Prof. Dr. C. Balestra PhD
Past Pres. European Underwater & Baromedical Soc.
VP Dan Europe Res.& Edu.
VP Belgian Soc. Of Underwater and Hyperbaric Medicine
Haute Ecole Bruxelles-Brabant(HE2B)
Pôle Universitaire Bruxelles Wallonie
Environmental & Occupational (Integrative) Physiology Laboratory

HPNS and FUTURE Research Deep Saturation Diving Friend or Foe?

"HPNS is harmless long term"

vs

"of course HPNS causes excite-toxic brain damage »

"the divers have brain damage from HPNS"

vs

"No - they have PTSD »

"No - they are making it up to claim compensation because employment opportunities for saturation divers are reducing"

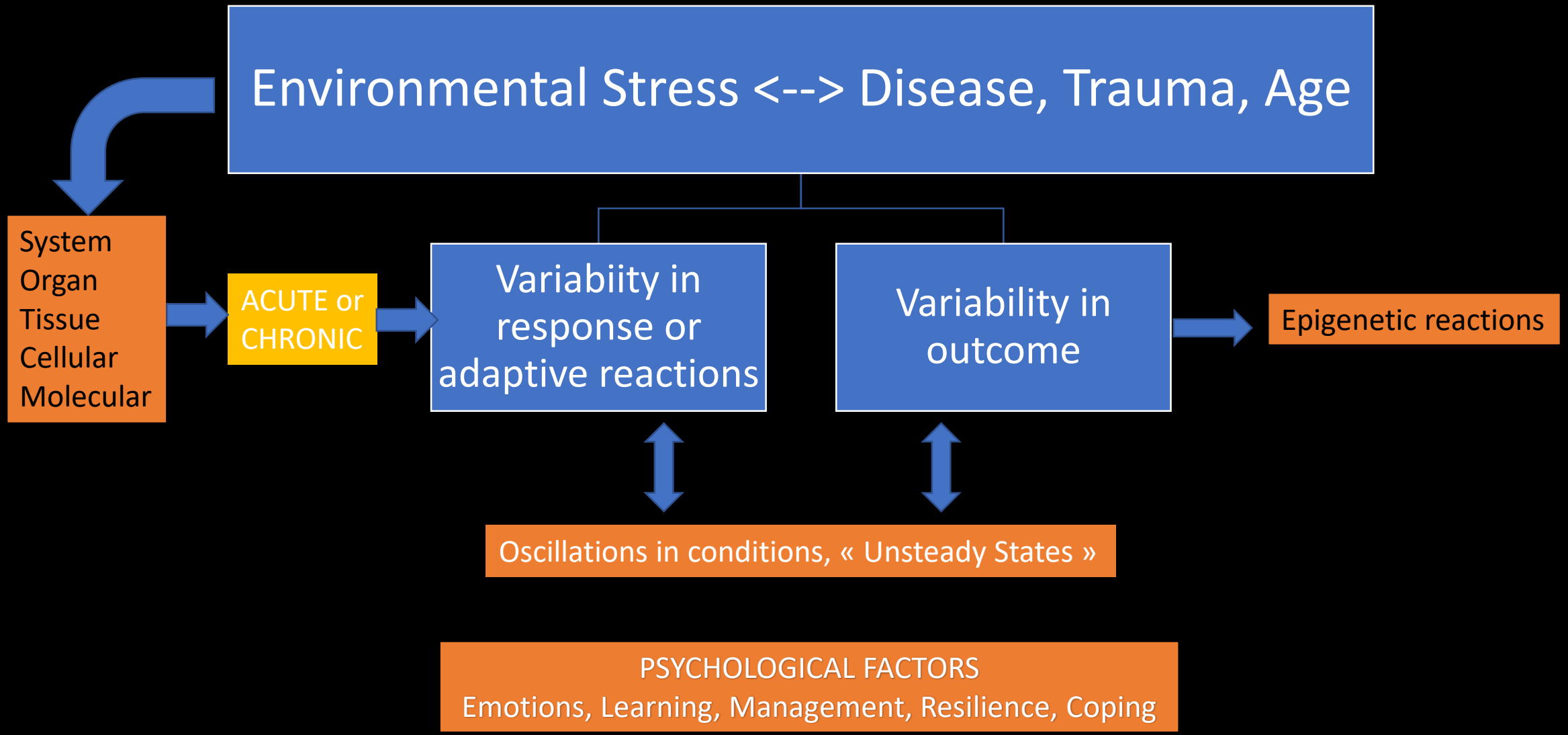
vs

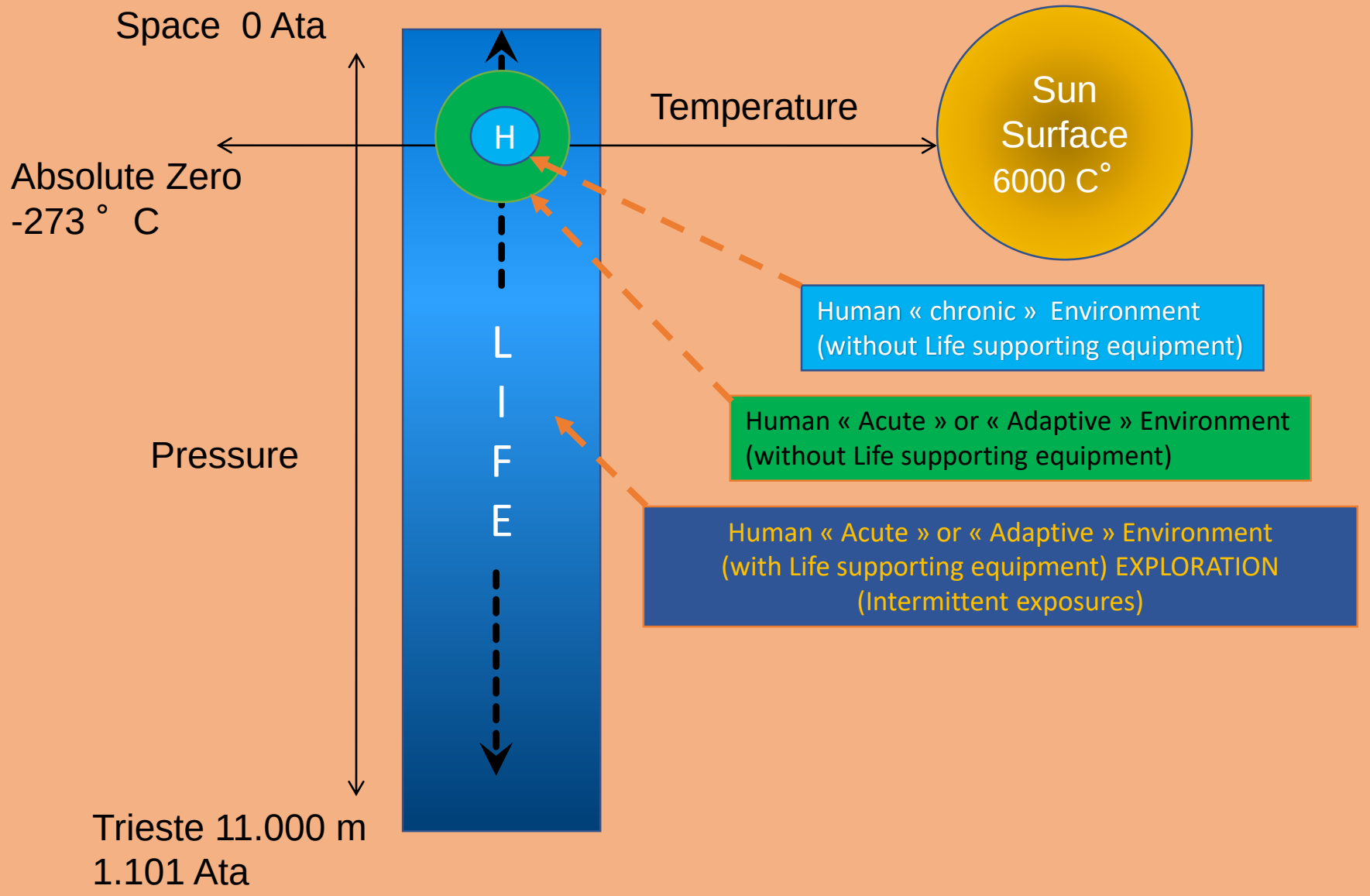
"we can't explain it so it must be mass psychogenic illness"

SATURATION is NOT ONLY HPNS

- Long term effects
- Oxytoxicyty
- Oxydative stress
- Microbiota changes
- PTSD like symptoms
- Mood disorders
- Recovery
- Adaptation
- Inflammation
- Bubbles effects
- Confinement

- High VO2max is a good protection to natural oxydative stress
- Recovery time importance
- Nutrition
- Well being
- Hygiene
- Quality of air


Environmental Stress <--> Disease, Trauma, Age
System
Organ
Tissue
Cellular
Molecular
ACUTE or
CHRONIC
Variabiity in
response or
adaptive reactions
Variability in
outcome
Epigenetic reactions
Oscillations in conditions, « Unsteady States »
PSYCHOLOGICAL FACTORS
Emotions, Learning, Management, Resilience, Coping


Space 0 Ata
Absolute Zero
-273 ° C
Pressure
Trieste 11.000 m
1.101 Ata
H
L
I
F
E
Temperature
Sun
Surface
6000 C°
Human « chronic » Environment
(without Life supporting equipment)
Human « Acute » or « Adaptive » Environment
(without Life supporting equipment)
Human « Acute » or « Adaptive » Environment
(with Life supporting equipment) EXPLORATION
(Intermittent exposures)

The Physiology and Pathology of Exposure

to

STRESS

A treatise based on the concepts of the

GENERAL-ADAPTATION-SYNDROME

and the

DISEASES OF ADAPTATION

by

HANS SELYE

M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada)

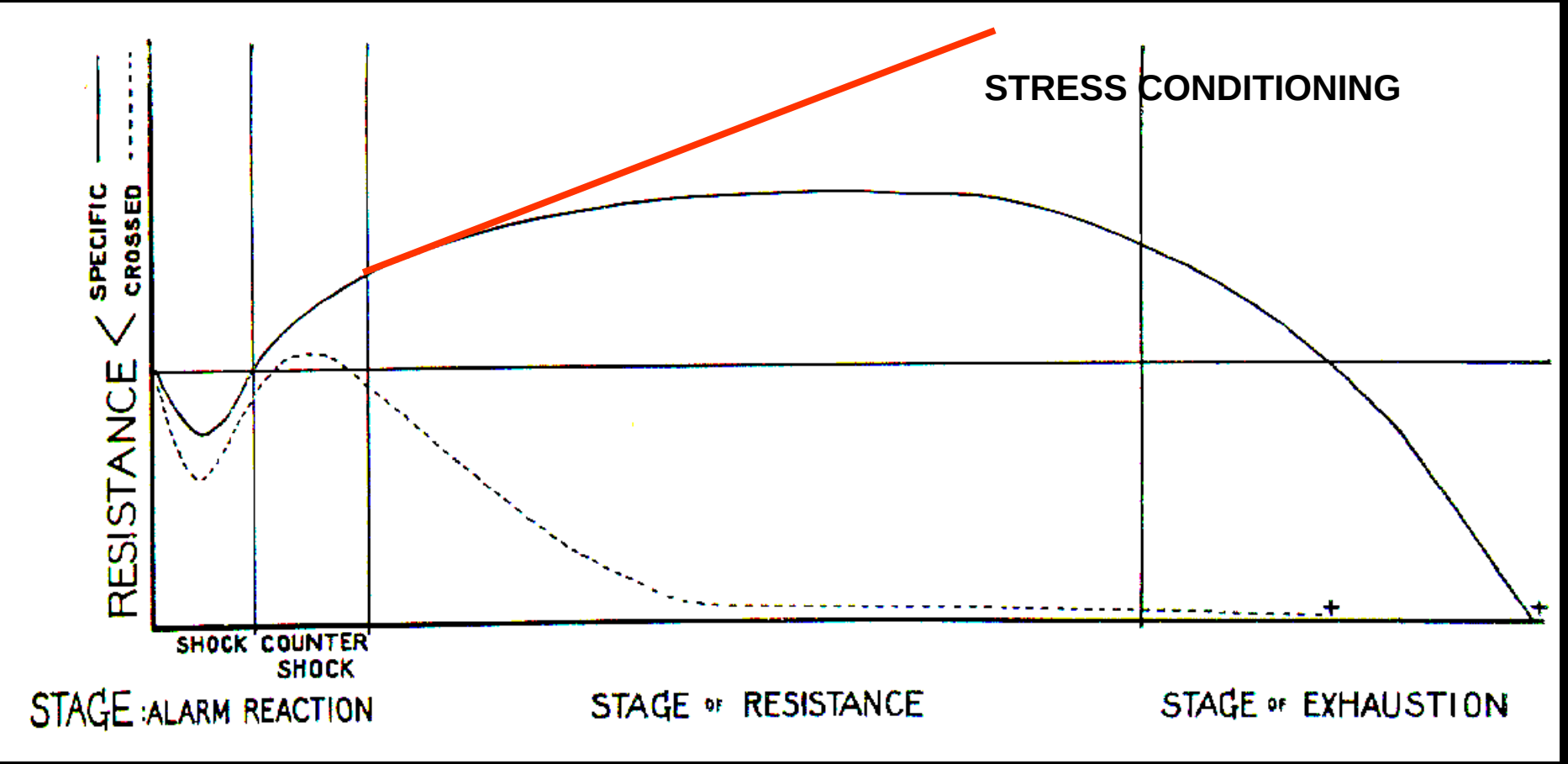
Professor and Director
of the
Institut de Médecine et de Chirurgie expérimentales
Université de Montréal

