. hubertus.vanhedel@kispi.uzh.ch.
2 Department of Physical Medicine and Rehabilitation, Harvard Medical School, at Spaulding Rehabilitation Hospital, Charlestown MA, USA.
3 University College Dublin, Dublin, Ireland.
4 Acute Neurological Rehabilitation Unit, Wellington Hospital, London, UK.
5 Shirley Ryan AbilityLab, Chicago, USA.
6 Rehabilitation Center for Children and Adolescents, University Children's Hospital Zurich, Mühlebergstrasse 104, CH-8910, Affoltern am Albis, Switzerland.
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9 Department of Physical Medicine and Rehabilitation, MossRehab, Philadelphia, USA.
10 Clinic for Neuropediatrics and Neurological Rehabilitation, Epilepsy center for children and adolescents, Schön Klinik Vogtareuth, Vogtareuth, Germany.
11 Paediatric Neurology, Developmental Medicine and Social Paediatrics, Ludwig Maximilian University, Hauner Children's Hospital, Munich, Germany.
12 Sheltering Arms Physical Rehabilitation Center, Richmond, USA.
13 Rehabilitation Centre Kladruby, Kladruby, Czech Republic.
14 Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea.
15 Department of Physical Medicine and Rehabilitation, University of Pittsburgh and VA Pittsburgh Health Care System, Pittsburgh, USA.

Erratum in

Correction to: Advanced Robotic Therapy Integrated Centers (ARTIC): an international collaboration facilitating the application of rehabilitation technologies. [J Neuroeng Rehabil. 2018]

Abstract

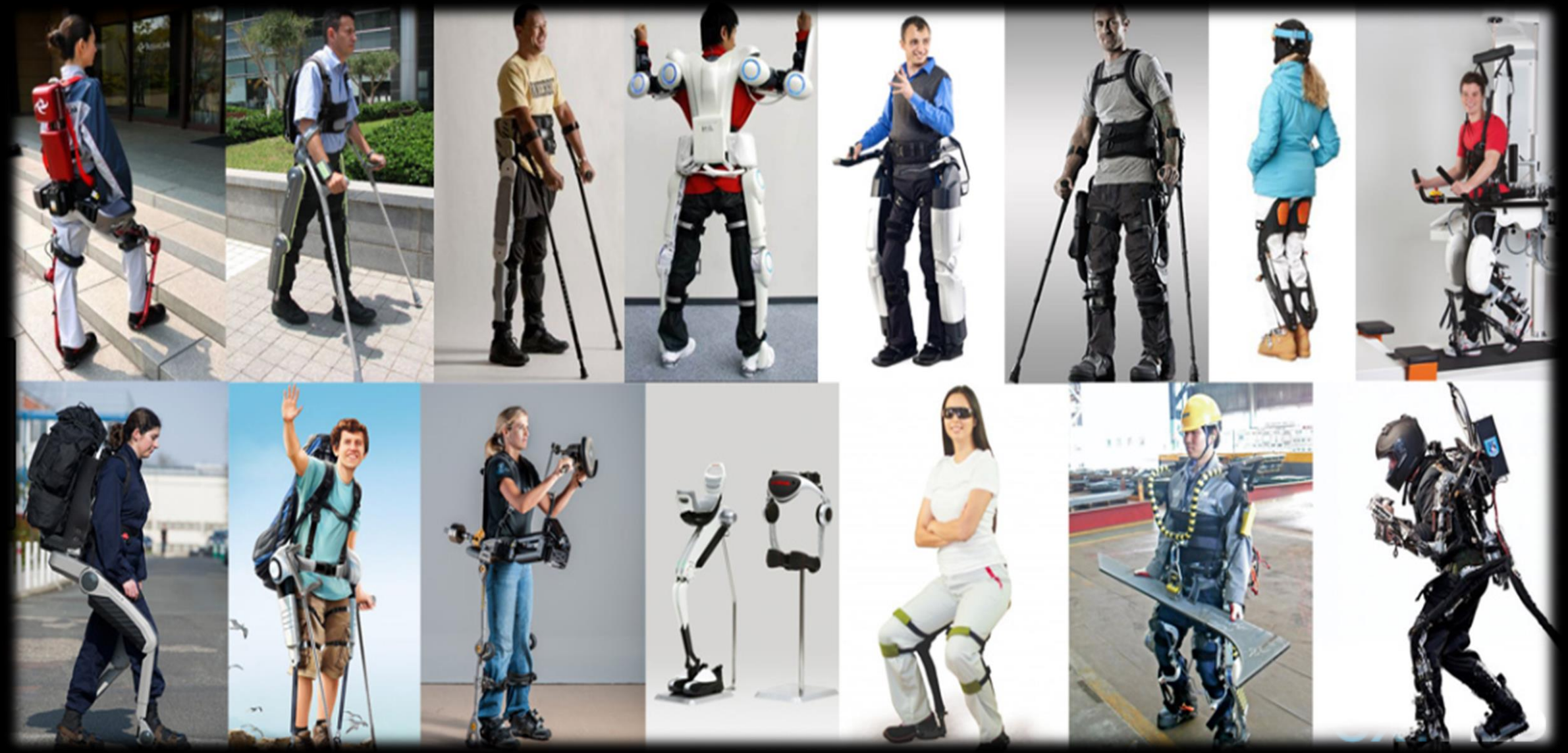
BACKGROUND: The application of rehabilitation robots has grown during the last decade. While meta-analyses have shown beneficial effects of robotic interventions for some patient groups, the evidence is less in others. We established the Advanced Robotic Therapy Integrated Centers (ARTIC) network with the goal of advancing the science and clinical practice of rehabilitation robotics. The investigators hope to exploit variations in practice to learn about current clinical application and outcomes. The aim of this paper is to introduce the ARTIC network to the clinical and research community, present the initial data set and its characteristics and compare the outcome data collected so far with data from prior studies.

