THE NORMOBARIC OXYGEN PARADOX: FROM BREATH-HOLD DIVING TO THE PATIENT’S BED

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I declare no real or potential conflict of interest.

Any views or opinions presented in this presentation are solely those of the author and do not necessarily represent those of any organization that author belongs to.
OXYGEN SENSING FOOLS JANUS
Meganeuropsis Dragonfly

Oxygen Content of Earth’s Atmosphere
During the Course of the Last Billion Years

[Graph showing the oxygen content of Earth’s atmosphere over the last billion years, with a peak around 500 million years ago and another around 250 million years ago.]
GIGANTISM = PROTECTION

During Carboniferous, oxygen content in the atmosphere was around 28%.
WE NEED BASICALLY 3 INGREDIENTS

Trigger (deltas- Hif)
Target (Stem Cells)
Supporting environment (Oxygenated tissue)
Stem cell mobilization by hyperbaric oxygen

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1Institute for Environmental Medicine and Departments of 2Emergency Medicine, 3Surgery, and 4Physiology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

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Thom, Stephen R., Vecna M. Bhopale, Omalda C. Velazquez, Lee J. Goldstein, Lynne H. Thom, and Donald G. Buerk. Stem cell mobilization by hyperbaric oxygen. Am J Physiol Heart Circ Physiol 290: H1378–H1386, 2006. First published November 18, 2005; doi:10.1152/ajpheart.00888.2005.—We hypothesized that exposure to hyperbaric oxygen (HBO2) 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) O2 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. Elevation 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, HBO2 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 CFUs. Bone marrow NO concentration increased by 1,008 ± 255 nM in association with HBO2. 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 HBO2-induced elevation in stem cell factor and circulating stem cells. We conclude that HBO2 mobilizes stem/progenitor cells by stimulating NO synthesis.

nitric oxide; CD34; CD133; CXCR4; eKit; colony-forming cells; progenitor cells

28, 32). Hematopoietic SPCs are typically obtained for the purpose of bone marrow transplantation by administration of chemotherapeutic agents and growth factors (36). Utilizing these agents to obtain autologous SPCs for treating disorders such as organ and limb ischemia, and refractory wounds, has been considered, but application is thwarted because of risks such as acute arterial thrombosis, angina, sepsis, and death (7, 20, 21, 27, 29, 30, 36).

Nitric oxide (NO) plays a key role in triggering SPC mobilization from the bone marrow via release of the stem cell active cytokines, eKit ligand (stem cell factor, SCF) (1, 8). Because HBO2 can activate NO synthase in different tissues, we hypothesized that exposure to HBO2 may stimulate SPC mobilization to the peripheral circulation (33, 34). In a murine model, we found HBO2 augments SPC mobilization and recruitment to ischemic wounds and hastens ischemic wound healing (Goldstein LJ, Gallagher K, Bairdhy V, Bauer SM, Bauer RJ, Buerk DG, Thom SR, Velazquez OC, unpublished observations). SPCs have been shown to home to ischemic wounds, where they are required for angiogenesis (3).

HBO2 therapy is administered for a variety of maladies in a hyperbaric chamber where patients breathe pure O2 at partial pressures up to 3.0 atmospheres absolute (ATA). HBO2 is used in a standard fashion as prophylactic treatment to reduce the incidence of osteoradionecrosis (ORN) in patients who must undergo surgery involving tissues previously exposed to radiotherapy (6, 15). We obtained peripheral blood samples from 19 volunteers and from a group of patients undergoing HBO2 treatment for ORN.
Shortly after the limb is amputated, the epithelium layer covers the exposed limb bud, forming the wound epithelium (WE).

A group of stem cells collects below this layer, forming the blastema.

The WE signals the stem cells below it to rebuild the limb, recreating the limb from the point of injury out towards the hand.

The final regenerated limb is indistinguishable from the original.

LESS STEM CELLS NEEDED THAN FORESEEN
Glycolysis
(Embden-Meyerhof glycolytic pathway)

Pyruvic acid (from glycolysis) is decarboxylated to form a two-carbon acetyl residue that reacts with coenzyme A to form acetyl-CoA, which then reacts with oxaloacetate to begin the Krebs cycle (citric acid cycle).

Glycolysis

Cytoplasm

Mitochondria

Electron transport chain

Outer compartment of mitochondrion

Inner compartment of mitochondrion

NADH dehydrogenase

bc1 complex

Cytochrome oxidase complex

Channel protein

Oxygen

H+ inner membrane

Ubiquinone (Q)

NADH

FADH2
WHAT DOSE DO WE NEED.......ARE WE USING TOO HIGH DOSES?
FISH AND MOUSE
THERAPEUTIC USE OF ENVIRONMENTAL CHANGES

• Apart from some « sanatoria » and other plane flights to cure pertussis.