1950

Hans Selye, MD 1907-1982
Université de Montreal

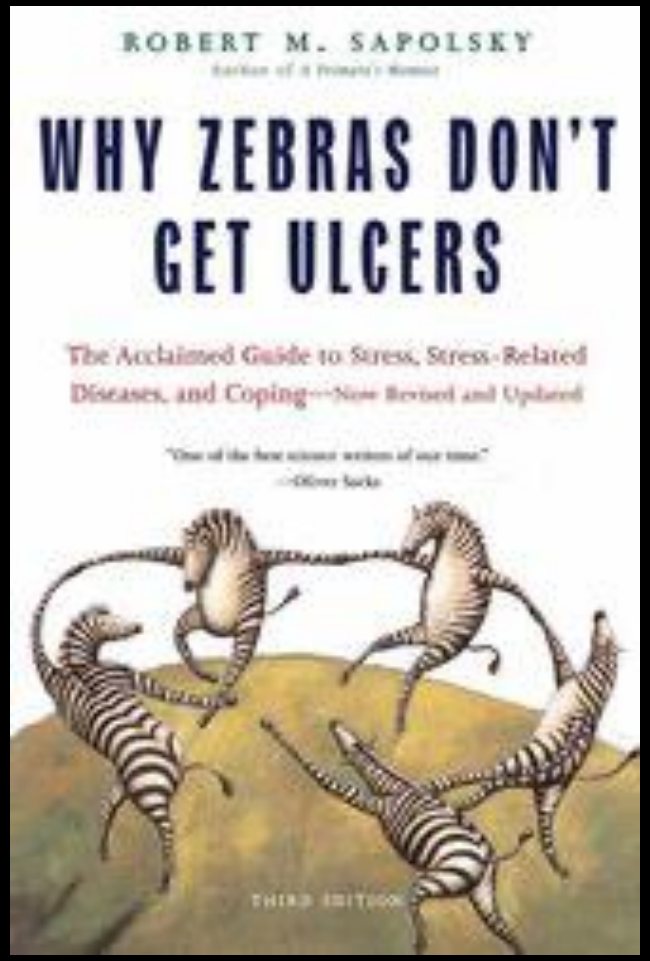
G.A.S

All Stress Responses Are Triphasic



Selye, H. 1950, p55. The Physiology and Pathology of Exposure to Stress

The ultimate stress book



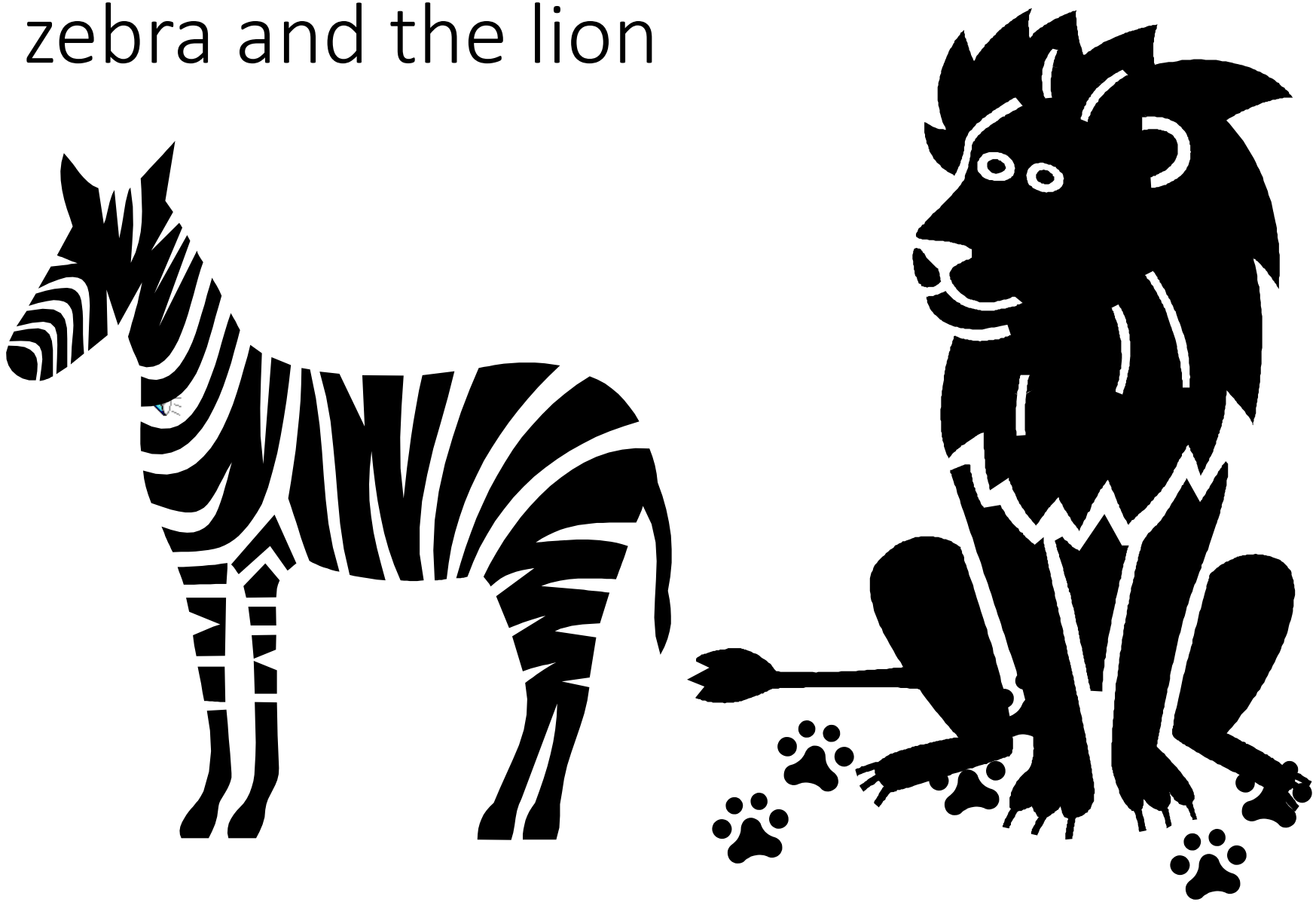
Why Zebras Don't Get Ulcers: Stress, Performance & Coping

— Robert Sapolsky, PhD

Professor of Biological Sciences and Neurology

at Stanford University

The zebra and the lion



The zebra’s stress lasts about 3 minutes.

A few more tips on stress hardiness

The Four A's

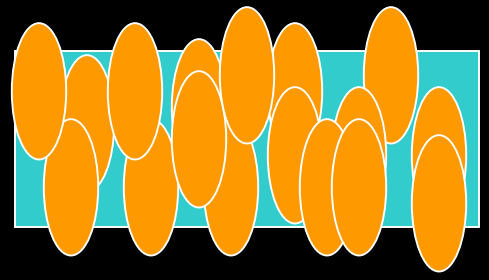
Avoid the stressor
Alter the stressor
Adapt to the stressor
Accept the stressor