METHODS: ARTIC is a pragmatic observational study of clinical care. The database includes patients with various neurological and gait deficits who used the driven gait orthosis Lokomat® as part of their treatment. Patient characteristics, diagnosis-specific information, and indicators of impairment severity are collected. Core clinical assessments include the 10-Meter Walk Test and the Goal Attainment Scaling. Data from each Lokomat® training session are automatically collected.

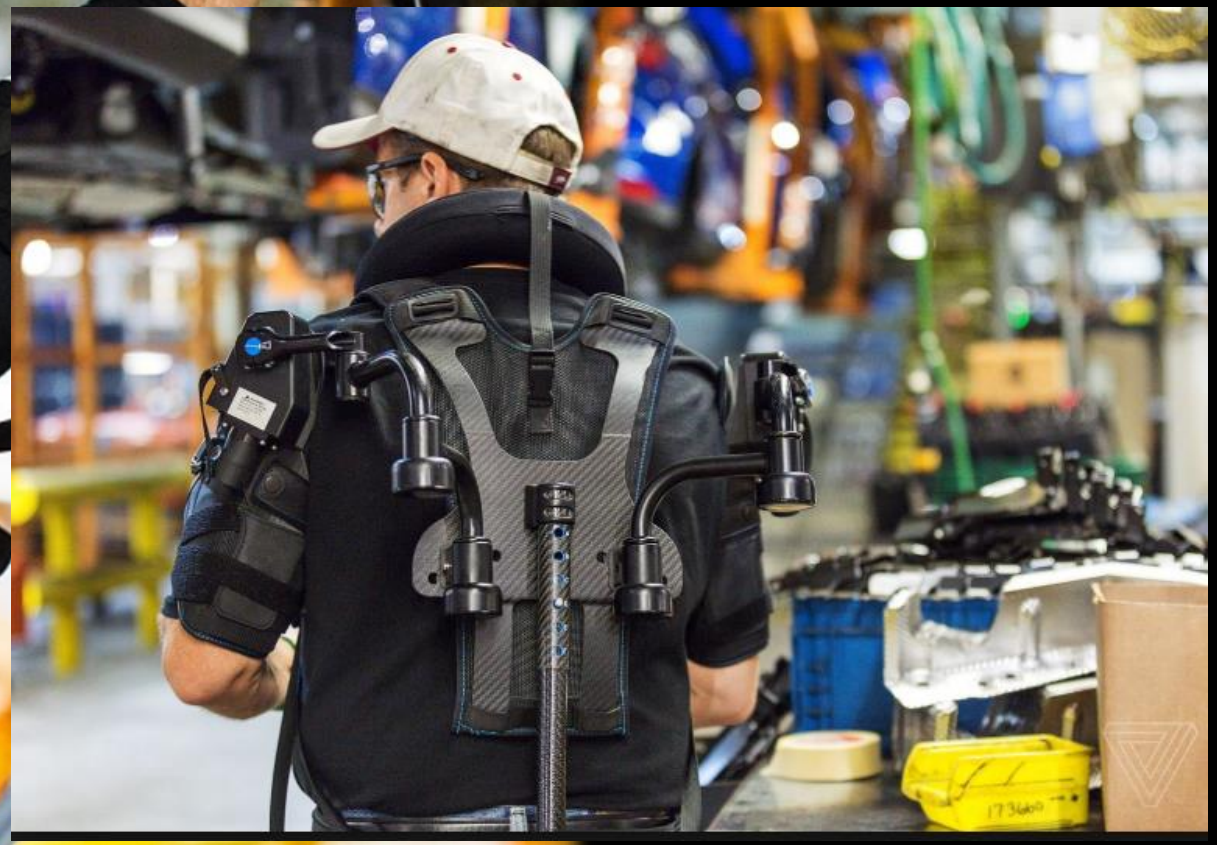
RESULTS: At time of analysis, the database contained data collected from 595 patients (cerebral palsy: n = 208; stroke: n = 129; spinal cord injury: n = 93; traumatic brain injury: n = 39; and various other diagnoses: n = 126). At onset, average walking speeds were slow. The training intensity increased from the first to the final therapy session and most patients achieved their goals.