• The real therapeutic use of environmental changes combined Oxygen and Pressure
Life without blood

Study of the influence of high atmospheric pressure and hypothermia on dilution of the blood

by


From the Surgical Department of the University of Amsterdam

In 1948 we (first al research) minutes; the reason for this...
« LIFE WITHOUT BLOOD »
BOEREMA 1960

Hyperbaric oxygen.
20 m depth.
0,5 % hématócrit
EMPIRICAL USE, ADAPTATION OF WHAT WAS ALREADY USED FOR DIVERS

Is empirism wrong?
WOULD A TOO LOW DOSE BE A PLACEBO?
THE PERFECT PROTOCOL

- One homogenous sample measured before and after intervention

- The same sample being measured before and after the time needed for the intervention but without it

- Time machine needed !!
The term “placebo” comes from the St. Jerome’s Latin translation of the Bible in Psalm 114:9 *Placebo Domino in regione vivorum*: “I will please”. This reference was used in the offices for the dead and is related to liturgy that funnels by definition a number of feelings, sensibility, understanding and analysis.
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967

Fig 1. Rationale of the study.
Fig 2. Experimental design.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967
Fig 3. No-treatment group.
Fig 4. Means (+SD) for all the measurements in the oxygen group.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967
Fig 5. Means (+SD) for all the measurements in the aspirin group.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967
Fig 6. Means (+SD) for all the measurements in the mixed group.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967
Fig 8. Model that explains the findings of the present study.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967
IN A NUTSHELL

• Ritual is the clue, mixing placebos doesn’t work (goes back to the origin of placebo)
• Physiotherapy sessions or Hyperbaric Oxygen sessions are a «ritual» by essence.
• It appears that totally exclude placebo effect is not feasible.
MISTAKE.......
IF VASCULARISATION IS STILL PRESENT AND EFFECTIVE, LOWER DOSES ARE OF INTEREST.
NORMOBARIC OXYGEN & LYMPH DRAINAGE

Original Research
Normobaric oxygen can enhance protein captation by the lymphatic system in healthy humans.

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1DAN Europe, IDAN Research Division, 2Université Libre de Bruxelles Institut Supérieur d’Éducation Physique et Kinésithérapie, Brussels, Belgium; 3Hôpital Erasme Université Libre de Bruxelles, General Human Biology Dept., Brussels, Belgium. *These authors contributed equally to this work.

Figure 2. Statistical comparison between the control absorption speed (angular variation) in the axillary region, the pre-oxygen situation and after 30 minutes of normobaric oxygen breathing. *p<0.05; **p<0.01.

Angular variation of lymphoscintigraphic trace

- Control
- Pre O2
- +O2
Microvascular unit

Venule

Arteriovenous shunt (S)

Pre-capillary sphincters exist at the origin of each capillary

Metarteriole

Capillaries

Arteriole
LASERFLOW SPECKLE DOPPLER
Non-visible laser for measurement

Visible laser for area marking

Color camera

Detector camera
MANUAL LYMPHATIC DRAINAGE (LEDUC)
UPPER LIMD EDEMA TREATEMENT
CUTANEOUS PERFUSION NO EDEMA (MICROVASCULARISATION)
PERFUSION LYMPHOEDEMA
(AXYLLARY LYMPHECTOMY)
LaserFlow Doppler Variation
n=8 (20 min treatment)

% of control values

- Normative
- Patient
- MLD

0.001
0.03
ns

0.004 **
**

0,001
0,004
0,03

** Robin Hood: Prince of Thieves **

Original Motion Picture Soundtrack
Composed and Conducted by Michael Kamen
O₂ → Capillary → O₂ → Cellules

O₂ → Capillary → O₂ → Cells
Maximum $O_2$ Diffusion Distance From a Functional Capillary

Silver 1976
Kroch's Mathematical Model (1919)

**ARTERIAL END**
- $P_O_2 = 100$ mmHg
- $R = 64$ MICROMETERS

**VENOUS END**
- $P_O_2 = 34$ mmHg
- $R = 36$ MICROMETERS

- **ARterial End**
  - $P_O_2 = 2000$ mmHg
  - $R = 247$ MICROMETERS

- **VENous End**
  - $P_O_2 = 100$ mmHg
  - $R = 64$ MICROMETERS

1 ATA - AIR

3 ATA - OXYGEN
HYPOXIA → HBO → REDUCTION IN CELLULAR ENERGY → EDEMA → HBO → INCREASED DIFFUSION DISTANCE → HBO → HYPOXIA
SPINAL CORD INJURY

Haemorrhage
Oedema
Hypoxia
Acute Phase Proteins

Blood Endothelium Tissues

Margination Chemotaxis

Platelets

ICAM-1

ELAM-1

Neutrophil

TGF-β

IL-8

MCP

IL-1

IL-1/TNF

Mononuclear Phagocyte

Tissue

CNS

FEVER

Cortisol

Inflamed Tissue

Stroma

Hepatocyte

Acute Phase Proteins

IL-1, IL-6

TNF

IL-1/TNF

IL-6

IL-1/TNF

Acute Phase Proteins

Blood

Endothelium
1991 GREG SEMENZA
HIF-1ALPHA
INTRODUCTION

• Erythropoietin (EPO) regulates RBC homeostasis but also known as antiapoptotic neuroprotective agent

• Polypeptid (cytokine) hormone (Bazan, 1990)
Production in renal proximal tubular cell, in response to tissue hypoxia (Goldwasser, 1957)

Normal plasma values: 5 - 25 mU/ml

POSSIBLE OTHER STIMULUS?