HPNS

1975 BENNETT The Pressure Reversal Effect

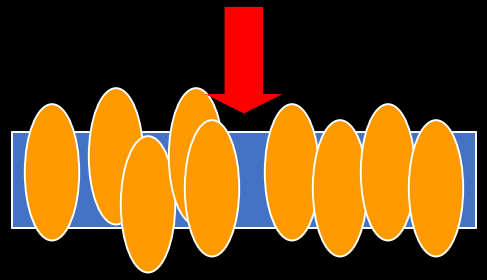
Normal membrane

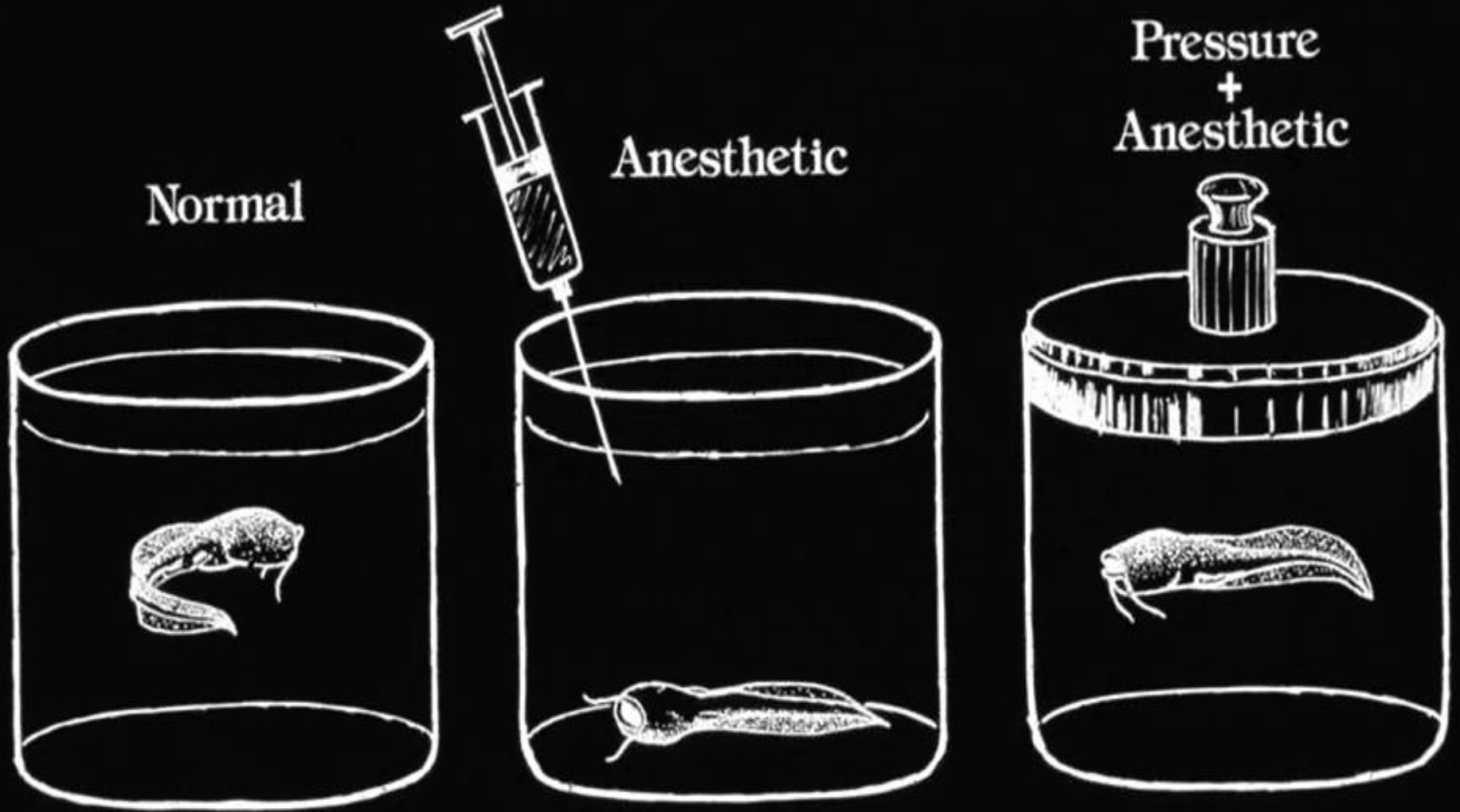
Membrane +
Narcosis

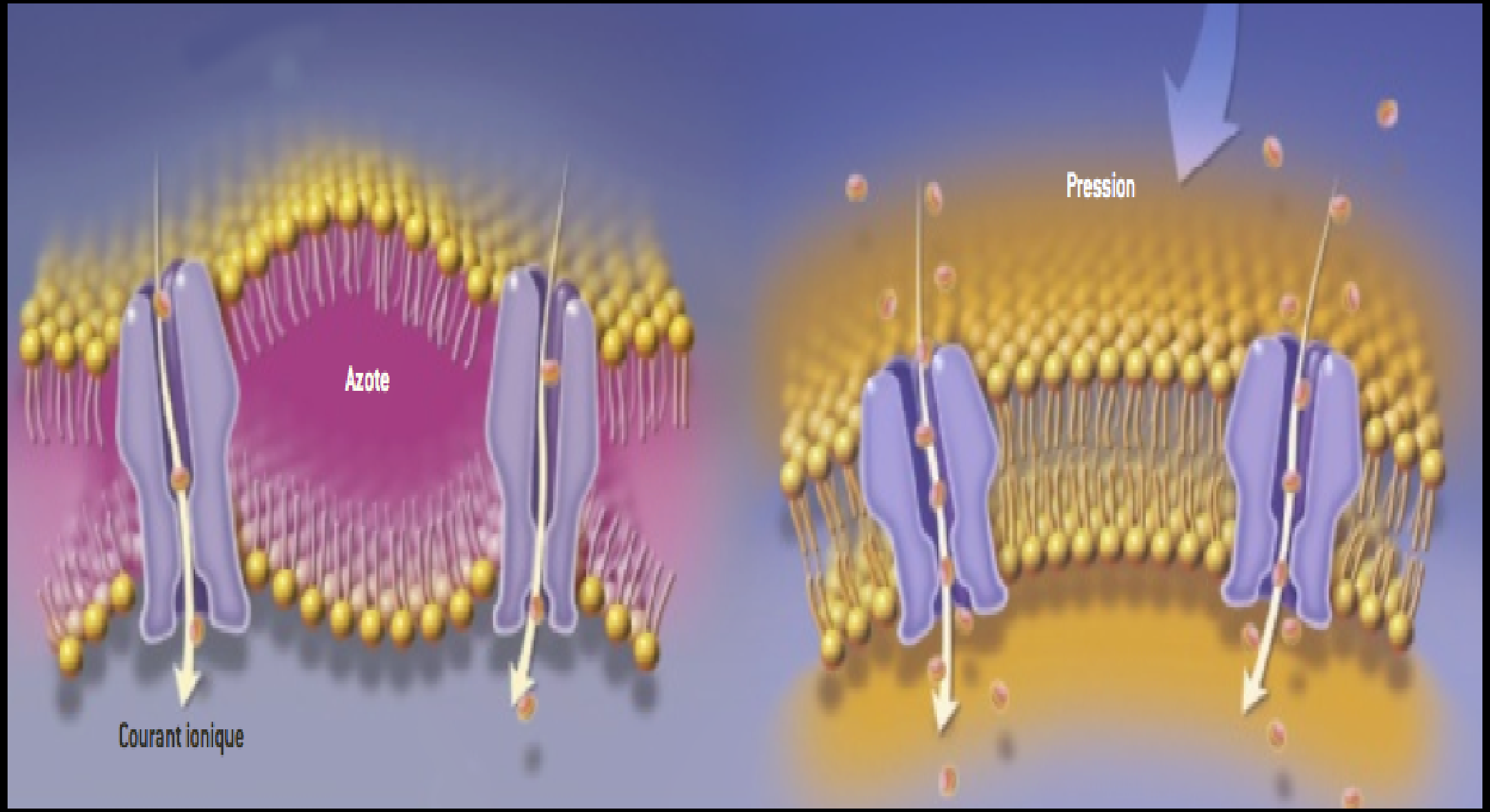


Membrane +
Hydostatic pressure

Membrane +
Hydostatic pressure
+ Narcosis




Normal
Anesthetic
Pressure
+
Anesthetic


Azote
Courant ionique
Pression

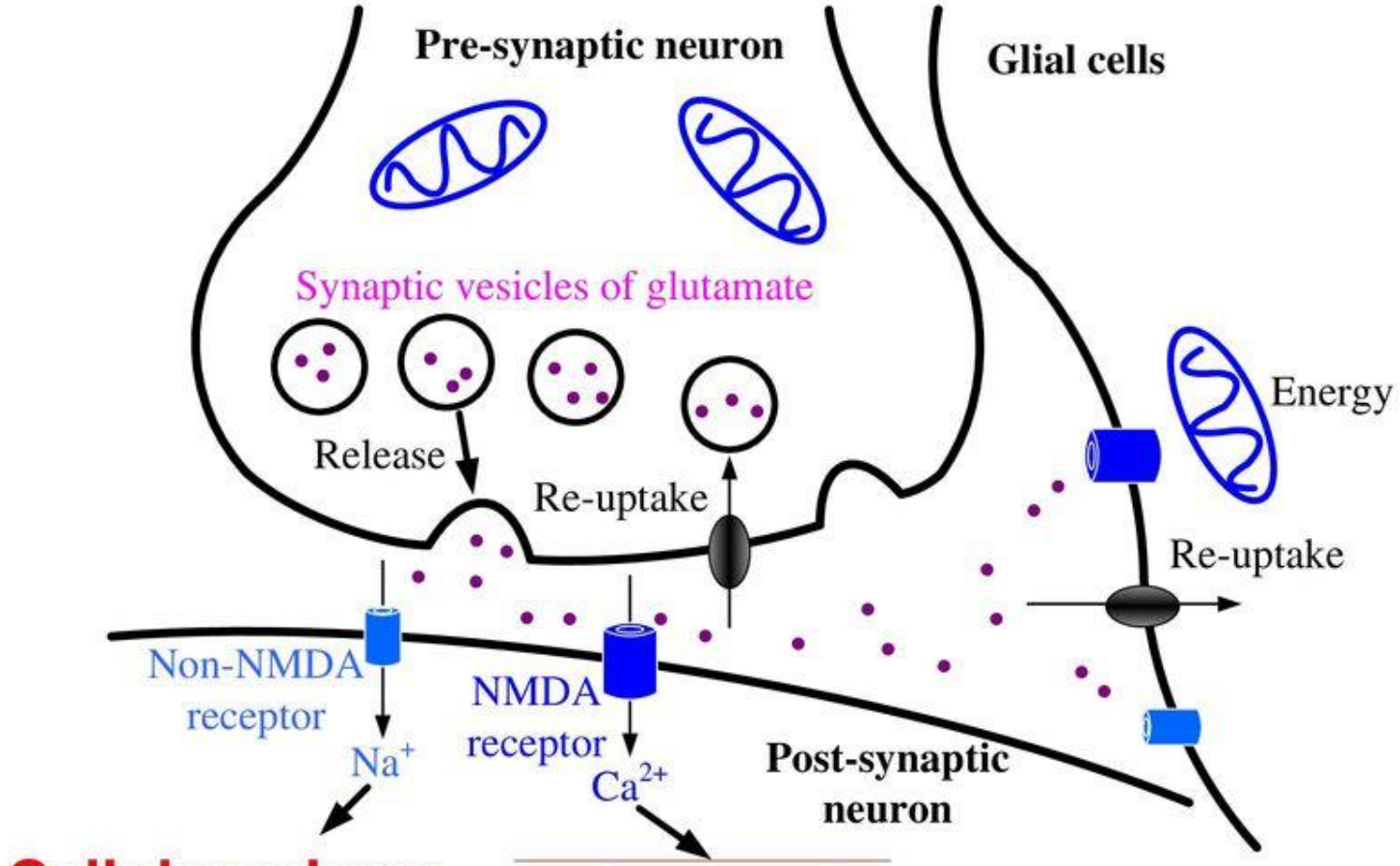
HPNS SIGNS AND SYMPTOMS

- Tremors of the hands
- Myoclonic jerking of the limbs
- Increased reflexes
- Nausea and vomiting
- Loss of appetite, weight loss
- Dizziness
- Fatigue and somnolence (microsleep)
- Animals – convulsions
- EEG theta (3-7 hz) ↑
- EEG alpha (8-13 hz) ↓
- Evoked potentials ↑
- Decrement in performance
- Poor sleep, vivid dreams
- Visual/auditory hallucinations
- Dyspnea

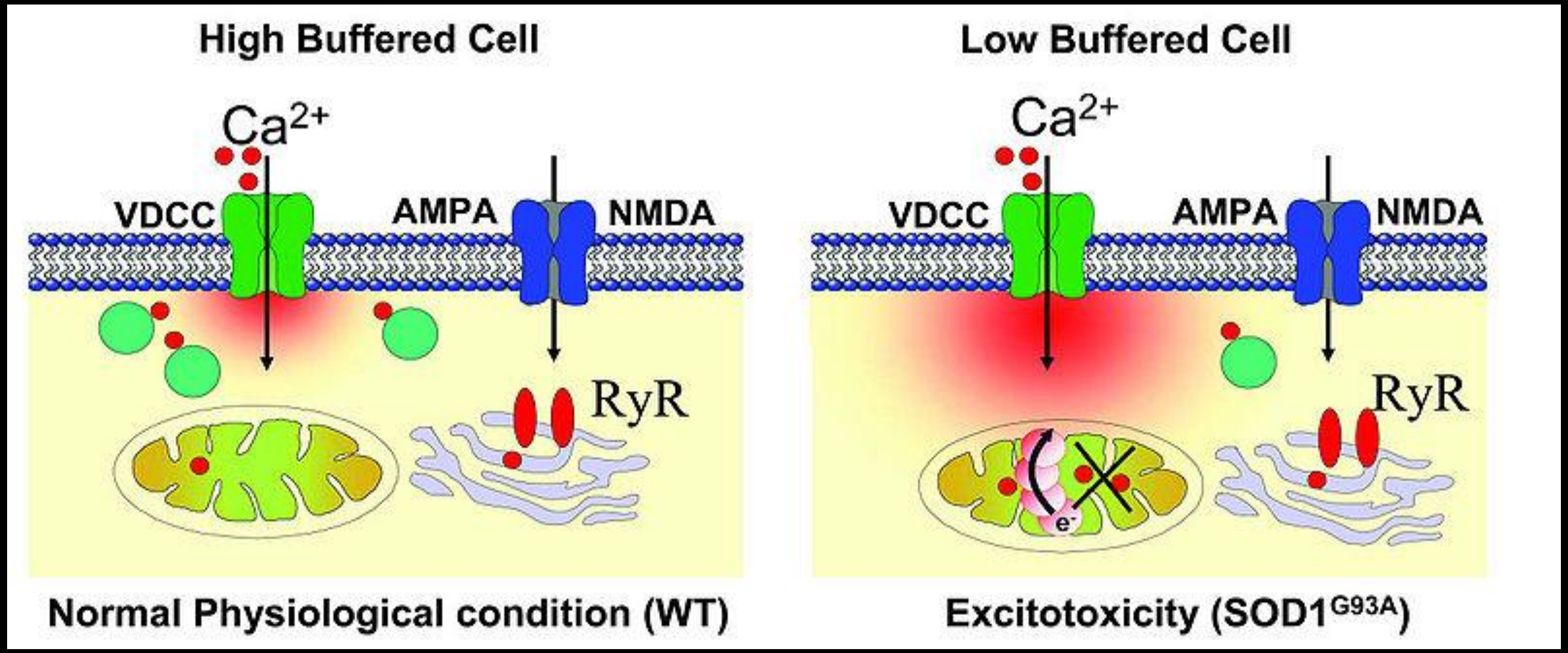
HALLUCINATIONS

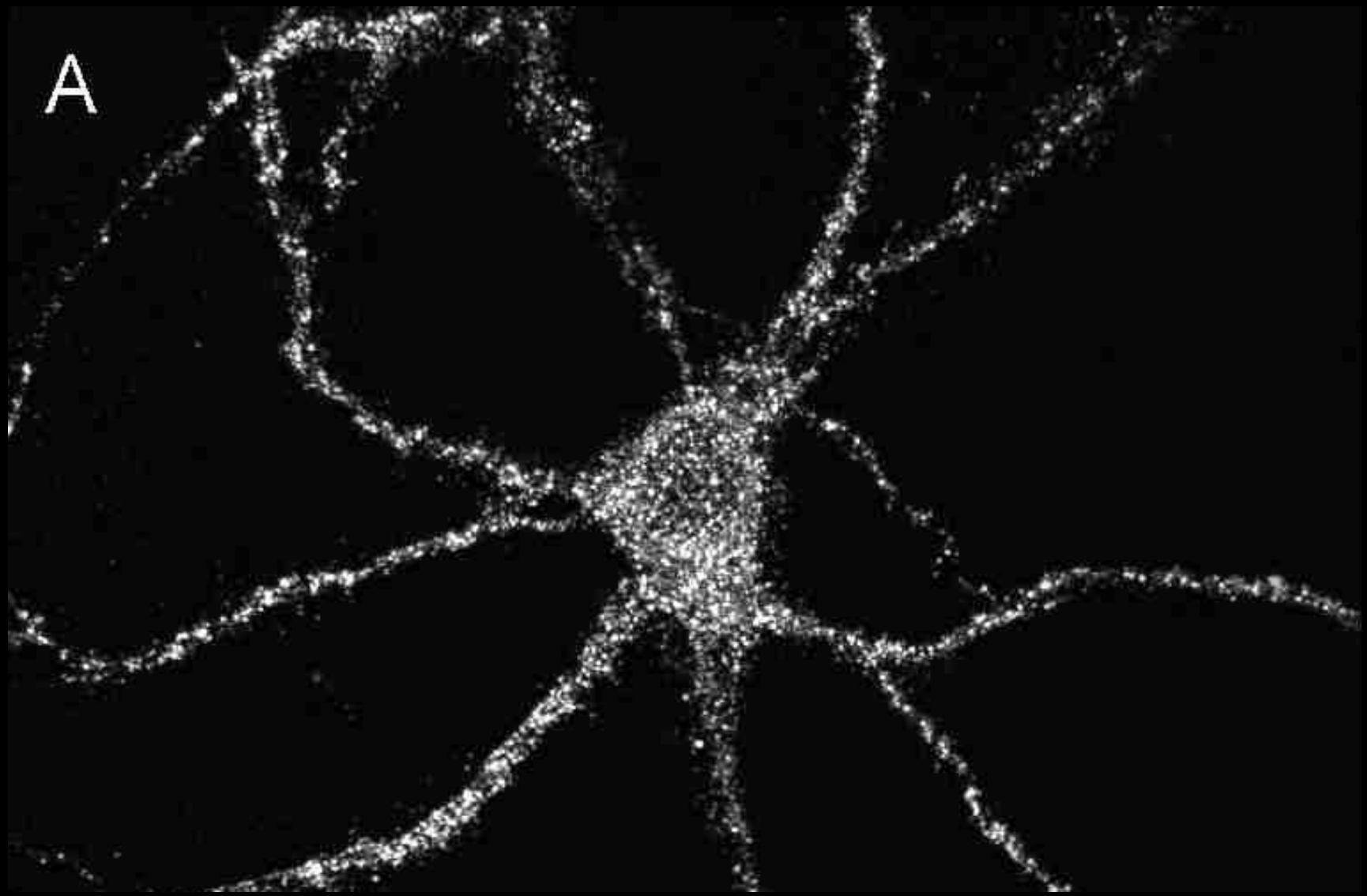
- Auditory (music)
- Visual (birds in chamber)
- Out of body experiences
- Hypomania (1 case)

Glutamate Excitotoxicity

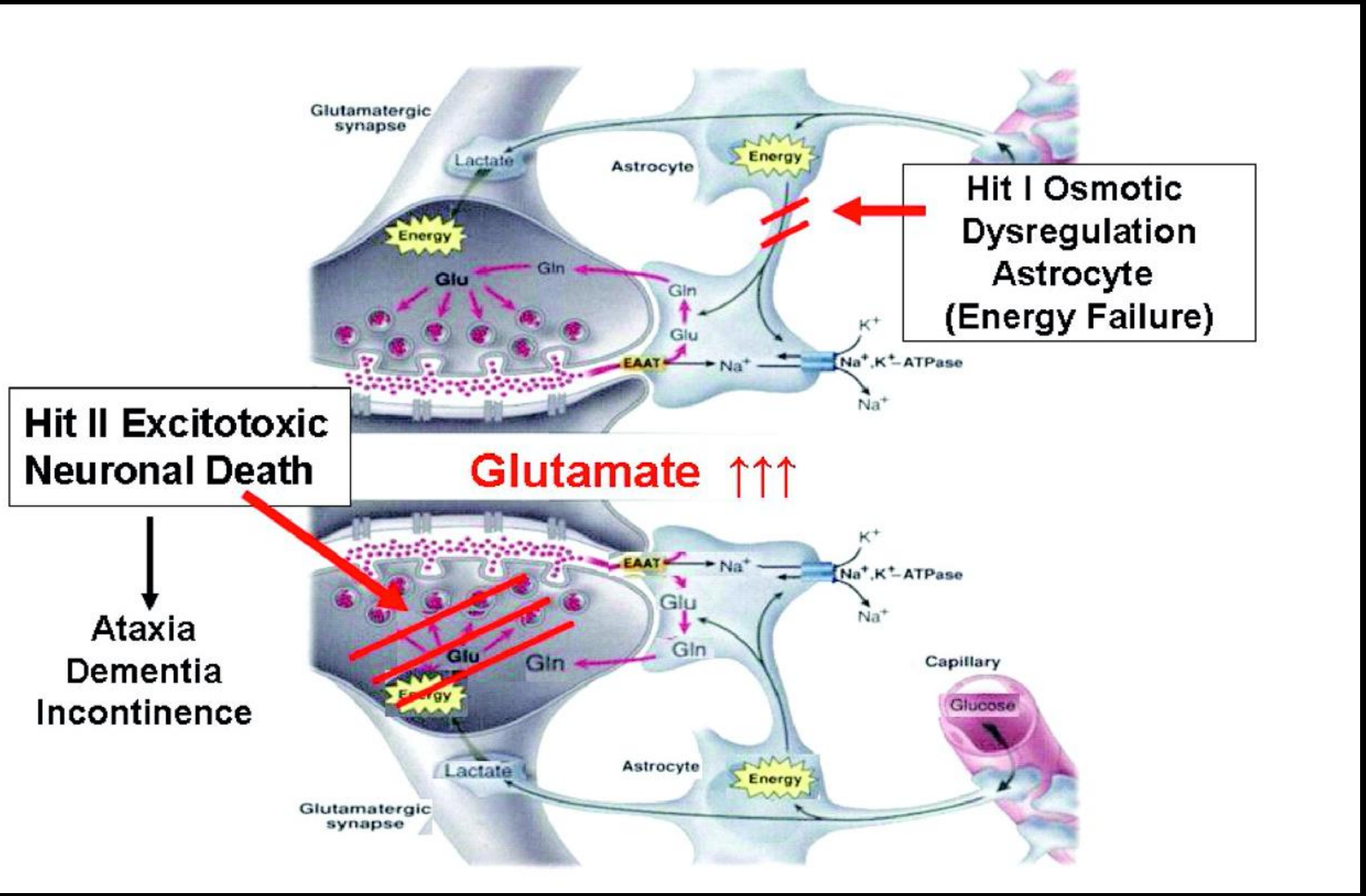


Moritani et al. *AJNR* 2005


High Buffered Cell
Ca2+
VDCC
AMPA
NMDA
RyR
Normal Physiological condition (WT)
Low Buffered Cell
Ca2+
VDCC
AMPA
NMDA
RyR
e-
Excitotoxicity (SOD1G93A)



Dendritic Spines:
LTP, Memory



Leading to long term CNS alterations (Recovery time?)