CONCLUSIONS: The characteristics of the patients matched epidemiological data for the target populations. When patient characteristics differed from epidemiological data, this was mainly due to the selection criteria used to assess eligibility for Lokomat® training. While patients included in randomized controlled interventional trials have to fulfill many inclusion and exclusion criteria, the only selection criteria applying to patients in the ARTIC database are those required for use of the Lokomat®. We suggest that the ARTIC network offers an opportunity to investigate the clinical application and effectiveness of rehabilitation technologies for various diagnoses. Due to the standardization of assessments and the use of a common technology, this network could serve as a basis for researchers interested in specific interventional studies expanding beyond the Lokomat®.

ADAPTIVE LIVING EXOSKELETONS



INDUSTRIAL EXOSUITS



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WEARABLE EXOSUITS

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INDUSTRIAL EXOSKELETONS

OXYMED

DISABILITY EXOSUITS

MILITARY EXOSKELETONS

SPORT SUITS

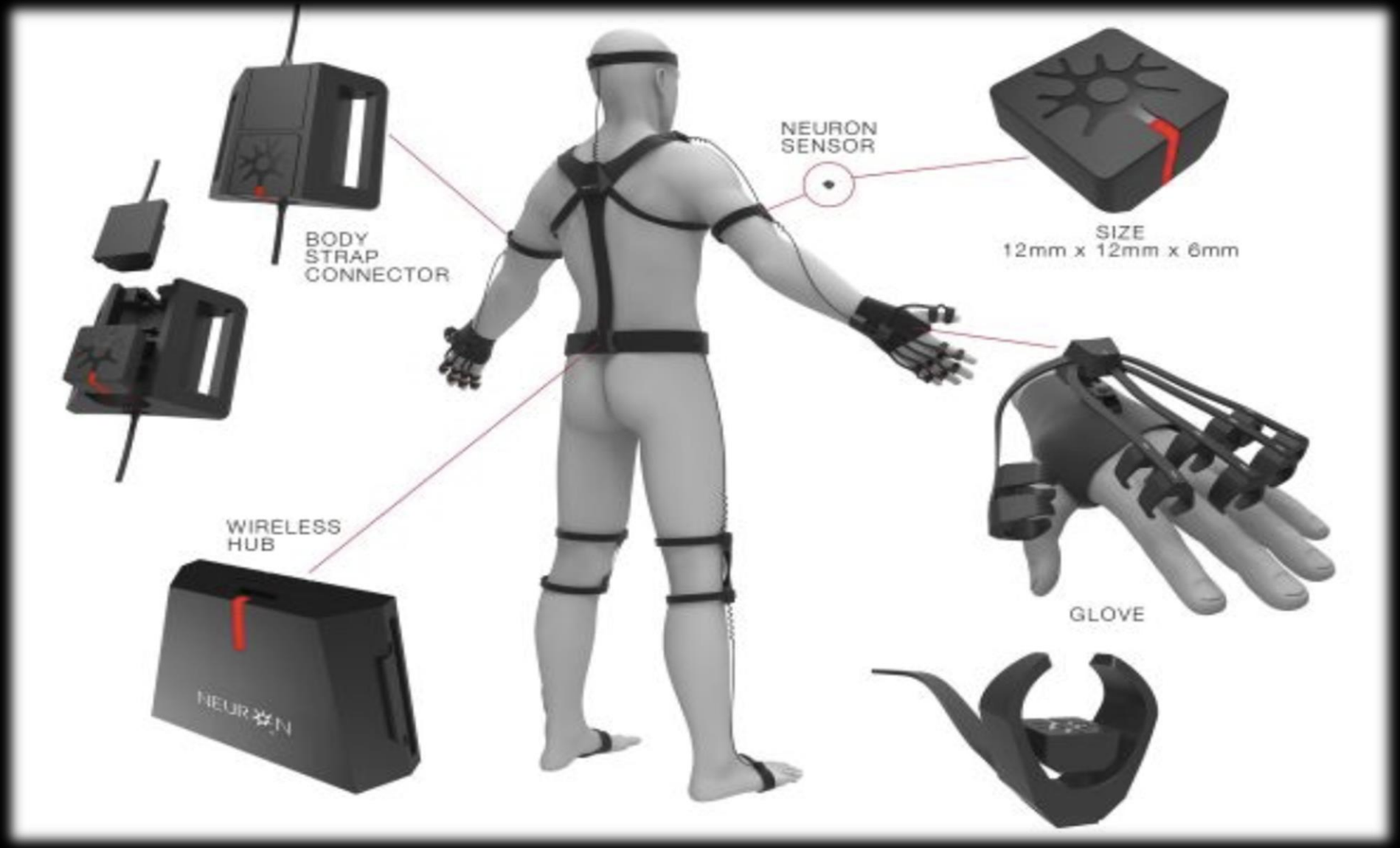

Power Pack
Torque Co
Automat
Recogniti
Integrate


SOFT EXOSUIT FOR
RUNNING
OXYMED

LIFESYTLE & LEISURE

TESLA EXOSUITS

TESLA INTERFACE



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TESTLA REHABILITATION

TESLASUIT


Teslasuit
virtual reality reinvented
The world's first full-body haptic feedback, motion capture, thermo controlled suit. Enjoy incredible real world sensations as never before.
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EXO-PANDA, SHENYANG CHINA

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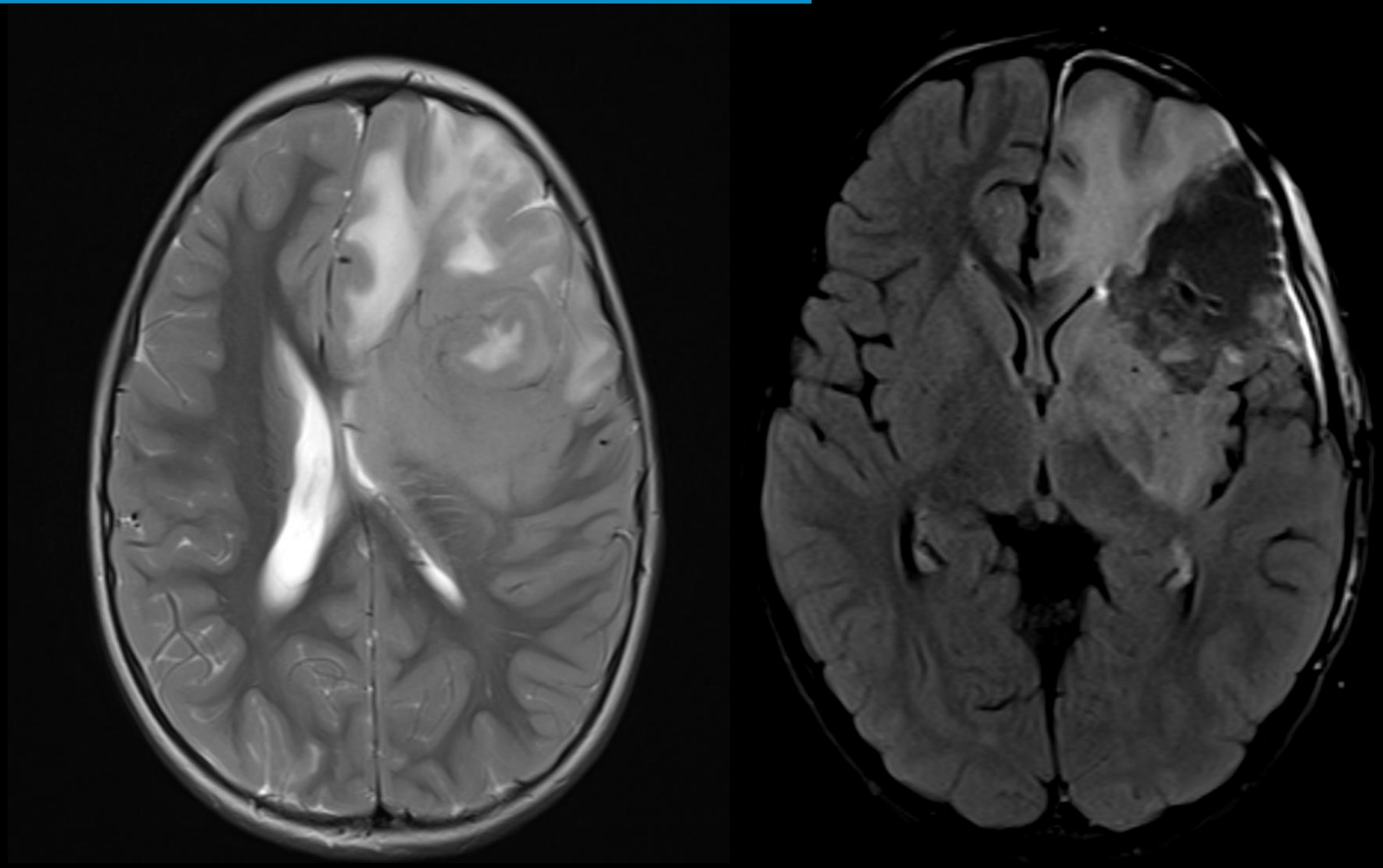
GLIOBLASTOMA MULTIFORME – AGE 7