- Serum EPO measurements in apnea divers after 3 dives to -40 m (1999 Malta EUBS Meeting)
- [EPO] markedly elevated!
- Hypothesis: tissular pO$_2$ variation as a stimulus for EPO production
Descent

Increase of alveolar pO₂

Tissue hyperoxia

0m

-40m
Alveolar $pO_2$ decrease

Ascent

Return to normoxia

-40m

0m
CONCEPT OF "RELATIVE HYPOXIA"

Tissue N₂-O₂ balance: increase in relative N₂ content

"Trigger time": at least 45 minutes = sustained change
NORMOBARIC HYPEROXIA

- 2cc blood samples
- -20°C freezing of plasma
- RIA assay < 24hrs
Percentual variation of EPO plasmatic concentration

% of control values

Time (hours)

2 hours of NOB (from -2 to 0)

**

*
Percentual variation from control group

Control group mean levels

% from control group

Control group mean levels

*  
**  
***  

time (h)
Plasma [EPO] after 120 min. of normobaric 100% oxygen breathing

\[ y = 2.57x + 86.15 \]
\[ R^2 = 0.93 \quad p = 0.0001 \]

[EPO] variation % of control

Post NOB time (hours)
[EPO] Plasma variation after HOB

\[ y = -1.59 + 80.54 \]

\[ R^2 = 0.61 \quad p = 0.038 \]

Hours post HOB (120 min. of 100% O2)

2.8 ATA
Serum erythropoietin levels in healthy humans after a short period of normobaric and hyperbaric oxygen breathing: the "normobaric oxygen paradox"
Costantino Balestra, Peter Germonpré, Jacques R. Poortmans and Alessandro Marroni
doi:10.1152/japplphysiol.00964.2005

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This information is current as of February 9, 2006.
HERE ARE THE ACTORS

- ROS
- HIF-1α
- β
- VHL
- GSH
- GSSG
Normal situations

Normoxia

HIF1-α

HIF1-α

HIF1-α

OH

OH

OH

Ub

VHL

Prolyl-Hydroxylase

HIF1-α

Extreme situation! In less severe hypoxia, GSH neutralises all of the OH

Hypoxia

GSH neutralises some, not all OH and converts to GSSG

EPO + VEGF

Prolyl-Hydroxylase

GSH

HIF1-α

Not all OH and converts to GSSG
Normobaric hyperoxia

Hyperoxia induces extra GSH

GSH synthetase

HIF1-α

Hyperoxia

Ub

Prolyl-Hydroxylase

Return to Normoxia

Extra GSH neutralises all OH after return to normoxia

EPO + VEGF

Prolyl-Hydroxylase

GSH neutralises all OH after return to normoxia

HIF1-α

Ub
Hyperbaric hyperoxia

Excessive production of OH, limited increase in extra GSH synthesis

GSH synthetase

HIF1-α

Prolyl-Hydroxylase

Return to Normoxia

Time lapse before restitution of GSH out of GSSG; in mean time: spill of OH to permit Ub

Excessive production of OH, limited increase in extra GSH synthesis
Normobaric hyperoxia

Hyperoxia induces extra GSH after return to normoxia.

GSH synthetase

Extra GSH neutralises all OH after return to normoxia.
THE ABYSS PROJECT (PONZA ITALY)

<table>
<thead>
<tr>
<th>Immersion days</th>
<th>Serum EPO % of control value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre dive</td>
<td>100</td>
</tr>
<tr>
<td>7 days</td>
<td>50</td>
</tr>
<tr>
<td>14 days</td>
<td>100</td>
</tr>
<tr>
<td>2 h post</td>
<td>150</td>
</tr>
<tr>
<td>24 h post</td>
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</table>

EPO Modulation in a 14-Days Undersea Scuba Dive

Authors

Affiliations
Affiliation addresses are listed at the end of the article

Key words
- erythropoietin (EPO)
- hyperbarism
- hyperoxia
- scuba dive
- reactive oxygen species (ROS)
- normobaric oxygen paradox (NOP)

Abstract

Erythropoiesis is affected during deep saturation dives. The mechanism should be related to a downregulation of serum Erythropoietin (s-EPO) concentration or to a toxic effect of the hyperbaric hyperoxia. We evaluated s-EPO and other haematological parameters in 6 scuba divers before, during and after a 14-days Guinness saturation dive (8–10 m). Athletes were breathing air at 1.8–2 ATA, under the control of a team of physicians. Serum parameters were measured before diving (T0) and: 7 days (T1), 14 days (T2) after the beginning of the dive and 2 h (T3) and 24 h (T4) after resurfacing. Hgb, and many other haematological parameters did not change whereas Ht, s-EPO, the ratio between s-EPO predicted and that observed and reticulocytes (absolute, percent) declined progressively from T0 to T3. At T4 a significant rise in s-EPO was observed. Hgb did not vary but erythropoiesis seemed to be affected as s-EPO and reticulocyte counts showed. All these changes were statistically significant. The experiment, conducted in realistic conditions of dive length, oxygen concentration and pressure, allows us to formulate some hypotheses about the role of prolonged hyperbarism on erythropoiesis. The s-EPO rise, 24 h after resurfacing, is clearly documented and related to the "Normobaric Oxygen Paradox". This evidence suggests interesting hypotheses for new clinical applications such as modulation of s-EPO production and Hgb content triggered by appropriate O2 administration in pre-surgical patients or in some anemic disease.
CLINICAL APPLICATION: METHODS

Two randomized groups of patients target number n=24
Post cardiac surgery
No hypoxia allowed
No Haemoglobin levels drop
EPO Level in Cardiac Patients post O2 administration (randomly assigned groups)

- 50% oxygen n=9, $y = 18.62x + 85$, $r^2 = 0.97$, $p = 0.014$
- 100% oxygen n=10, $y = 5.78x + 102.8$, $r^2 = 0.96$, $p = 0.018$

Post Oxygen session (hours) vs. % of control values
Increase in endogenous erythropoietin synthesis through the normobaric oxygen paradox in cardiac surgery patients

Editor—Exogenous erythropoietins (EPOs) are used worldwide to reduce allogenic blood transfusion exposure. However, their use can be associated with some serious adverse effects and has a significant economic impact on public health systems because of the high cost of these drugs.