SCIENTIFIC REPORTS

OPEN

The effect of high pressure on the NMDA receptor: molecular dynamics simulations

Alice Bliznyuk[1,2], Yoram Grossman[2] & Yevgeny Moskovitz[3]

Received: 25 June 2018
Accepted: 9 July 2019
Published online: 25 July 2019

Professional divers exposed to ambient pressures above 11 bar develop the high pressure neurological syndrome (HPNS), manifesting as central nervous system (CNS) hyperexcitability, motor disturbances, sensory impairment, and cognitive deficits. The glutamate-type N-methyl-D-aspartate receptor (NMDAR) has been implicated in the CNS hyperexcitability of HPNS. NMDARs containing different subunits exhibited varying degrees of increased/decreased current at high pressure. The mechanisms underlying this phenomenon remain unclear. We performed 100 ns molecular dynamics (MD) simulations of the NMDAR structure embedded in a dioleoylphosphatidylcholine (DOPC) lipid bilayer solvated in water at 1 bar, hydrostatic 25 bar, and in helium at 25 bar. MD simulations showed that in contrast to hydrostatic pressure, high pressure helium causes substantial distortion of the DOPC membrane due to its accumulation between the two monolayers: reduction of the Sn-1 and Sn-2 DOPC chains and helium-dependent dehydration of the NMDAR pore. Further analysis of important regions of the NMDAR protein such as pore surface (M2 α-helix), Mg^{2+} binding site, and TMD-M4 α-helix revealed significant effects of helium. In contrast with previous models, these and our earlier results suggest that high pressure helium, not hydrostatic pressure *per se*, alters the receptor tertiary structure via protein-lipid interactions. Helium in divers' breathing mixtures may partially contribute to HPNS symptoms.

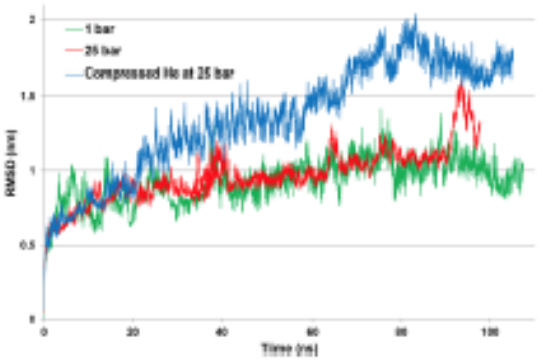


Figure 2. RMSD of the NMDAR during 100 ns of MD simulation. RMSD were calculated as the deviation from the initial NMDAR structure model at 0 ns. Result of the simulation at 1 bar pressure (control) is shown in green, at 25 bar hydrostatic pressure in red, and in helium at 25 bar in blue.

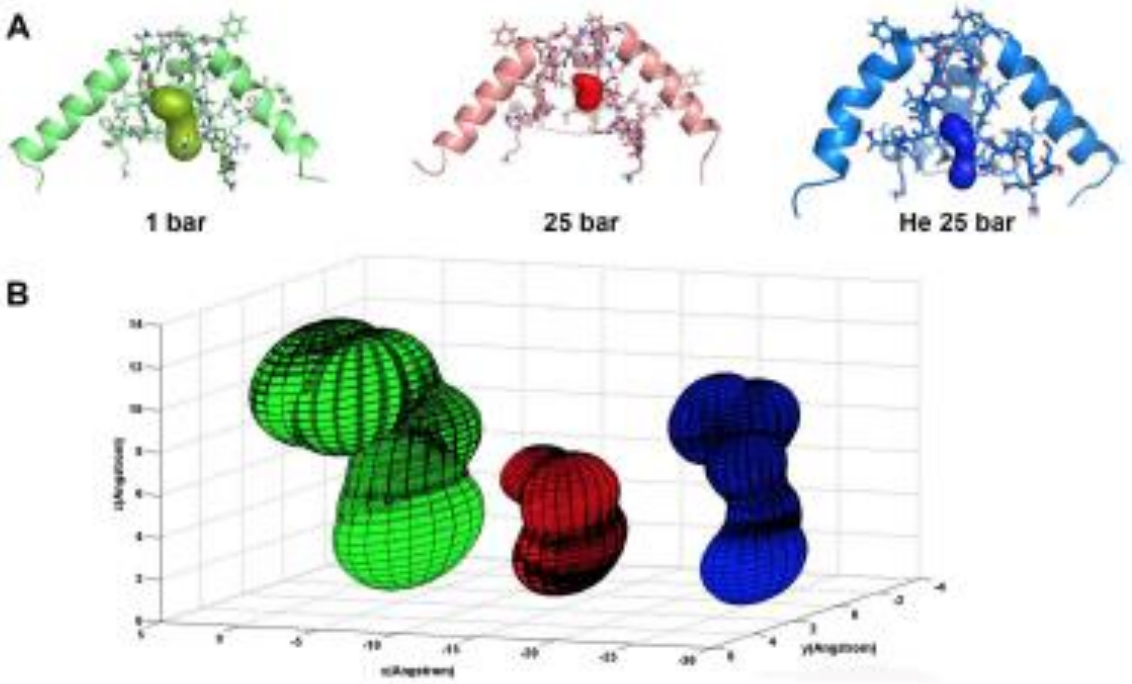


Figure 7. Simulated surface of an NMDAR pore under different pressure conditions. (**A**) Pore surface position in the TMD of the NMDAR under different conditions. (**B**) Simulated pore surface of the NMDAR under control conditions at 1 bar (green), at 25 bar hydrostatic pressure (red) and in helium at 25 bar (blue).

High Pressure Stress Response: Involvement of NMDA Receptor Subtypes and Molecular Markers

Alice Bliznyuk[1,2], Michael Hollmann[3] and Yoram Grossman[1]*

[1] Zlotowski Center for Neuroscience, Department of Physiology and Cell Biology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheba, Israel, [2] Israel Naval Medical Institute, Haifa, Israel, [3] Department of Biochemistry I – Receptor Biochemistry, Faculty of Chemistry and Biochemistry, Ruhr University Bochum, Bochum, Germany

Professional divers who are exposed to high pressure (HP) above 1.1 MPa suffer from high pressure neurological syndrome (HPNS), which is characterized by reversible CNS hyperexcitability and cognitive and motor deficits. HPNS remains the final major constraints on deep diving at HP. Prolonged and repetitive exposure to HP during deep sea saturation dives may result in permanent memory and motor impairment. Previous studies revealed that CNS hyperexcitability associated with HPNS is largely induced by *N*-methyl-D-aspartate receptors (NMDARs). NMDARs that contain the GluN2A subunit are the only ones that show a large (~60%) current increase at He HP. NMDAR subtypes that contain other GluN2 members show minor decrease or no change of the current. Immunoprecipitation was used in order to test the hypothesis that current augmentation may result from inserting additional NMDARs into the membrane during the 20–25 min compression. The results indicated that there is no increase in surface expression of NMDARs in the oocyte membrane under HP conditions. In contrast, consistent increase in glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and β-actin was discovered. GAPDH and β-actin are cytosolic proteins which involve in various cellular control processes, increase of their expression suggests the presence of a general cellular stress response to HP. Understanding the precise hyperexcitation mechanism(s) of specific NMDAR subtypes and other possible neurotoxic processes during HP exposure could provide the key for eliminating the adverse, yet reversible, short-term effects of HPNS and hopefully the deleterious long-term ones.

OPEN ACCESS

Edited by:
Costantino Balestra, Haute École Bruxelles-Brabant (HE2B), Belgium

Reviewed by:
François Guerrero, ersité de Bretagne Occidentale, France
Alessandro Marroni, DAN Europe Foundation, Malta

***Correspondence:**
Alice Bliznyuk
shuturov@gmail.com

Link the findings with the divers perceptions during and post-saturation.

frontiers in Psychology

ORIGINAL RESEARCH
published: 11 January 2019
doi: 10.3389/fpsyg.2018.02774

Commercial Divers' Subjective Evaluation of Saturation

Jean Pierre Imbert[1], *Costantino Balestra*[2,3], *Fatima Zohra Kiboub*[4,5*], *Øyvind Loennechen*[5] and *Ingrid Eftedal*[4,5,6]

Questionnaire responses: part 1

59% of the divers declared having headaches: 44% of them near and 56% of them after surfacing

A relative paleness was observed on most of the divers at surfacing

Questions	Participant's number	Scores	Response Percentage
Q1: During this last decompression, have you experienced headaches?	34	Yes = 11 No = 23	32% 68%
Q2: During this last decompression, if you had headache, when did the symptoms declare?	11	Near surface = 6 After surfacing = 5	55% 45%
Q3: During this last decompression, if you had headache, grade its severity on a scale from 1 (light) to 10 (severe)	10	4 (grade 1 to 2) 6 (grade 6 to 9)	40% 60%
Q4: Usually, do you experience headache during or after decompression?	34	Never = 14 Sometimes = 10 Often = 5 Always = 5 Sometimes + often = 15	41% 29% 15% 15% 44%
Q5: Usually, if you had headache, when do the symptoms declare?	16	Near surface = 9 After surfacing = 7	44% 56%
Q6: Usually, if you had headache, how long does the headache last?	13	Few hours = 3 Half a day = 3 One day = 4 More than 1 day = 3	23% 23% 31% 23%
Q7: When back home after a saturation, do people around you say you look pale?	20	Yes = 19 No = 1	95% 5%

Questionnaire responses: part 2

71% of the divers reported a post-saturation fatigue that took 1 to 10 days to recede

Questions	Participant's number	Scores	Response Percentage
Q8: After this last saturation, have you experienced fatigue?	24	Yes = 17 No = 7	71% 29%
Q9: After this last saturation, if you experienced fatigue, grade its severity on a scale from 1 (light) to 10 (severe)	17	(Mean ± SD) 3.4 ± 1.92	100%
Q10: Usually, after a saturation, do you experience fatigue?	22	Yes = 18 No = 4	82% 18%
Q11: Usually, if you experienced fatigue, is it physical or mental?	19	Physical = 17 Mental = 2	89% 11%
Q12: Usually, after a saturation, grade your wellbeing or mood on a scale from 1 (bad) to 5 (normal) and 10 (excellent)	22	(Mean ± SD) 6.18 ± 1.56	100%
Q13: Usually, after a saturation, grade your alertness on a scale from 1 (bad) to 5 (normal) and 10 (excellent)	22	(Mean ± SD) 6.23 ± 1.91	100%
Q14: Usually, after a saturation, how many days does it take to return to normal?	26	(Mean ± SD) 4.31 ± 2.92	51%

ORIGINAL RESEARCH ARTICLE Provisionally accepted The full-text will be published soon. Notify me

Front. Physiol. | doi: 10.3389/fphys.2019.01386

Evaluation of divers' neuropsychometric effectiveness and High-Pressure Nervous Syndrome via test battery package and questionnaires in operational setting

 Simin Berenji Ardestani[1, 2*],  Costantino Balestra[3, 4], Elena V. Bouzinova[5],  Øyvind Loennechen[6] and Michael Pedersen[2]

[1]Aarhus University, Denmark

[2]Department of Clinical Medicine, Faculty of Health, Aarhus University, Denmark

[3]Other, Italy

[4]Environmental, Occupational & Ageing Physiology Lab, Haute Ecole Bruxelles-Brabant (HE2B), Belgium

[5]Department of Biomedicine, Faculty of Health, Aarhus University, Denmark

[6]Independent researcher, Norway

OXYDATIVE STRESS

F. Z. Kiboub et Al. 2018

frontiers in Physiology

Front Physiol. 2018; 9: 937.
Published online 2018 Jul 16. doi: [10.3389/fphys.2018.00937]

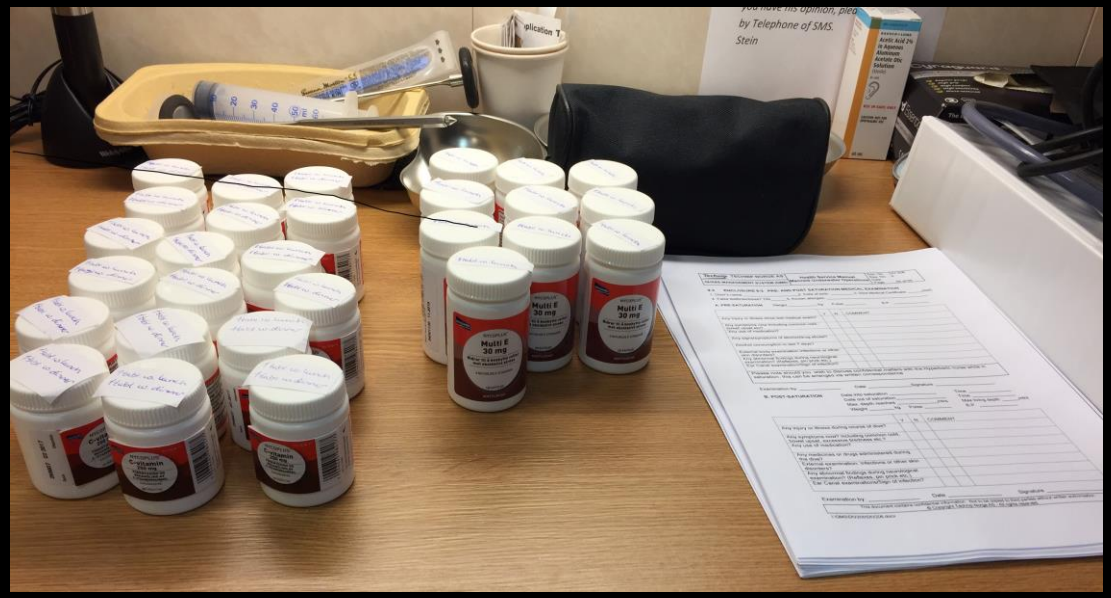
PMCID: PMC6054983
PMID: 30061845

Blood Gene Expression and Vascular Function Biomarkers in Professional Saturation Diving

Fatima Z. Kiboub,[1,2,*] Andreas Møllerløkken,[3] Astrid Hjelde,[1] Arnar Flatberg,[4] Øyvind Loennechen,[2] and Ingrid Eftedal[1,5]

Vitamin C and E

- Vitamin C and E have been reported to:
  - Ameliorate oxidative stress effects on the heart, pulmonary and brachial artery in scuba divers[1].
  - Combined with tea catechins, they prevent hepatic disturbances in experimental saturation divers[2].