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CYTOKINE TESTING PRE HBOT

OXYMED HEALTH

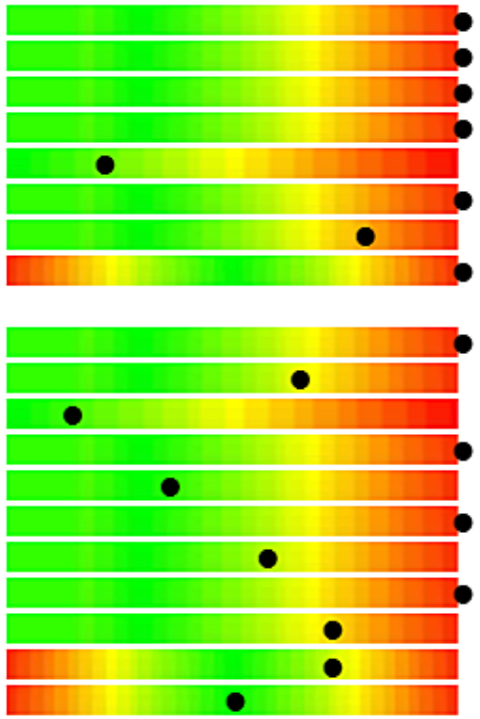
Date of Birth : 21-Oct-2009
Sex : M
Collected : 01-Mar-2017

Lab id: UR#:

OXYMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

INTEGRATIVE MEDICINE

BLOOD - SERUM	Result	Range	Units
CYTOKINES,Extensive Panel			
ProInflammatory Cytokines (TH1)			
Interleukin 1	*3463.0* *H	0.0 - 2.8	pg/mL
Interleukin 6	*1252.0* *H	0.0 - 11.0	pg/mL
Interleukin 7	*67.8* *H	0.0 - 16.0	pg/mL
Interleukin 8	*>2500.0* *H	0.0 - 28.0	pg/mL
Interleukin 17	10.4	< 13.0	pg/mL
TNFa	*816.00* *H	0.00 - 13.00	pg/mL
TNFb	*164.0* *H	0.0 - 156.0	pg/mL
S100B	*151.8* *H	60.0 - 100.0	pg/mL
AntiInflammatory Cytokines (TH2)			
GM-CSF	*1620.0* *H	0.0 - 80.0	pg/mL
Interleukin 2	7.4	0.0 - 10.0	pg/mL
Interleukin 3	<3.2	< 5.0	pg/mL
Interleukin 4	*127.2* *H	0.0 - 19.0	pg/mL
Interleukin 5	3.8	0.0 - 13.0	pg/mL
Interleukin 10	*99.7* *H	0.0 - 7.0	pg/mL
Interleukin 12	7.9	0.0 - 14.0	pg/mL
Interleukin 13	*21.7* *H	0.0 - 6.0	pg/mL
INFg	25.8	0.0 - 28.0	pg/mL
TGFb	57.7	28.0 - 64.0	pg/mL
Brain Derived Neurotrophic Factor BDNF	33.2	20.0 - 50.0	ng/mL