Correspondence

The normobaric oxygen paradox (NOP) is a new mechanism of triggering endogenous EPO production described in healthy human volunteers. Participants were asked to breathe normobaric oxygen for 2 h at an inspired oxygen fraction ($F_{10}$) of 100%. After 2 h in the hyperoxic state, participants were quickly switched back to normoxic conditions while breathing air. The authors found that EPO levels were significantly increased during the next 12–36 h compared with baseline levels. This study demonstrated that a sudden and sustained decrease in tissue oxygen tension, without a low level of tissue oxygen tension, could lead to an increase in serum EPO levels in these healthy individuals.

We conducted a prospective, randomized, double-blind pilot trial at one university medical centre to assess the presence of this mechanism among patients undergoing cardiac surgery. After institutional Ethics Committee approval, 20 patients who gave written informed consent were studied. Inclusion criteria were age > 18 yr, non-urgent valvular and/or coronary artery bypass graft surgery with the planned use of extracorporeal circulation, and expected postoperative mechanical ventilation in the intensive care unit (ICU). Exclusion criteria were severe preoperative renal disease, severe respiratory disease, and massive intraoperative bleeding. The protocol did not require any modification of the anaesthetic or the surgical routine management of the patient in the operating theatre.

At arrival in the ICU, patients were randomized to two

Conflict of interest

None declared.
Oxygen breathing may be a cheaper and safer alternative to exogenous erythropoietin (EPO)

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The Balestra study is clear evidence that oxygen breathing can stimulate endogenous EPO, but it is less clear whether this method can effectively treat anemia. A test that lends support to this hypothesis has been performed.

Fig. 1 is the hemoglobin chart of a 42-year old female patient undergoing chemotherapy for stage III breast cancer. The treatment consisted of Adriamycin and Cytoxan, followed by Taxol. As the graph shows, an anemic trend commenced and worsened along with the beginning of chemotherapy treatment.

About 85 days into chemotherapy, treatment with oxygen breathing commenced. This consisted of breathing aviation oxygen (>99% pure oxygen) via a cannula for about 90 min, two to three times
The graph shows the hemoglobin (Hgb) levels over the course of chemotherapy treatment. The treatments included biweekly administration of Adriamycin and Cytoxan, followed by weekly Taxol. Periods of oxygen therapy are also indicated. The Hgb levels decrease significantly during the chemotherapy phases and show an upward trend as oxygen therapy is administered.
Hemoglobin level

- Stop of O2
- For Holidays
- Restart of NOB

Days of treatment

Hb g/dl
PLOTTING THE 2 PATIENTS DATA

Levels of Hb (g/dl) in two patients breathing oxygen. The first 100% O₂ every other day with adjuvant drug therapy (Darbepoetin Alpha + IV iron) (Myelofibrosis). The second breathing 40% O₂ 3 times per week with no other erythroid stimulating agents (Chemotherapy).
The 'normobaric oxygen paradox': a simple way to induce endogenous erythropoietin production and concomitantly raise hemoglobin levels in anemic patients

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EPO and doping

Costantino Balestra · Peter Germanpré

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To the Editor,

It is with great interest that we read exchanges on intermittent hypoxic (Boring 2009; Ferretti 2009) exposure as a potential doping procedure. Erythropoietin (EPO) does introduce potential concerns in terms of doping, both due to its effects and side effects. An earlier publication on exogenous EPO (Nosakes 2008) clearly showed an increase of sub-maximal performance with a significant increase of time to exhaustion after prolonged rHuEPO administration. It is clear that in healthy subjects, at sub-maximal effort levels, cardiac output is sufficient to maintain adequate oxygen delivery to active muscles. Accordingly, it appears that EPO achieves more than increasing blood oxygen carrying capacity alone. Being both a hormone and a cytokine, the actual actions of EPO are complex: EPO is neuroprotective and even neuroregenerative in both the peripheral and central nervous system. Moreover, EPO also has ant apoptotic effects that may be coupled to antioxidant activity.

Exercise-induced plasma volume contraction is linked to urine testing for exogenous EPO has been available for several years. It has been used in international cycling events. However, this does not exclude the possibility of endogenous EPO induction. Intermittent hypoxia (Sanchis-Gomar et al. 2009) is the natural trigger for EPO production, and is widely used by (endurance) athletes since many years. We have recently described the use of intermittent hypoxia to stimulate EPO production (Balestra et al. 2006). This has subsequently been shown to be capable of increasing haemoglobin levels in a chronically anaemic patient (Bork 2007).

The mechanism proposed to explain this “normobaric oxygen paradox” involves a complex play of oxygen-free radicals (OFRs) presence and their “scavenging” enzymes in the cell. In the presence of OFR, the continuously produced hypoxia-inducible factor alpha (HIF-1α) is instantly linked to the (tumour suppressing) Von Hippel Lindau Protein (VHLp). This complex is subsequently ubiquitinated in the prolyl-oxidase pathway and finally recycled in the proteasome. In a hypoxic state, the absence of OFR prevents...
Hb Variation after 100% O2 breathing
(30 minutes every other day)

Day 14 means 4 days after cessation of NOB
Pulsed high oxygen induces a hypoxic-like response in human umbilical endothelial cells and in humans
F. Cimino, C. Balestra, P. Germonpré, D. De Bels, F. Tillmans, A. Saija, A. Speciale and F. Virgili
doi: 10.1152/japplphysiol.00922.2012

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This information is current as of December 2, 2012.
HYPOXIA = HYPEROXIA

Hb Variation after O2 breathing (30 minutes every other day)

Pre day 2 day 4 day 6 day 8 day 10 Day 14 day 17 Day 20

90 95 100 105 110 115 120 125

100% (n=12)
15% (n=12)