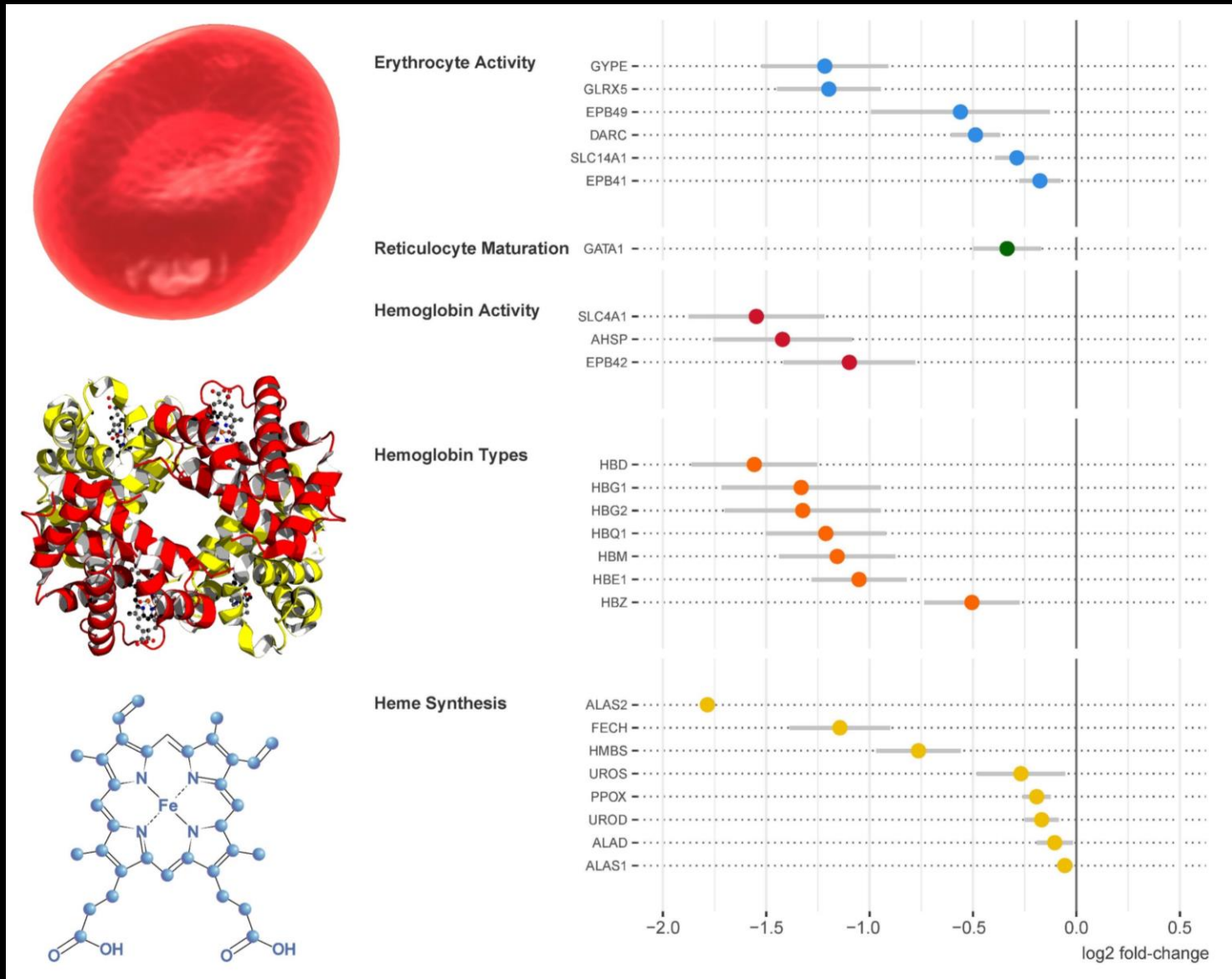
Experimental group instructed to take 500 mg vitamin C and 30 mg vitamin E supplements / day

- 1. Mak S. et al. Am. J. Physiol. Heart Circ. Physiol. (2002); Obad A. et al. FASEB J. (2006) and Obad A. et al. J. Physiol. (2007)
- 2. Ikeda M. et al. Tohoku J. Exp. Med. (2004)

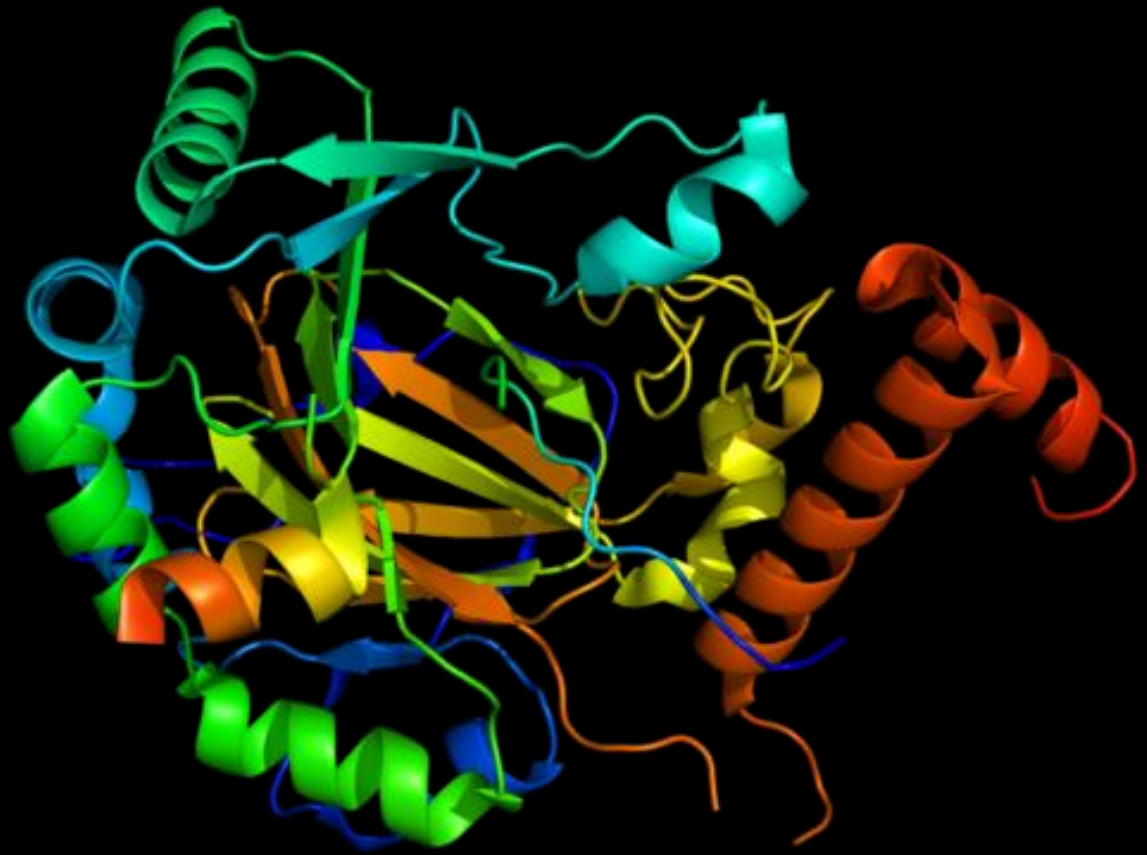
Changes in oxygen transport genes expression

No effect of antioxidant vitamin C and E

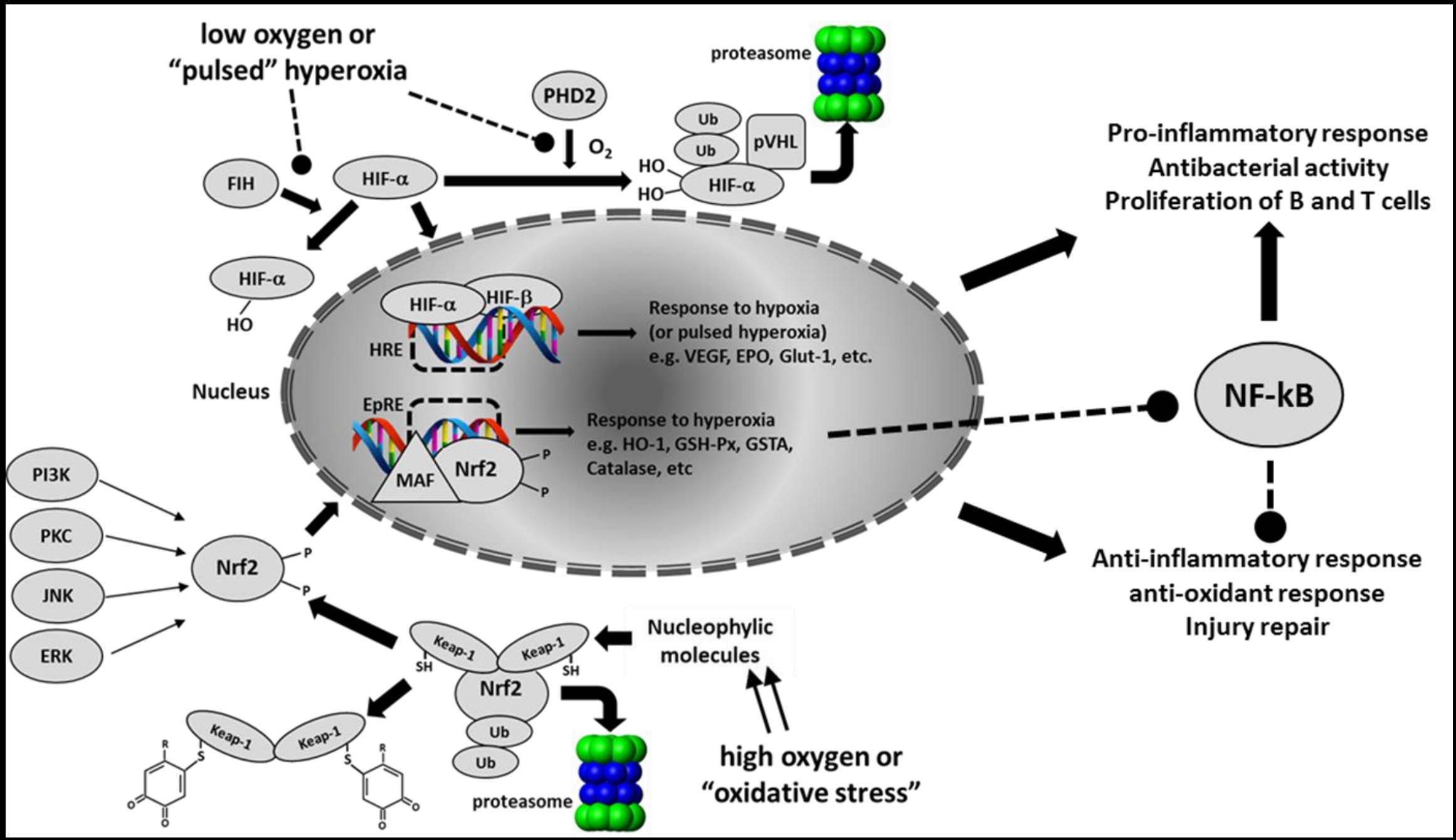
Genes involved in oxygen transport were downregulated on multiple levels after saturation diving



1991 Greg Semenza
HIF-1 and HIF-2 (NOBEL PRIZE 2019)




Nobelförsamlingen
Gregg L. Semenza
Johns Hopkins University
Sir Peter J. Ratcliffe
Oxford University
William G. Kaelin, Jr.
Dana-Farber Cancer Institute
JONATHAN NACKSTRAND/AFP/AFP VIA GETTY IMAGES


low oxygen or
"pulsed" hyperoxia
PHD2
O_2
proteasome
Ub
Ub
pVHL
HO
HO
HIF-α
FIH
HIF-α
HIF-α
HO
HIF-α
HIF-β
HRE
Response to hypoxia
(or pulsed hyperoxia)
e.g. VEGF, EPO, Glut-1, etc.
Nucleus
EpRE
MAF
Nrf2
P
P
Response to hyperoxia
e.g. HO-1, GSH-Px, GSTA,
Catalase, etc
Pro-inflammatory response
Antibacterial activity
Proliferation of B and T cells
NF-kB
Anti-inflammatory response
anti-oxidant response
Injury repair
PI3K
PKC
JNK
ERK
Nrf2
P
P
Keap-1
Keap-1
SH
SH
Nrf2
Ub
Ub
proteasome
Nucleophylic
molecules
high oxygen or
"oxidative stress"
Keap-1
Keap-1
R
S
S
R
O
O
O
O

frontiers in Physiology

Front Physiol. 2018; 9: 1176.

