Non Healing Brain Wounds
Basic Characteristics and The Use of Hyperbaric Oxygen Therapy

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The injured Brain

Brain stroke

Non healing foot ulcer
What do we need for recovery of injured non necrotic tissue?

- **Energy (oxygen)**
- **Triger**
- **Stem cells**
- **Angiogenesis**
Oxygen – limiting factor for brain activity & recovery

Efrati & Hadanny 2015
Oxygen – Limiting factor for brain activity

Cognitive function at dual tasking at normobaric (Placebo) and hyperbaric conditions (intervention)

Efrati et al. Front Integr Neurosci. 2017
Stroke at high altitude

- Altitudes higher than 2,500 m
- \( \text{paO}_2 \) reached 63–66 mmHg
- 10 - 15% of all strokes in the US, Europe and Australia

\textbf{The 30-day mortality rate is approximately 40%.}
P= plain (low altitude)
H=High altitude
S= Standard physiology
I=Intracranial hemorrhage

LPR=lactate/pyruvate ratio

Zhu et al. critical care 2015
Stroke (hemorrhagic) at high altitude
Neurological results

P= plain (low altitude)
H=High altitude
S= Standard physiology
I=Intracranial hemorrhage

Zhu et al. critical care 2015
Brain tissue oxygenation in patients with severe TBI

HBO = 1.5 ATA, 100% O2; NBO = 1 ATA, 100% O2

Rockswold et al, 2010
Cerebral metabolic rate of oxygen in patients severe TBI

HBO = 1.5 ATA, 100% O2; NBO - 1 ATA, 100% O2

* Rockswold et al, 2010
HBOT & Brain
Basics Interactions

- Improve mitochondrial function
- Improve BBB and secondary inflammatory reaction
- Direct anti-inflammatory effects
  - Down regulation of ICAM-1 and other inflammatory cytokines
  - Reduce the adhesion and diminished infiltration of leucocytes
  - Reduced COX-2 expression
- Decrease the synthesis of caspase 3, caspase 9, bcl-2 and p53 and accordingly reduce apoptosis
- Reduce expression of HIF-1
- Increase Na+-K+ ATPase activity
- Stabilized transmembrane ion gradients
- Upregulation of antioxidant enzymes
- Suppression of NADPH oxidase
- Increase expression of neurotrophin
- Increase nitric oxide function
- Suppression of Nogo-A, Ng-R, and RhoA expression
- Up-regulation of axon guidance agents
- Effect mediated by glial cells and asrocytes

(References will be supply as an appendix)
What do we need for recovery of injured non necrotic tissue?

- **Energy (oxygen)**
- **Trigger**
- **Stem cells**
- **Angiogenesis**
Hyperoxic - Hypoxic Paradox

HIF 1α in HUVEC

Hyperoxic - Hypoxic Paradox
MMPs in HUVEC

F. Cimino et al, J Appl Physiol. 2012
Hyperoxic - Hypoxic Paradox
HIF in the Brain (animal model)

A

B

C

D

E

F

Hyperoxic - Hypoxic Paradox
HIF 1α in Humans PBMC

% PBMC

Baseline | Pre HBOT | HBOT #30 | HBOT #60 | Post HBOT

**
HIF 1 Alpha expression during HBOT

HBO SESSION #1

HBO SESSION #30

HBO SESSION #60

% PBMC

Baseline Pre HBOT HBOT #30 HBOT #60 Post HBOT
What do we need for recovery of injured non necrotic tissue?

- **Energy (oxygen)**
- **Trigger**
- **Stem cells**
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Hematopoietic Stem Cells
(CD34+/CD90+)

On going wok
Mesenchymal Stem Cells

(\text{CD}34-/\text{CD}45-/\text{CD}73+/\text{CD}90+/\text{CD}105+)

On going wok
What do we need for recovery of injured non necrotic tissue?

- Energy (oxygen)
- Trigger
- Stem cells
- Angiogenesis
HBOT & Angiogenesis
Trigger: HIF 1α

HBOT promote brain angiogenesis

Perfusion MRI of Post TBI patients
(10±3 yrs after the acute event)
HBOT and Brain angiogenesis

- Cerebral Blood Flow
- Cerebral Blood Volume
- MTT
- Dynamic Contrast Enhancement
  - $K_{trans}$ - transfer constant
  - $V_p$ - fractional volume of blood plasma in tissue

**HBOT can induce Angiogenesis in the chronic damaged brain!**
What do we need for recovery of injured non necrotic tissue?