Day 14 means 4 days after cessation of NOB

% of control value

Hb variation after different PO2 breathing (30 min every other day) (100% and 15%)

Days of treatment

% of control values

R² = 0.75
p = 0.0001

y = 1.07x + 99.7

Days of treatment
HUVEC CELLS

INTERMITTENT OXYGEN HYPOXIA-HYPEROXIA


The importance of oxygen concentration sensing by cells in a wide range of cellular responses renders the full understanding of HIF activity an attractive tool to open new avenues in the development of therapeutics able to target HIF pathway, either repressing or activating the expression of a large spectrum of genes in turn involved in a wide spectrum of diseases (29, 30). According to this pivotal role in metabolism regulation, in the last decade, HIF has been the object of a large number of investigations, which addressed the basis of its mechanism of action. It is established that HIF-1 acts as a heterodimer, consisting of HIF-1α and HIF-1β subunits. HIF-1α represents the regulatory subunit that is primarily activated under conditions of oxygen deprivation, when hydroxylation by prolyl and asparaginyl hydroxylases is inhibited. This results in stabilization and transactivation of HIF-1α, which induces the expression of ~100 target genes by binding to the hypoxia-responsive element (HRE) located in the regulatory DNA sequence (30).

Despite such an established understanding of the basic mechanism of action, some aspects of HIF modulation are still unresolved. A few years ago, our laboratory proposed a novel mechanism of regulation of HIF activity based on relative changes of oxygen availability rather than on steady-state hypoxic or hypoxic conditions (5).

On the basis of our experimental observations addressing the effect of redox relative hypoxia after hypoxia obtained by normoxic and hyperoxic breathing conditions, we hypothesized that the expression of one of the HIF target genes, erythropoietin (EPO), is modulated by the cellular availability
ORTHOPAEDIC PATIENTS

• Traumatic orthopaedic patients (n=80)
• Followed after surgery for 7 days
• Mean age +/- 80
• Randomized in two groups
  • 1 h/day Oxygen
  • 1 h/day Air
• Blinded, no therapeutic change
<table>
<thead>
<tr>
<th></th>
<th>Oxygen Group (n=40)</th>
<th>Air Group (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio M/F</td>
<td>32/8 (80% of M)</td>
<td>30/10 (75% of M)</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>60.4 ± 7.43</td>
<td>61.7 ± 8.41</td>
<td>0.4832</td>
</tr>
<tr>
<td>Delay to intervention (Days)</td>
<td>2.03 ± 1.03</td>
<td>2.28 ± 0.96</td>
<td>0.2638</td>
</tr>
<tr>
<td>Side ratio (Left/Right)</td>
<td>19/21</td>
<td>22/18</td>
<td></td>
</tr>
<tr>
<td>Type of intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal femoral intramedullar nail</td>
<td>31</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Hernarthroplasty</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Perioperative blood loss (ml)</td>
<td>475 ± 282</td>
<td>424 ± 378</td>
<td>0.3862</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
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<tr>
<td>Creatmin</td>
<td>52.5 ± 15.5</td>
<td>47.1 ± 21.7</td>
<td>0.1007</td>
</tr>
<tr>
<td>Urea</td>
<td>0.663 ± 0.234</td>
<td>0.763 ± 0.237</td>
<td>0.0656</td>
</tr>
<tr>
<td>Glomerular filtration (ml/min)</td>
<td>88.4 ± 22.1</td>
<td>80.3 ± 24.8</td>
<td>0.0512</td>
</tr>
<tr>
<td>Associated pathologies</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Neurologic diseases</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Cardiopathy</td>
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<td>6</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
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<td>7</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Transfusion</td>
<td>3</td>
<td>14</td>
<td>0.0052</td>
</tr>
<tr>
<td>No transfusion</td>
<td>37</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>
## TRANSFUSION RATE

<table>
<thead>
<tr>
<th></th>
<th>Transfusion</th>
<th>No transfusion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>3</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Air</td>
<td>14</td>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>63</td>
<td>80</td>
</tr>
</tbody>
</table>

$p = 0.019$, two tailed Fischer’s exact test

- $1.2 \pm 0.7$ RBC/patient Air
- $0.12 \pm 0.44$ RBC/patient $O_2$  

$<0.01$
Original Contribution

Can the normobaric oxygen paradox (NOP) increase reticulocyte count after traumatic hip surgery?

Pierre Lafère MD (Staff Anesthesiologist) a,d, Thomas Schubert MD (Staff Surgeon) b, David De Bels MD (Assistant Professor of Critical Care Medicine) c,e,* Peter Geronpré MD (Head, Center for Hyperbaric Oxygen Therapy) d,e, Costantino Balestra PhD (Head, Environmental and Occupational Physiology Laboratory) e,f

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Received 28 November 2011; revised 25 June 2012; accepted 26 June 2012

Abstract

Study Objective: To determine if the normobaric oxygen paradox (NOP) was effective in increasing reticulocyte count and reducing postoperative requirements for allogeneic red blood cell transfusion after traumatic hip surgery.

Design: Prospective, randomized, double blinded, multi-center study.

Setting: Surgical wards of two academic hospitals.

Patients: 85 ASA physical status 1 and 2 patients undergoing surgery for traumatic hip fracture.

Interventions: Patients were randomly assigned to receive 30 minutes of air [air group (control); n = 40] or 30 minutes of 100% oxygen (O2 group; n = 44) at 15 L/min every day from the first postoperative day (POD 1) until discharge.