PMCID: PMC6113572

Published online 2018 Aug 21. doi: [10.3389/fphys.2018.01176]

PMID: 30246801

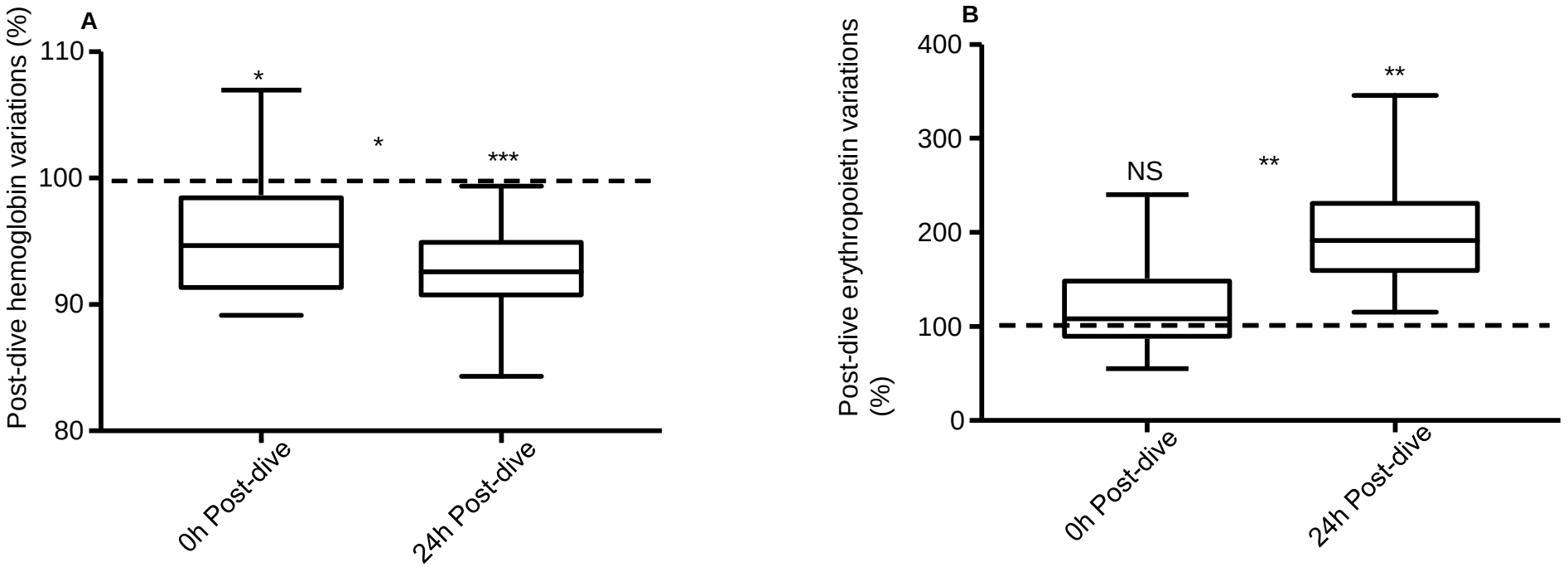
Hemoglobin and Erythropoietin After Commercial Saturation Diving

Fatima Z. Kiboub,[1,2,*] Costantino Balestra,[3] Øyvind Loennechen,[2] and Ingrid Eftedal[1,4]

Hofso D , Ulvik R J , Segadal K , Hope A . Changes in erythropoietin and hemoglobin concentrations in response to saturation diving . Eur J Appl Physiol 2005 ; 95 : 191 – 196

Hb was reduced by 4% post-saturation and 8% 24h later.

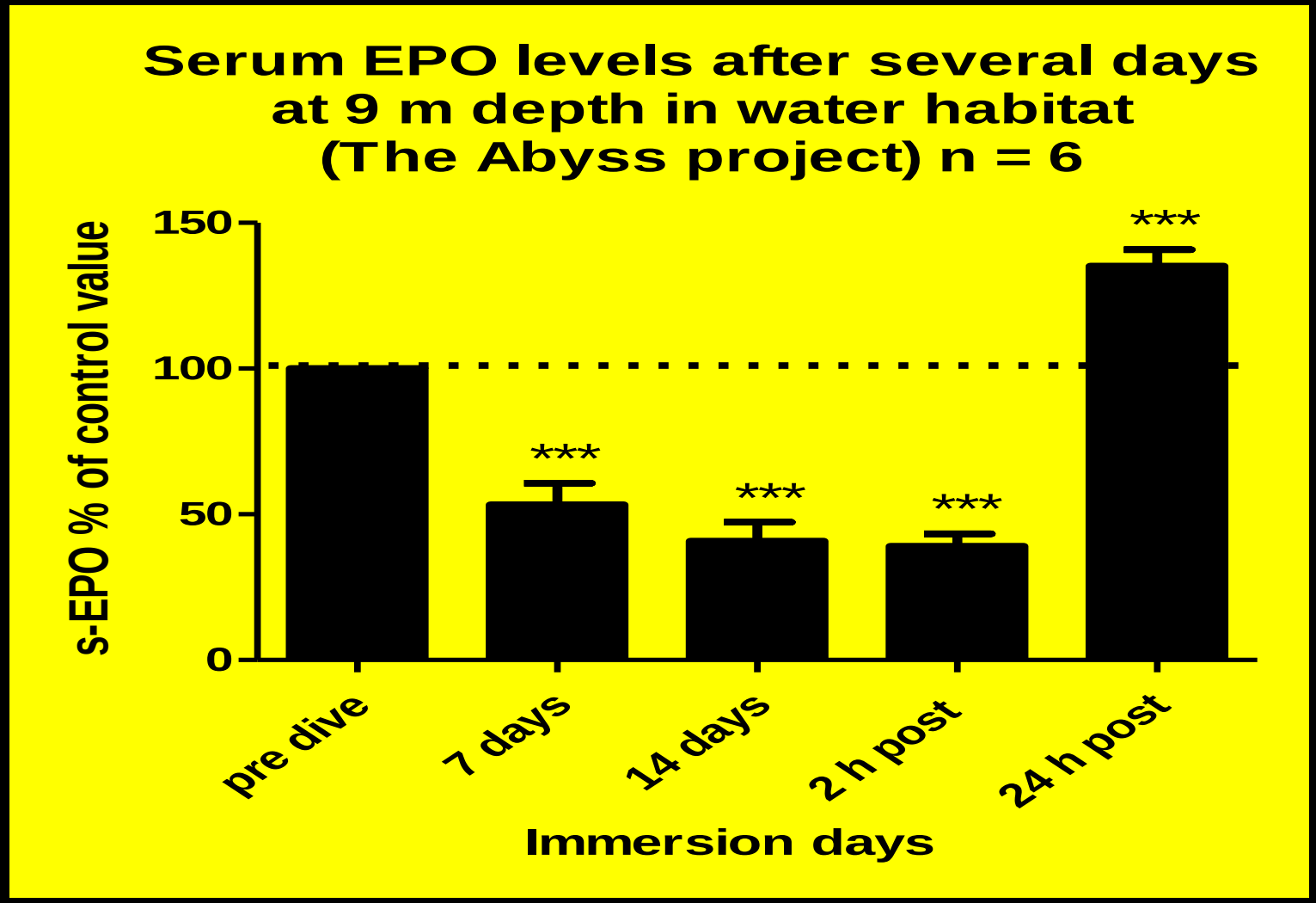
EPO was unchanged post-saturation and increased 99% 24h later.



(A) Hb and (B) EPO levels 0 h post-dive and 24 h post-dive expressed as percentages of pre-saturation diving levels (dotted line) in 13 saturation divers. *$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$ and NS, non-significant.

Revelli L, Vagnoni S, D'Amore A, Di Stasio E, Lombardi CP, Storti G, Proietti R, Balestra C & Ricerca BM. (2013). EPO modulation in a 14-days undersea scuba dive. *International journal of sports medicine* **34,** 856-860.

The Abyss Project 2008



Research Article

Spirometry and oxidative stress after rebreather diving in warm water

Gerardo Bosco [1], Alex Rizzato [1], Silvia Quartesan [1], Enrico Camporesi [2], Simona Mrakic-Sposta [3], Sarah Moretti [3], Costantino Balestra [4], Alessandro Rubini [1]

[1] Environmental Physiology & Medicine Lab, Department of Biomedical Sciences, University of Padova, Italy

[2] TEAMHealth Research Institute, TGH, Tampa, Florida, USA

[3] CNR Institute of Bioimaging and Molecular Physiology, Segrate (Milano), Italy

[4] Environmental & Occupational Physiology Laboratory, Haute Ecole Bruxelles-Brabant (HE2B), Brussels, BE, Auderghem, Belgium

CORRESPONDING AUTHOR: Alex Rizzato – *alex.rizzato@studenti.unipd.it*

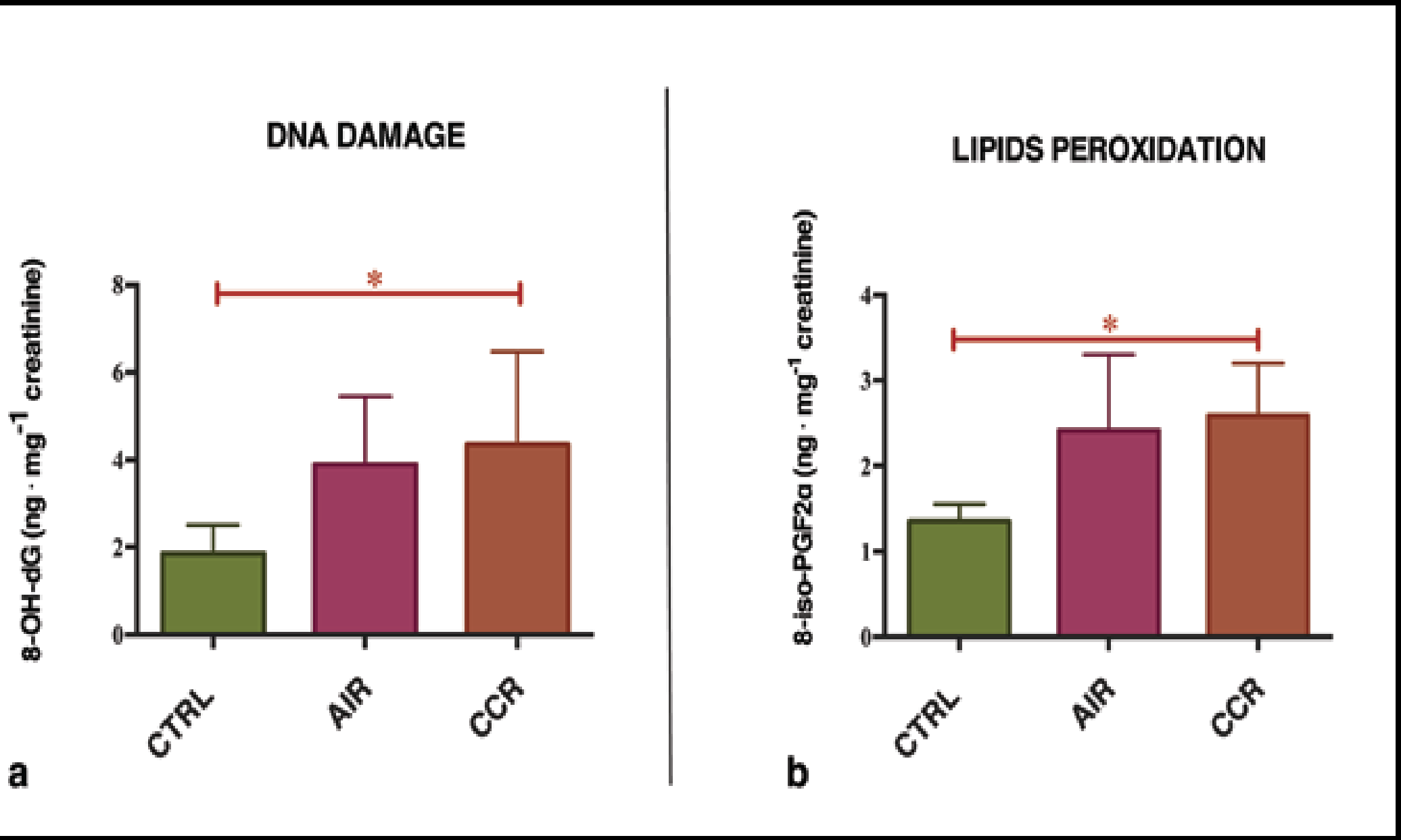
ABSTRACT

Introduction: Hyperbaric oxygen (HBO_2) therapy and use of enriched air can result in oxidative injury affecting the brain, lungs and eyes. HBO_2 exposure during diving can lead to a decrease in respiratory parameters. However, the possible effects of acute exposure to oxygen-enriched diving on subsequent spirometric performance and oxidative state in humans have not been recently described recently. We aim to investigate possible effects of acute (i) hyperbaric and (ii) hyperbaric hyperoxic exposure using scuba or closed-circuit rebreather (CCR) on subsequent spirometry and to assess the role of oxidative state after hyperoxic diving.

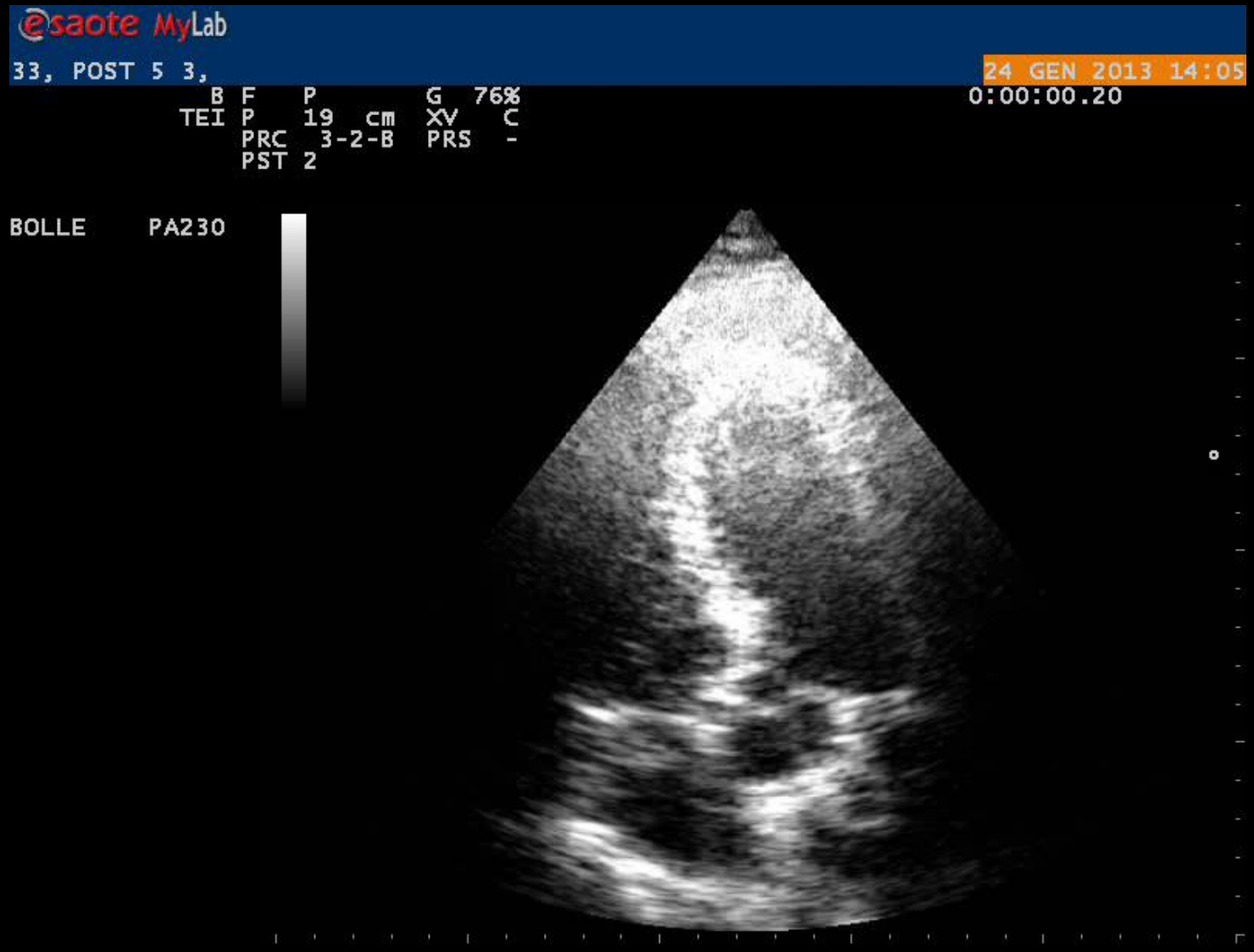
Methods: Spirometry and urine samples were obtained from six well-trained divers (males, mean ± SD, age: 43.33 ± 9.16 years; weight: 79.00 ± 4.90 kg; height: 1.77 ± 0.07 meters) before (CTRL) and after a dive breathing air, and after a dive using CCR (PO_2 1.4). In the crossover design (two dives separated by six hours) each subject performed a 20-minute session of light underwater exercise at a depth of 15 meters in warm water (31-32°C). We measured urinary 8-isoprostane and 8-OH-2-deoxyguanosine evaluating lipid and DNA oxidative damages.