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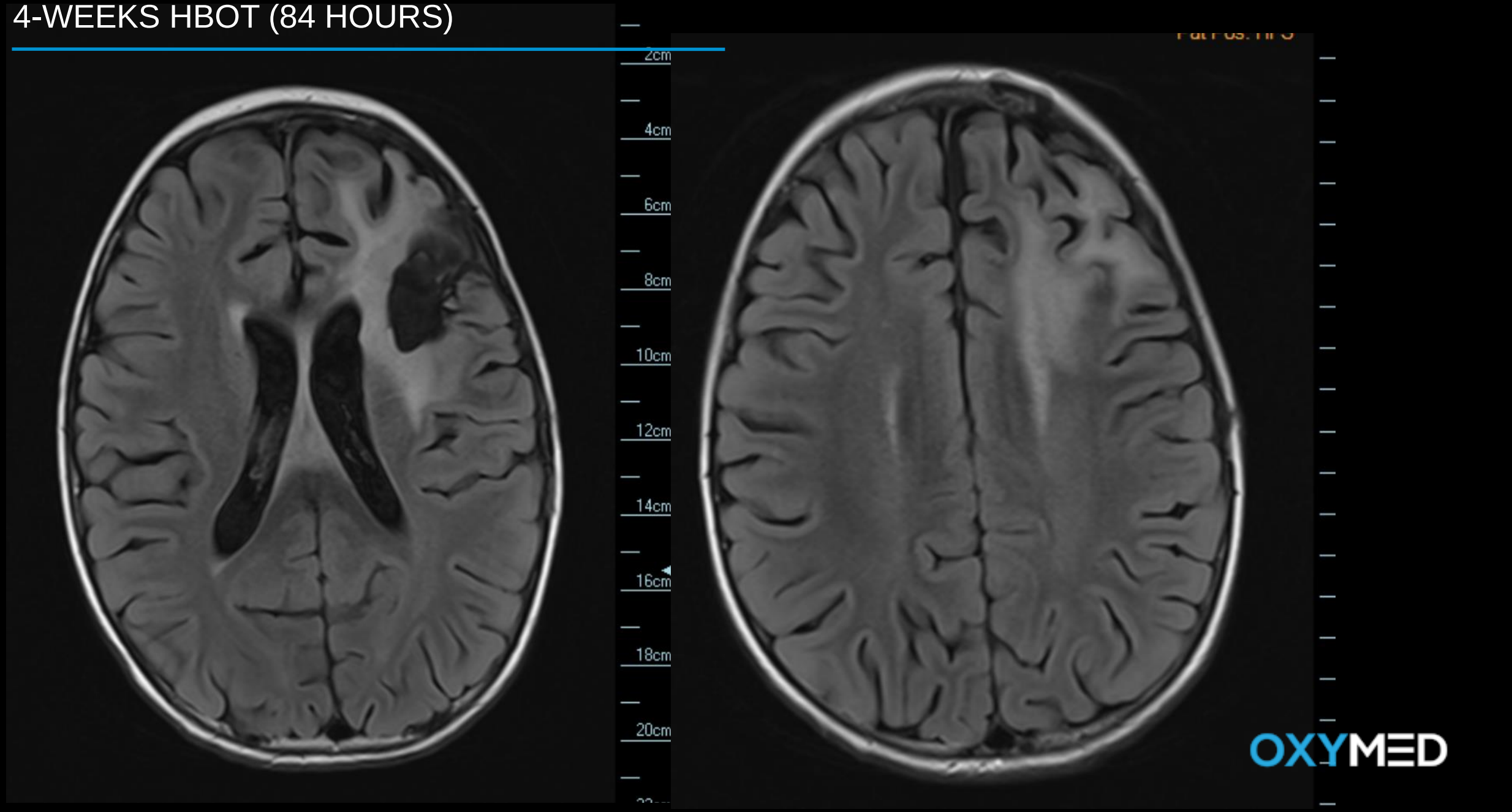
4-WEEKS HBOT (84 HOURS)