Measurements: Venous blood samples were taken at admission and after surgery on POD 1, POD 3, and POD 7. Hemoglobin (Hb), hematocrit (Hct), reticulocytes, hemodynamic variables, and transfusion requirements were recorded, as were hospital length of stay (LOS) and mortality.

Main Results: Full analysis was obtained for 80 patients. On hospital discharge, the mean increase in reticulocyte count was significantly higher in the O2 group than the air group. Percent variation also increased: 144.9% ± 41.4% vs 104.7% ± 32.6%, respectively; P < 0.001. No difference in Hb or Hct levels was noted at discharge. Allogeneic red blood cell transfusion was 7.5% in the O2 group versus 33% in the air group (P = 0.0032). Hospital LOS was significantly shorter in the O2 group than the air group (7.2 ± 0.7 days vs 7.8 ± 1.6 days, respectively; P < 0.05).
Both Surgeons received Congratulations From the Blood bank one year after the Experiment…….Guess Why??
Hyperoxia may be beneficial

Enrico Calzia, MD, PhD; Pierre Asfar, MD, PhD; Balázs Hauser, MD, PhD; Martin Matejovic, MD, PhD; Costantino Ballestra, PhD; Peter Radermacher, MD, PhD; Michael Georgieff, MD, PhD

The current practice of mechanical ventilation comprises the use of the least inspiratory O₂ fraction associated with an arterial O₂ tension of 55 to 80 mm Hg or an arterial hemoglobin O₂ saturation of 88% to 95%. Early goal-directed therapy for septic shock, however, attempts to balance O₂ delivery and demand by optimizing cardiac function and hemoglobin concentration, without making use of hyperoxia. Clearly, it has been well-established for more than a century that long-term exposure to pure O₂ results in pulmonary and, under hyperbaric conditions, central nervous O₂ toxicity. Nevertheless, several arguments support the use of ventilation with 100% O₂ as a supportive measure during the first 12 to 24 hrs of septic shock. In contrast to patients without lung disease undergoing anesthesia, ventilation with 100% O₂ does not worsen intrapulmonary shunt under conditions of hyperinflammation, particularly when low tidal volume-high positive end-expiratory pressure ventilation is used. In healthy volunteers and experimental animals, exposure to hyperoxia may cause pulmonary inflammation, enhanced oxidative stress, and tissue apoptosis. This, however, requires long-term exposure or injurious tidal volumes. In contrast, within the timeframe of a perioperative administration, direct O₂ toxicity only plays a negligible role. Pure O₂ ventilation induces peripheral vasoconstriction and thus may counteract shock-induced hypotension and reduce vasopressor requirements. Furthermore, in experimental animals, a redistribution of cardiac output toward the kidney and the hepato-splanchnic organs was observed. Hyperoxia not only reverses the anesthesia-related impairment of the host defense but also is an antibiotic. In fact, perioperative hyperoxia significantly reduced wound infections, and this effect was directly related to the tissue O₂ tension. Therefore, we advocate mechanical ventilation with 100% O₂ during the first 12 to 24 hrs of septic shock. However, controlled clinical trials are mandatory to test the safety and efficacy of this approach. (Crit Care Med 2010; 38[Suppl]:S559–S568)

Key Words: early goal-directed therapy; septic shock; vasoconstrictor; intrapulmonary shunt; hypoxic pulmonary vasoconstriction; oxygen radicals; oxidative stress; oxygen toxicity; nitric oxide; apoptosis; leukocyte endothelial interaction; normobaric oxygen paradox; erythropoietin
Original articles

The ‘normobaric oxygen paradox’: does it increase haemoglobin?

David De Bels, Sigrid Theunissen, Jacques Devriendt, Peter Germonpré, Pierre Lafere, Joseph Valsamis, Thyl Snoeck, Philippe Meeus and Costantino Balestra

Abstract


Background: A novel approach to increasing erythropoietin (EPO) using oxygen (O₂) (the ‘normobaric oxygen paradox’) has been reported in healthy volunteers. We investigated whether the EPO increase is sufficient to induce erythropoiesis by comparing two protocols of O₂ administration.

Methods: We compared the effect of daily versus alternate days 100% O₂, breathed for 30 minutes, on haemoglobin concentrations during a 12-day period. Nine subjects underwent the two protocols six weeks apart.

Results: We observed a significant increase in haemoglobin (as a percentage of baseline) in the alternate-days group compared to the daily group and to baseline after four days (105.5 ± 5.7 % vs. 99.6 ± 3.3 % difference from baseline; P < 0.01). At the end of the experimental period, haemoglobin values increased significantly compared to baseline in both groups. There was a significant percentage rise in reticulocyte count in the alternate-days group compared to the daily group (182 ± 94 % vs. 93 ± 34 %; P < 0.001).

Conclusion: The normobaric oxygen paradox seems effective in increasing haemoglobin in non-anaemic, healthy volunteers, providing sufficient time is allowed between O₂ applications. The exact time interval is not clearly defined by this study but should probably be at least or greater than two days. Further studies are needed to define more precisely clinical applications in the use of O₂ as a pharmaceutical agent.