INTRODUCTION

Hyperbaric oxygen (HBO_2) is a widely applied therapeutic approach in which an individual breathes near 100% oxygen intermittently while inside a hyperbaric chamber with a pressure equal or exceeding 1.4 atmospheres absolute (ATA). It is used for the treatment of diseases such as: decompression illness, ischemia-reperfusion injury, necrotizing infections, chronic non-healing wounds, gas gangrene and others [1,2]. Hyperbaric oxygen therapy as well as the use of oxygen-enriched air or closed-circuit rebreather (CCR) during diving can potentially result in oxidative injury, which affects the brain, lungs and eyes, mainly due to the toxic effects of oxygen free radicals [3-5]. Central nervous system oxygen toxicity (CNS-OT) and pulmonary oxygen toxicity are the most concerning effects of breathing an enriched air mixture [6-8]. As previously reported [9], exposure to HBO_2 may lead to temporary reductions in pulmonary function. Experiments specifically designed to investigate the possible effects of


DNA DAMAGE
8-OH-dG (ng · mg-1 creatinine)
0
2
4
6
8
*
CTRL
AIR
CCR
a
LIPIDS PEROXIDATION
8-iso-PGF2α (ng · mg-1 creatinine)
0
1
2
3
4
*
CTRL
AIR
CCR
b

INFLAMMATION
&
Effect of BUBBLES


esaote MyLab
33, POST 5 3,
24 GEN 2013 14:05
B F P G 76%
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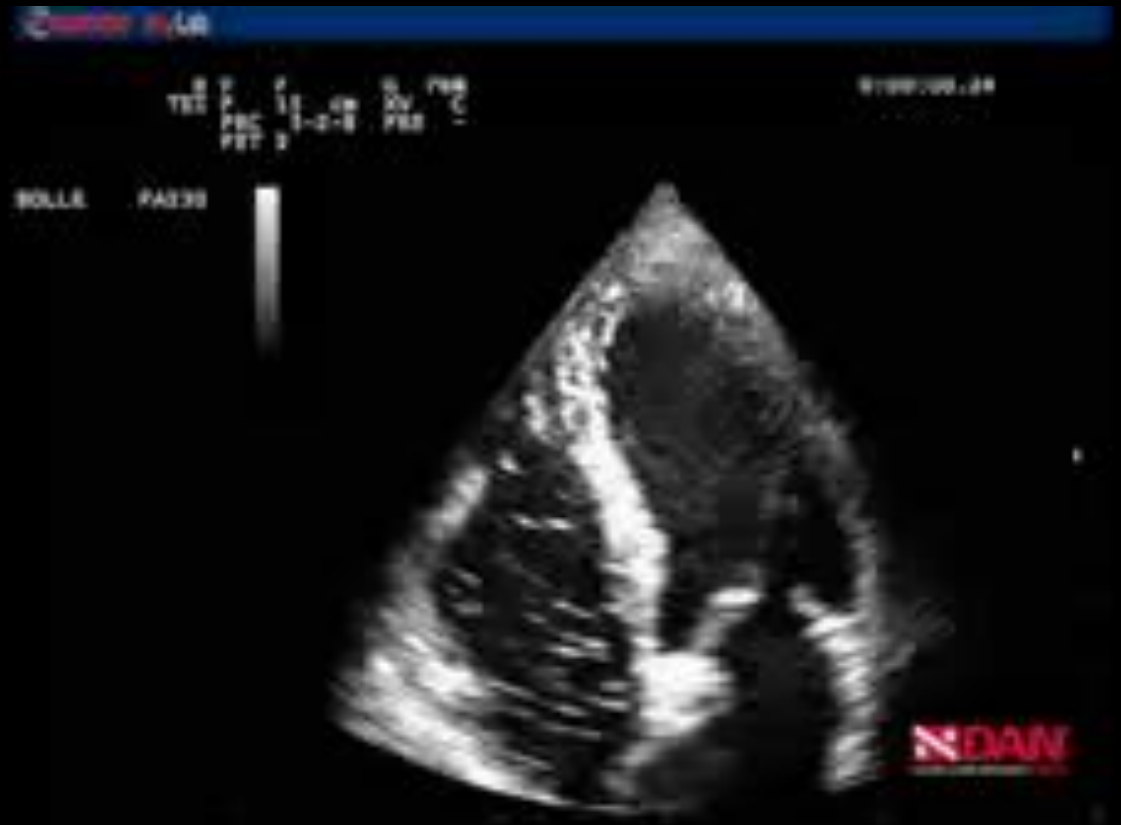
PRC 3-2-B PRS -
PST 2
BOLLE PA230

Breath-Hold Diving



Medicine & Science IN Sports & Exercise

The Official Journal of the American College of Sports Medicine
www.acsm-msse.org

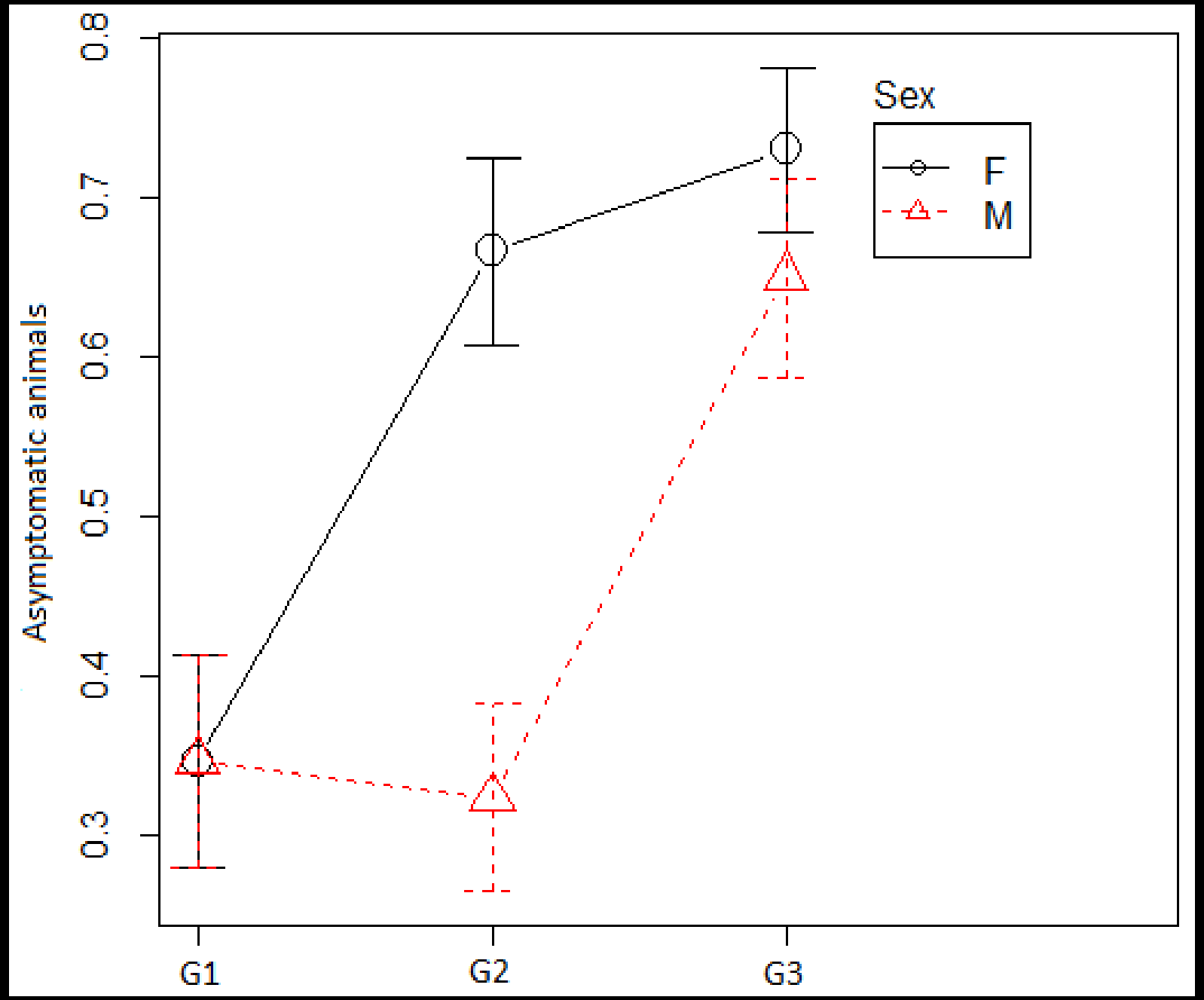
. . . Published ahead of Print

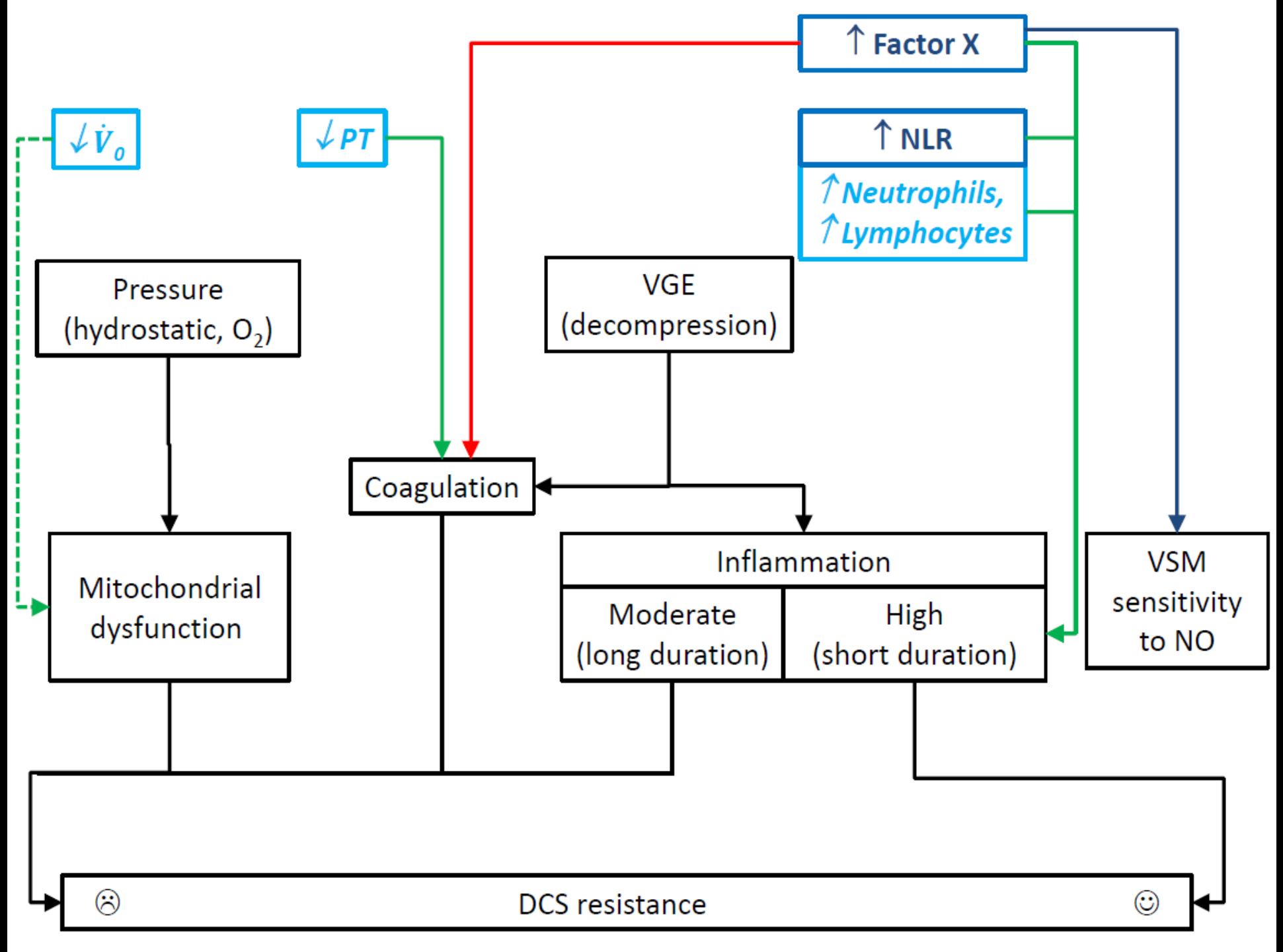
Evidence of Heritable Determinants of Decompression Sickness in Rats

Jacky Lautridou[1], Peter Buzzacott[1,2], Marc Belhomme[1], Emmanuel Dugrenot[1], Pierre Lafère[1], Costantino Balestra[3], and François Guerrero[1]

[1]University of Western Brittany, ORPHY EA 4324, IBSAM, Brest, France; [2]School of Sports Science, Exercise and Health, University of Western Australia, Crawley, Australia; [3]Environmental & Occupational Physiology Laboratory, (ISEK), Haute Ecole Bruxelles-Brabant (HE2B), Brussels, Belgium

Accepted for Publication: 17 July 2017


Asymptomatic animals
0.3
0.4
0.5
0.6
0.7
0.8
G1
G2
G3
Sex
F
M


↑ Factor X
↓ $\dot{V}_O$
↓ PT
↑ NLR
↑ Neutrophils,
↑ Lymphocytes
Pressure
(hydrostatic, O_2)
VGE
(decompression)
Coagulation
Mitochondrial
dysfunction
Inflammation
Moderate
(long duration)
High
(short duration)
VSM
sensitivity
to NO
☹
DCS resistance
☺

The Number of X Chromosomes Influences Inflammatory Cytokine Production Following Toll-Like Receptor Stimulation

Nicolas Lefèvre[1,2], Francis Corazza[2], Joseph Valsamis[3], Anne Delbaere[4], Viviane De Maertelaer[5], Jean Duchateau[6] and Georges Casimir[1,6]*

[1] Department of Pulmonology, Allergology and Cystic Fibrosis, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium, [2] Laboratory of Translational Research, Université Libre de Bruxelles, Brussels, Belgium, [3] Laboratory of Hormonology, Hôpital Universitaire Brugmann, Université Libre de Bruxelles, Brussels, Belgium, [4] Fertility Clinic, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium, [5] Department of Biostatistics and Medical Computing, Université Libre de Bruxelles, Brussels, Belgium, [6] Laboratory of Pediatrics, Université Libre de Bruxelles, Brussels, Belgium

Sex differences are observed in the evolution of numerous inflammatory conditions. Women exhibit better clinical courses compared to men in acute inflammatory processes, yet worse prognosis in several chronic inflammatory diseases. Inflammatory markers are significantly different between prepubertal boys and girls, whose sex steroid levels are very low, suggesting genetics play a role. To evaluate the potential influence of the X chromosome, we studied cytokine production and protein phosphorylation following Toll-like receptor (TLR) activation in whole blood and purified neutrophils and monocytes of healthy adults of both sexes as well as subjects with Klinefelter syndrome. We recorded higher levels of inflammatory cytokines in men compared to both women and patients with Klinefelter syndrome following whole blood stimulation. In purified monocytes, production of inflammatory cytokines was also higher in men compared to women, while Klinefelter subjects expressed the same pattern of cytokine production as males, in contrast with whole blood analyses. These differences remained after adjusting for sex steroid levels. Our study revealed higher cytokine inflammatory responses in men than women, yet also compared to subjects with Klinefelter syndrome, who carry two copies of the X chromosome, like women, and thus potentially benefit from the cellular mosaicism of X-linked genes.