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CYTOKINES 106 HOURS HBOT

OXYMED HEALTH

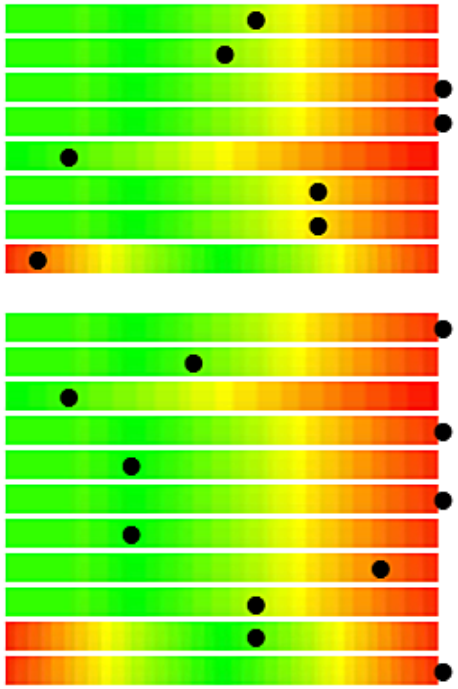
Date of Birth : 21-Oct-2009
Sex : M
Collected : 02-May-2017

Lab id: UR#:

OXYMED, 643 CHAPEL STREET
SOUTH YARRA VIC 3141

INTEGRATIVE MEDICINE

BLOOD - SERUM	Result	Range	Units
Hyperbaric Oxygen Therapy (HBO)	106.0		Hours
CYTOKINES,Extensive Panel			
ProInflammatory Cytokines (TH1)			
Interleukin 1	1.9	0.0 - 2.8	pg/mL
Interleukin 6	4.9	0.0 - 11.0	pg/mL
Interleukin 7	*24.8* *H	0.0 - 16.0	pg/mL
Interleukin 8	*48.4* *H	0.0 - 28.0	pg/mL
Interleukin 17	7.8	< 13.0	pg/mL
TNFa	10.80	0.00 - 13.00	pg/mL
TNFb	144.0	0.0 - 156.0	pg/mL
S100B	*13.6* *L	60.0 - 100.0	pg/mL
AntiInflammatory Cytokines (TH2)			
GM-CSF	*1510.3* *H	0.0 - 80.0	pg/mL
Interleukin 2	3.6	0.0 - 10.0	pg/mL
Interleukin 3	<3.0	< 5.0	pg/mL
Interleukin 4	*44.4* *H	0.0 - 19.0	pg/mL
Interleukin 5	1.8	0.0 - 13.0	pg/mL
Interleukin 10	*14.8* *H	0.0 - 7.0	pg/mL
Interleukin 12	2.4	0.0 - 14.0	pg/mL
Interleukin 13	*7.1* *H	0.0 - 6.0	pg/mL
INFg	17.7	0.0 - 28.0	pg/mL
TGFb	50.2	28.0 - 64.0	pg/mL
Brain Derived Neurotrophic Factor BDNF	*382.0* *H	20.0 - 50.0	ng/mL



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CYTOKINES COMPARISON

OXYMED HEALTH

Date of Birth : 21-Oct-2009
Sex : M
Collected : 01-Mar-2017
02-May-2017

Lab id: UR#:

OXYMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

INTEGRATIVE MEDICINE

BLOOD - SERUM	Result	Hours		
CYTOKINES,Extensive Panel	0	106.0		
ProInflammatory Cytokines (TH1)				
Interleukin 1	*3463.0* *H	1.9	0.0 - 2.8	pg/mL
Interleukin 6	*1252.0* *H	4.9	0.0 - 11.0	pg/mL
Interleukin 7	*67.8* *H	*24.8* *H	0.0 - 16.0	pg/mL
Interleukin 8	*>2500.0* *H	*48.4* *H	0.0 - 28.0	pg/mL
Interleukin 17	10.4	7.8	< 13.0	pg/mL
TNFa	*816.00* *H	10.80	0.00 - 13.00	pg/mL
TNFb	*164.0* *H	144.0	0.0 - 156.0	pg/mL
S100B	*151.8* *H	*13.6* *L	60.0 - 100.0	pg/mL
AntiInflammatory Cytokines (TH2)				
GM-CSF	*1620.0* *H	*1510.3* *H	0.0 - 80.0	pg/mL
Interleukin 2	7.4	3.6	0.0 - 10.0	pg/mL
Interleukin 3	<3.2	<3.0	< 5.0	pg/mL
Interleukin 4	*127.2* *H	*44.4* *H	0.0 - 19.0	pg/mL
Interleukin 5	3.8	1.8	0.0 - 13.0	pg/mL
Interleukin 10	*99.7* *H	*14.8* *H	0.0 - 7.0	pg/mL
Interleukin 12	7.9	2.4	0.0 - 14.0	pg/mL
Interleukin 13	*21.7* *H	*7.1* *H	0.0 - 6.0	pg/mL
INFg	25.8	17.7	0.0 - 28.0	pg/mL
TGFb	57.7	50.2	28.0 - 64.0	pg/mL
Brain Derived Neurotrophic Factor BDNF	33.2	*382.0* *H	20.0 - 50.0	ng/mL