Key words

Oxygen, haematology, reactive oxygen species (ROS), physiology
Comparison baseline haemoglobin after 30 minutes of 100% O$_2$ breathing daily (protocol A; † $P < 0.01$) or on alternate days (protocol B; * $P < 0.01$); ns – not significant
Oxygen Sensing, Homeostasis, and Disease

TO THE EDITOR: Two points could have been added to the review article by Semenza (Aug. 11 issue) on a fundamental mechanism in cell, tissue, and organ metabolism. First, considering the metabolic signals modifying signal transduction, the author mentions hypoxia as the sole trigger to expression of hypoxia-inducible factor 1 (HIF-1). One study pointed out the possible role of nonhypoxic partial pressure of oxygen (PO2) variation as a trigger to HIF-1α. In this model, transient normobaric hypoxia followed by a return to normoxia led to a significant increase in serum erythropoietin concentration. This increase began 8 hours after the return to normoxia, which is consistent with the time frame of gene expression.

Second, in the section on co-opted adaptation to hypoxia in cancer, the author points out that intratumoral hypoxia is associated with increased risks of metastasis and death. This finding has been the trigger for research on the consequences of hypoxia on cancer-cell survival. A recent hypothesis is that transient normobaric hypoxia could be deleterious for tumor cells and, in parallel, beneficial (cytoprotective) for normal cells; this could open interesting therapeutic options in adjuvant treatments against cancer.

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No potential conflict of interest relevant to this letter was reported.


TO THE EDITOR: The review by Semenza examines the role of HIF-1α in the context of hypoxia and ischemia. However, we think that the role of HIF-1α can be seen from another point of view. HIF-1α does not appear to be the clear hypoxic marker. It is stabilized not only because of hypoxia but also by metabolic imbalances, induced by low extracellular pH values. The curious association of metabolic pathways and different metabolites with this marker causes doubt about the function of HIF-1 as a molecular regulator to oxygen deprivation. The fact that hypoxia always decreases the extracellular pH value discloses another face of HIF-1 beyond the phenomenon called hypoxia. The biologic function of this protein is rather that of a sensitive controller and regulator of an adaptive metabolic response to alterations of the pH value. That this function is independent from the oxygen status of cells is reflected by a multitude of HIF-1 detections at normoxia. Altogether, we suggest that HIF-1 is mainly a sensor and regulator for the extracellular pH value.

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The “Normobaric Oxygen Paradox”: a new tool for the anesthetist?

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ABSTRACT

Hypoxia is the natural trigger for endogenous EPO production but recently the use of intermittent hyperoxia to stimulate EPO has been postulated and this phenomenon has been called the “normobaric oxygen paradox” (NOP). The “NOP” is a mechanism by which oxygen regulates the expression of the Hypoxia Inducible Factor 1 alpha (HIF-1α). The HIF-1α-depending gene regulation is responsible for many different genetic expressions including EPO and VEGF. It has been proposed that relative changes of oxygen availability rather than steady state hypoxic or hypoxic conditions, play an important role in HIF transcriptional effects. According to this hypothesis, the cell interprets the return to normoxia after a hyperoxic event as an oxygen shortage, and induces HIF-1-regulated gene synthesis, including EPO. Being both a hormone and a cytokine, the actual actions of EPO are complex: its clinical utility has been postulated for neuroprotection and cardioprotection. The precise level of inspired oxygen and the exact time-frame for its iterative administration are not totally known. N-Acetyl-L-Cysteine (NAC) supplementation has been shown to help. All the reported data demonstrate how hyperoxic and hypoxic states can potentially be manipulated if oxygen is been considered as a multifaceted molecule more than just a gas.

(Minerva Anestesiol 2014:80:366-72)

Key words: Oxygen - Hyperoxia - Erythropoietin.
NAC - I - O₂
« Pluralitas non est ponenda sine necessitate »

Occham's Razor
The normobaric oxygen paradox: A novel way to administer oxygen as an adjuvant treatment for cancer

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ABSTRACT

The "normobaric oxygen paradox" is a dual mechanism by which oxygen regulates the expression of the Hypoxia Inducible Factor 1 alpha (HIF-1α). The HIF-1α-dependent gene regulation is responsible for many different genetic expressions including EPO and VEGF that are usually expressed in parallel. First, VEGF under-expression could decrease tumor angiogenesis leading to a decrease in tumor growth or even apoptosis of cancer cells. Second, induction of EPO-expression can provide cytoprotection. Altogether, this could be deleterious for cancer cells while helping non-malignant cells (at least neural and cardiac) cells to be protected from the side effects of chemotherapy. Eventually, HIF induction could boost immune response by inflammatory cells, increasing their antitumor activity.

INTRODUCTION

Cancer still remains one of the leading causes of death worldwide. The therapeutic arsenal is regularly increasing and most chemotherapeutic agents aim at inducing selective apoptosis of cancer cells. A deficit in the apoptotic machinery can be seen in more than 50% of cancers [1]. The "normobaric oxygen paradox" seems to have a beneficial effect on chemotherapy-induced anemia [2,3] while inducing modifications in the cellular mechanisms of adaptation to hypoxia. Hypoxia. This latter depends on oxygen free radicals availability. In fact, in presence of reactive oxygen species (ROS) and under normoxic conditions, the hypoxia Inducible Factor 1 alpha, (HIF-1α) is hydroxylated by prolyl-hydroxylase. This results in ubiquitylation by the Von Hippel Lindau tumor suppressing Protein (VHLp) and finally in the degradation of HIF-1α in the proteasome (see Fig. 1). In case of limited availability or absence of reactive oxygen species, the HIF-1α will not link with VHLp and thus can be dimerized with the HIF-1β. This HIF complex can thus bind to target promoters known as hypoxia responsive elements leading to the transcription of the erythropoietin gene as well as many other genes involved in cellular metabolism [5].
Research article

**Hyperoxia retards growth and induces apoptosis and loss of glands and blood vessels in DMBA-induced rat mammary tumors**