- Energy (oxygen)
- Trigger
- Stem cells
- Angiogenesis

What is the optimal wound for HBOT?
Case example 3: a 64 year old woman, suffering from left hemiparesis due to ischemic stroke that occurred 26 months prior to inclusion in the study.
Case example 2: a 62 years old woman suffering from right hemiparesis and aphasia due to ischemic stroke that occurred 14 months prior to her inclusion in the study.
Case example: 51-year-old woman that had mTBI (fall from a bus) 2 years prior to her inclusion.
Case example: 51-year-old woman that had mTBI (fall from a bus) 2 years prior to her inclusion.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post HBOT</th>
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</thead>
<tbody>
<tr>
<td>Memory</td>
<td>56</td>
<td>108</td>
</tr>
<tr>
<td>Attention</td>
<td>47</td>
<td>81</td>
</tr>
<tr>
<td>Executive Function</td>
<td>65</td>
<td>85</td>
</tr>
<tr>
<td>Information processing speed</td>
<td>85</td>
<td>95</td>
</tr>
</tbody>
</table>
MRI-DTI pre and post HBOT (cingulate)

Statistical analysis - FA

Pre HBOT

Post HBOT
MRI-DTI pre and post HBOT
(Inferior longitudinal fasciculus)

A

Pre HBOT  Post HBOT

B

ILF R

Statistical analysis -FA

Post HBOT > Pre HBOT

0.05  0.04  0.03  0.02  0.01

0.4

0.38

0.36

0.34

0.32

0.3

0.28

0.26

0.24

0.22

0.2

FA

pre-HBOT  post-HBOT

Number of fibers

ILF R

Pre-HBOT  Post-HBOT

0  4000  8000  12000
Example of MRI-DTI pre and post HBOT (Uncinate)
The aging brain

As we age, the white matter degenerates.

MRI scan of 25 year-old

MRI scan of 75 year-old
The aging brain
Amyloid & Blood flow in AD mice

The images were taken using a multiphoton microscope and illustrate the vasculature of an Alzheimer's disease mouse. Green shows blood flow and red amyloid deposition. The ring-like structures surrounding the blood vessels represent cerebral amyloid angiopathy.
HBOT reduces amyloid load in the old 3xTg mice
Blood vessels diameter, flow in 5xFAD AD model
HBOT increases blood flux in 5xFAD mice

A

5xFAD

Pre

Post
HBOT alleviates the reduction in vessels diameter and therefore contributes to increment in Flux.
HBOT reduces the presence of hypoxia in the hippocampus of 5xFAD mice

![Image of DAPI and HypoxyProbe staining](image)

**CA1**

- HypoxyProbe (a.u.)
- Genotype: wt, 5xFAD, wt, 5xFAD
- -HBOT: wt, 5xFAD, 5xFAD, wt
- +HBOT: wt, 5xFAD, 5xFAD, wt

**CA3**

- HypoxyProbe (a.u.)
- Genotype: wt, 5xFAD, 5xFAD, wt
- -HBOT: wt, 5xFAD, 5xFAD, wt
- +HBOT: wt, 5xFAD, 5xFAD, wt

* indicates statistical significance.
HBOT increase survival of new-born neurons in control and 5xFAD mice
What do we really need to select the non-healing wound in the brain?
Combination of Metabolic and Anatomic Brain Imaging

Example of rCBF-SPECT with CT findings in a case of right cortical stroke and 3D functional brain volume at 30% and 40% threshold. Functional brain volume was calculated using "NeuroGam" software (SEGAMI corp).
TcPO₂ of the Brain

My Brain

Post Stroke
The Living Brain
My brain
My Brain
Post Stroke
Post stroke

AP2P: 14.16 [uV]
IntraHC: 80 [msec]
avgLCPI: 0.65

LCPI:
Frontal left  0.582
Frontal right  0.533
Motor Left  0.811
Motor right  0.646
Occipital left  0.66
Occipital right  0.647
Before and After HBOT
Post stroke
Before and After HBOT
Post Stroke Patient
Aging Brain
Mild Cognitive Impairment
Aging Brain
Mild Cognitive Impairment
Before and After HBOT
Aging Brain
Mild Cognitive Impairment
Aging with Mild cognitive Impairment Before & After HBOT
The non-healing wounds...
See you in Israel 09.09.19...
See you in Israel 09.09.19...