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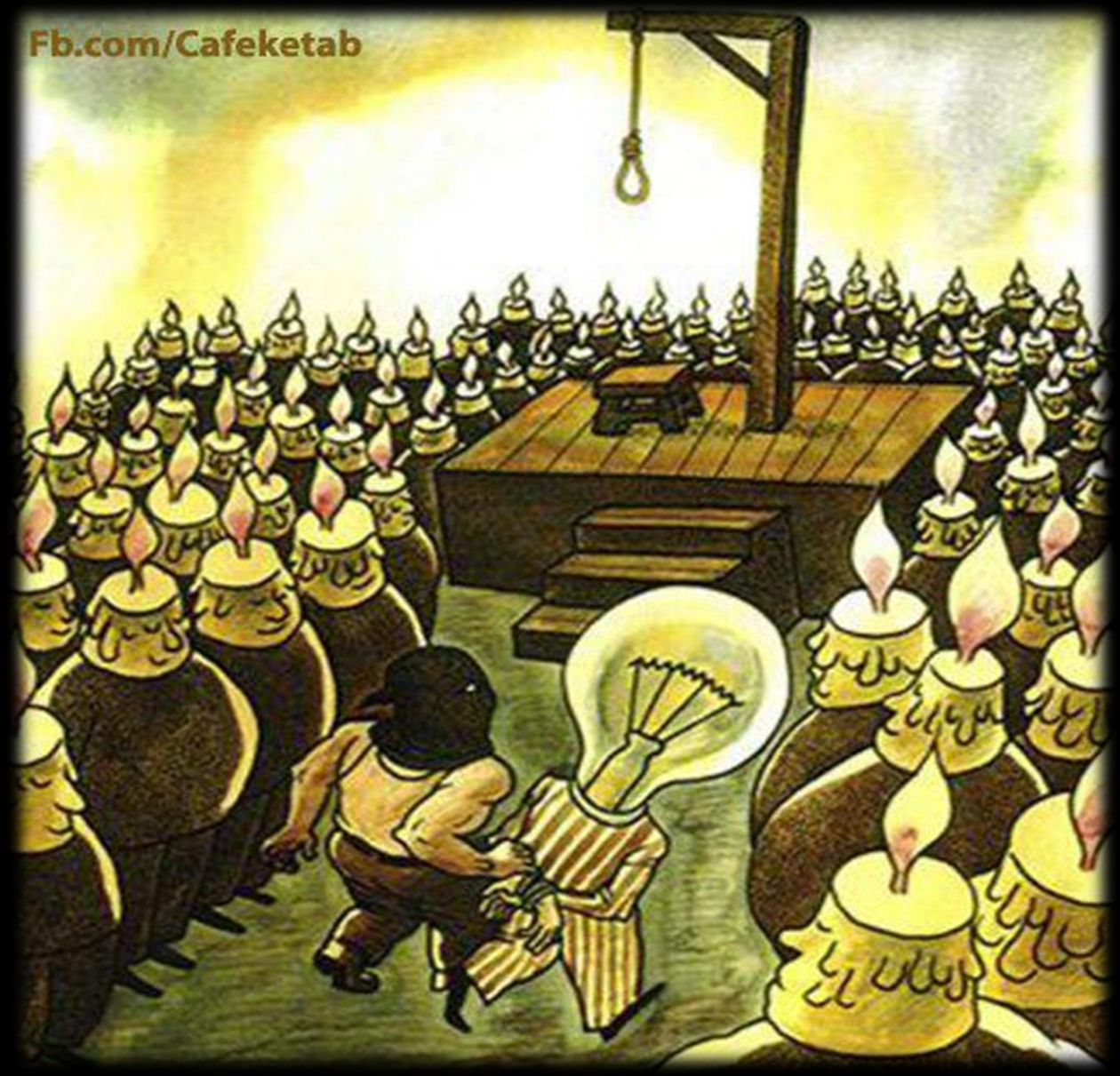
PIONEERS



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THANK YOU

"The purpose of my life is to be 'complete', to live in God's Grace and Blessing, to lift the 'Spirit of Humanity' for myself and others.

I am passionate with the vision that people of all nations will gain the opportunity to access the abundant benefits of Oxygenation. The cornerstone of HealthCare in the modern era".

Malcolm R. Hooper

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