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Figure 2
Examples of eosin-hematoxylin stained tumor-tissue of the central (A) and peripheral (B) part of the mammary tumor in control (left) and during hyperoxic treatment (right, 1 bar, \( pO_2 = 1.0 \)). The images under A are scaled to the same magnification (x 4) and the images under B to the same magnification (x 10). Scale bar indicate 500 \( \mu m \) (A) and 100 \( \mu m \) (B).
ABDOMINAL ONCOLOGIC PATIENTS
N=60

Absolute RETICULOCYTES count

% of control values

O2 p=0,0008
Control p=0,002
NACO2 NS

p=0,37
p=0,87

p=0,0008
NS
p=0,87
p=0,002
FRACTAL DIMENSION OF LEUKEMIC CELLS AFTER HYPEROXIA

Fractal dimension Comparison
Jurkat cells after 18h of 60% O$_2$ Hyperoxia

Normoxia  Hyperoxia

Fractal Dimension (arbitrary units) p<0.0001
Combination of carboplatin and intermittent normobaric hyperoxia synergistically suppresses benz[a]pyrene-induced lung cancer

Hea Yon Lee, In Kyong Kim, Hye In Lee, Hwa Young Lee, Hye Seon Kang, Chang Dong Yoo, Hyeon Hui Kang, Hwa Sik Moon, and Sang Haek Lee

Background/Aims: We explored the effects of intermittent normobaric hyperoxia alone or combined with chemotherapy on the growth, general morphology, oxidative stress, and apoptosis of benz[a]pyrene (B[a]P)-induced lung tumors in mice.

Methods: Female A/J mice were given a single dose of B[a]P and randomized into four groups: control, carboplatin (50 mg/kg intraperitoneally), hyperoxia (95% fraction of inspired oxygen, and carboplatin and hyperoxia. Normobaric hyperoxia (95%) was applied for 3 hours each day from weeks 2 to 8. Tumor load was determined as the average total tumor numbers and volumes. Several markers of oxidative stress and apoptosis were evaluated.

Results: Intermittent normobaric hyperoxia combined with chemotherapy reduced the tumor number by 55% and the load by 72% compared with the control B[a]P group. Intermittent normobaric hyperoxia, either alone or combined with chemotherapy, decreased the levels of superoxide dismutase and glutathione and increased the levels of catalase and 1-hydroxydeoxyguanosine. The Bax/Bcl-2 mRNA ratio, caspase 3 level, and number of transferrin-mediated-DOTP nick-end labeling positive cells increased following treatment with hyperoxia with or without chemotherapy.

Conclusions: Intermittent normobaric hyperoxia was found to be tumoricidal and thus may serve as an adjuvant therapy for lung cancer. Oxidative stress and its effects on DNA are increased following exposure to hyperoxia and even more with chemotherapy, and this may lead to apoptosis of lung tumors.

Keywords: Apoptosis; Carboplatin; Hyperoxia; Lung neoplasms; Oxidative stress

KEY MESSAGE

1. Intermittent normobaric hyperoxia with carboplatin displays a synergistic tumoricidal effect in a mouse lung cancer model.
2. Addition of hyperoxia to chemotherapy enhanced oxidative stress, which is considered to induce cell death mainly via apoptosis.
3. Intermittent normobaric hyperoxia may be a useful adjuvant therapy for lung cancer.
Parabolic flights

% of control values

Post Scopo
Pré Paraboles
2g
0g
Pause
Post Praboles
Post Sol

80
90
100
110

110
100
90
80

*
Functional comparison between critical flicker fusion frequency and simple cognitive tests in subjects breathing air or oxygen in normobaria

Walter Hemelryck, Miroslav Rozloznik, Peter Germonpré, Costantino Balestra and Pierre Lafère

Abstract


Introduction: Measurement of inert gas narcosis and its degree is difficult during operational circumstances, hence the need for a reliable, reproducible and adaptable tool. Although being an indirect measure of brain function, if reliable, critical flicker fusion frequency (CFFF) could address this need and be used for longitudinal studies on cortical arousal in humans.

Methods: To test the reliability of this method, the comparison between CFFF and three tests (Math-Processing Task, Trail-Making Task, and Perceptual Vigilance Task) from the Psychology Experiment Building Language battery (PEBL) were used to evaluate the effect of 10 minutes of 100% normobaric oxygen breathing on mental performance in 20 healthy male volunteers.

Results: Breathing normobaric oxygen significantly improved all but one of the measured parameters, with an increase of CFFF (117.3 ± 10.04% of baseline, P < 0.0001) and a significant reduction of time to complete in both the math-processing (2,103 ± 432.1 ms to 1,879 ± 417.5 ms, P = 0.0091) and trail-making tasks (1,992 ± 715.3 to 1,524 ± 527.8 ms, P = 0.0241). The magnitude of CFFF change and time to completion of both tests were inversely correlated (Pearson r = -0.9695 and -0.8731 respectively, P < 0.0001). The perceptual vigilance task did not show a difference between air and O₂ (P > 0.4).

Conclusions: The CFFF test provides an assessment of cognitive function that is similar to some tests from PEBL, but requires a less complicated set up and could be used under various environmental conditions including diving. Further research is needed to assess the combined effects of increased pressure and variations in inspired gas mixtures during diving.
NARCOSIS TEST

Are You Drunk?

YES ☐ NO ☐
“Creativity is contagious, pass it on”

- Albert Einstein

Creativity is intelligence having fun

- Albert Einstein
THINGS CAN ALWAYS GO WRONG EVEN WHIT FORESEEN EVENTS....
YOUR ATTENTION
I THANK YOU
FOR