Keywords: sex differences, cytokine, Toll-like receptors, X chromosome, sex steroids

A Single Simulated Heliox Dive Modifies Endothelial Function in the Vascular Wall of ApoE Knockout Male Rats More Than Females

Simin Berenji Ardestani[1,2], Vladimir V. Matchkov[3], Ingrid Eftedal[2,4] and Michael Pedersen[1]*

[1] Department of Clinical Medicine, Comparative Medicine Lab, Aarhus University, Aarhus, Denmark, [2] Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, NTNU: Norwegian University of Science and Technology, Trondheim, Norway, [3] Department of Biomedicine, Aarhus University, Aarhus, Denmark, [4] Faculty of Nursing and Health Sciences, Nord University, Bodø, Norway

Introduction: The number of divers is rising every year, including an increasing number of aging persons with impaired endothelial function and concomitant atherosclerosis. While diving is an independent modulator of endothelial function, little is known about how diving affects already impaired endothelium. In this study, we questioned whether diving exposure leads to further damage of an already impaired endothelium.

Methods: A total of 5 male and 5 female ApoE knockout (KO) rats were exposed to simulated diving to an absolute pressure of 600 kPa in heliox gas (80% helium, 20% oxygen) for 1 h in a dry pressure chamber. 10 ApoE KO rats (5 males, 5 females) and 8 male Sprague-Dawley rats served as controls. Endothelial function was examined *in vitro* by isometric myography of pulmonary and mesenteric arteries. Lipid peroxidation in blood plasma, heart and lung tissue was used as measures of oxidative stress. Expression and phosphorylation of endothelial NO synthase were quantified by Western blot.

Results and Conclusion: A single simulated dive was found to induce endothelial dysfunction in the pulmonary arteries of ApoE KO rats, and this was more profound in male than female rats. Endothelial dysfunction in males was associated with changing in production or bioavailability of NO; while in female pulmonary arteries an imbalance in prostanoid signaling was observed. No effect of diving was found on mesenteric arteries from rats of either sex. Our findings suggest that changes in endothelial dysfunction were specific for pulmonary circulation. In future, human translation of these findings may suggest caution for divers who are elderly or have prior reduced endothelial function.

Keywords: endothelial dysfunction, apolipoprotein E, atherosclerosis, cardiovascular, saturation diving

Metabolism

($nCells^3$)

Differs for Females and Males

Differs for Rats and Humans

Need for Human studies

Link with Micronuclei

frontiers in Physiology

HYPOTHESIS AND THEORY
published: 11 July 2019
doi: 10.3389/fphys.2019.00807

Static Metabolic Bubbles as Precursors of Vascular Gas Emboli During Divers' Decompression: A Hypothesis Explaining Bubbling Variability

Jean-Pierre Imbert[1], Salih Murat Egi[2,3], Peter Germonpré[3,4] and Costantino Balestra[3,5]*

[1] Divetech, Biot, France, [2] Department of Computer Engineering, Galatasaray University, Istanbul, Turkey, [3] DAN Europe Research Division, Divers Alert Network (DAN), Roseto, Italy, [4] Centre for Hyperbaric Oxygen Therapy, Military Hospital Brussels, Brussels, Belgium, [5] Environmental, Occupational and Ageing Physiology Laboratory, Haute Ecole Bruxelles-Brabant (HE2B), Brussels, Belgium

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Edited by:
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Reviewed by:
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***Correspondence:**

Introduction: The risk for decompression sickness (DCS) after hyperbaric exposures (such as SCUBA diving) has been linked to the presence and quantity of vascular gas emboli (VGE) after surfacing from the dive. These VGE can be semi-quantified by ultrasound Doppler and quantified via precordial echocardiography. However, for an identical dive, VGE monitoring of divers shows variations related to individual susceptibility, and, for a same diver, dive-to-dive variations which may be influenced by pre-dive pre-conditioning. These variations are not explained by currently used algorithms. In this paper, we present a new hypothesis: individual metabolic processes, through the oxygen window (OW) or Inherent Unsaturation of tissues, modulate the presence and volume of static metabolic bubbles (SMB) that in turn act as precursors of circulating VGE after a dive.

Magic formula

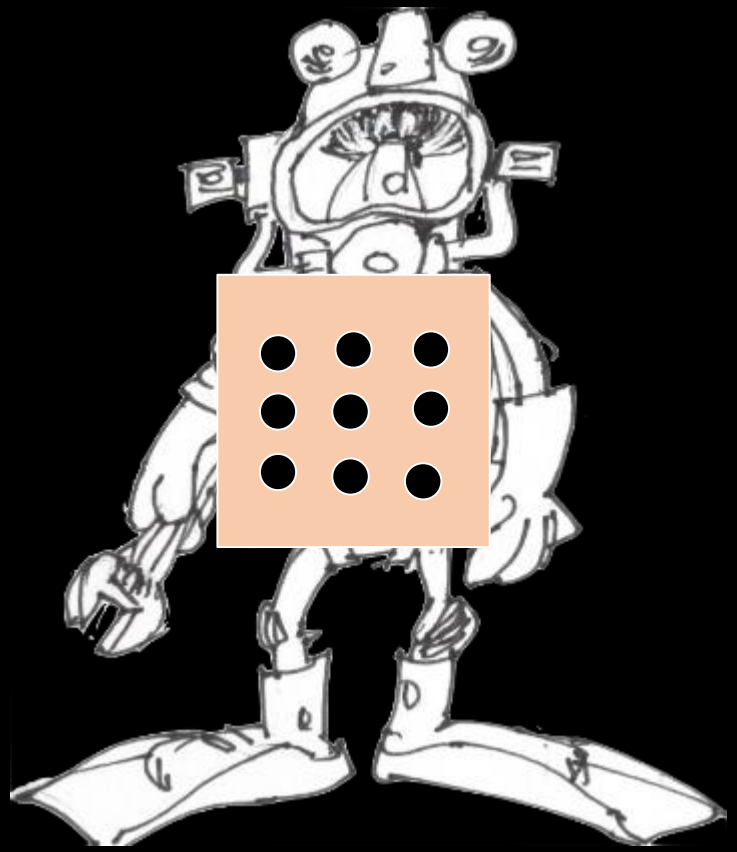
Long term
Life style

Age

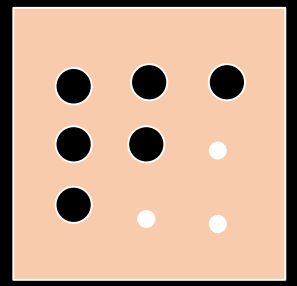
Fitness

Metabolism

Dive Oxygen



Recent history
Vibrations
Exercice



$$OW = m\tau\alpha \frac{1}{V^{1-m}}$$

ORIGINAL RESEARCH ARTICLE

Front. Physiol. | doi: 10.3389/fphys.2016.00586

Pre-dive whole-body vibration better reduces decompression-induced Vascular Gas Emboli than oxygenation or a combination of both.

 **Costantino Balestra**[2, 3], **Sigrid Theunissen**[2, 3], **Virginie Papadopoulou**[5], **Cedric Le Mener**[3], **Peter Germonpré**[2, 6], **François Guerrero**[2, 4] **and** **Pierre Lafere**[1, 2, 4*]

[1]Depatment of Anaesthesiology, CHRU de Brest, France

[2]DAN Europe Research Division, Italy

[3]Environmental, Occupational and Ageing Physiology Laboratory, Haute Ecole Paul-Henry Spaak, Belgium

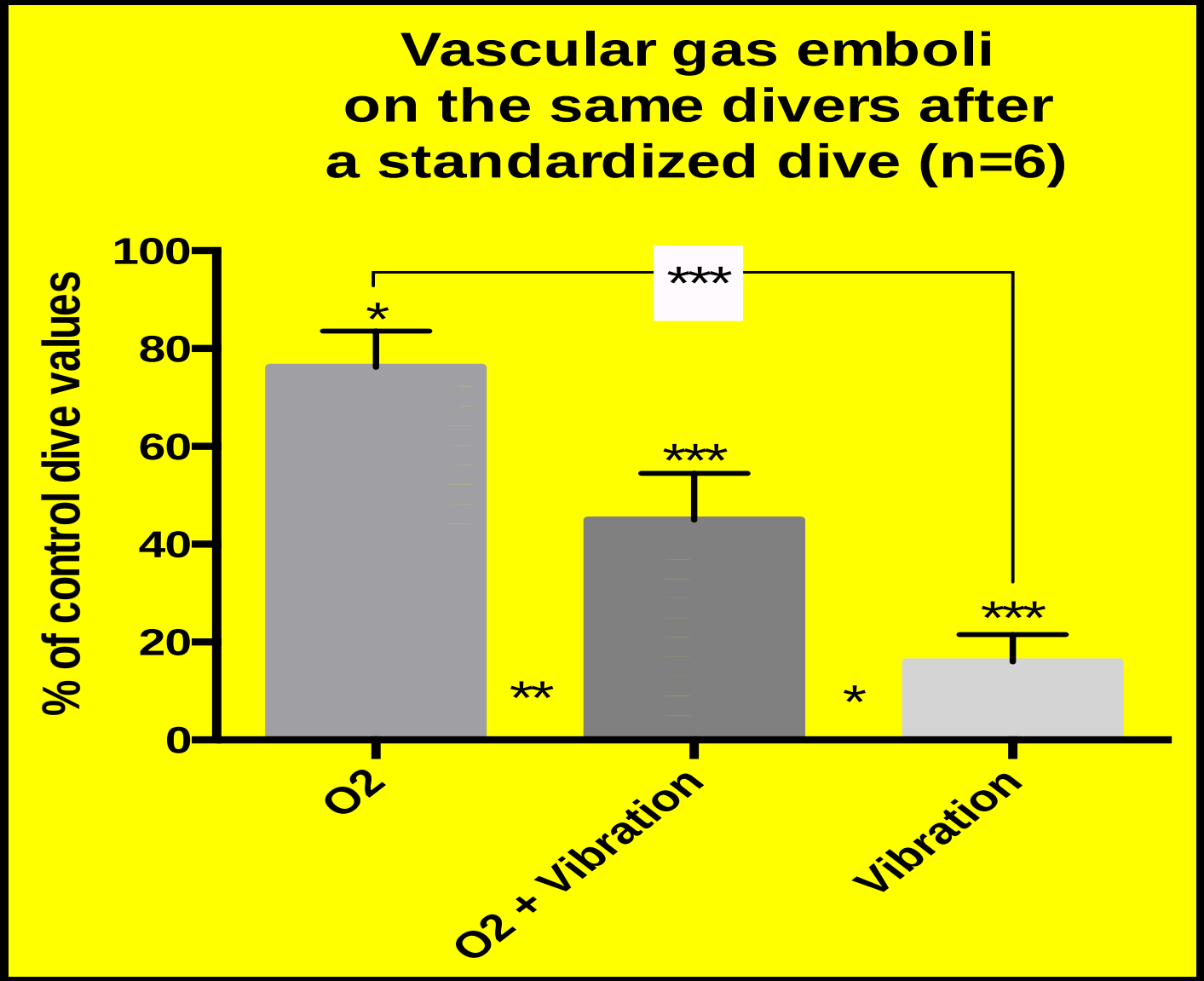
[4]ORPHY Laboratory, EA 4324, Université de Bretagne Occidentale, France

[5]Department of Bioengineering, Ultrasound Laboratory for Imaging and Sensing (ULIS), Imperial College London, United Kingdom

[6]Centre for Hyperbaric Oxygen Therapy, Military Hospital "Queen Astrid", Belgium

Purpose: Since non-provocative dive profiles are no guarantor of protection against decompression sickness, novel means including pre-dive “preconditioning” interventions, are proposed for its prevention. This study investigated and compared the effect of pre-dive oxygenation, pre-dive whole body vibration or a combination of both on post-dive bubble formation.

Methods: 6 healthy volunteers performed 6 no-decompression dives each, to a depth of 33 mfw for 20 minutes (3 control dives without preconditioning and 1 of each preconditioning protocol) with a


Vascular gas emboli
on the same divers after
a standardized dive (n=6)
% of control dive values
100
80
60
40
20
0
***
*
***
**
*
***
O2
O2 + Vibration
Vibration

Environment
Micro & Nano Particules

A

Micro- and nano-sized particles

Environmental

- natural sources, including forest fires, disasters, volcanoes eruption and bioparticles;
- anthropogenic origin (engine exhaust, wood combustion, coal consuming, etc)
-agriculture nanotechnologies;
- deposits from industry and medical nanotechnologies

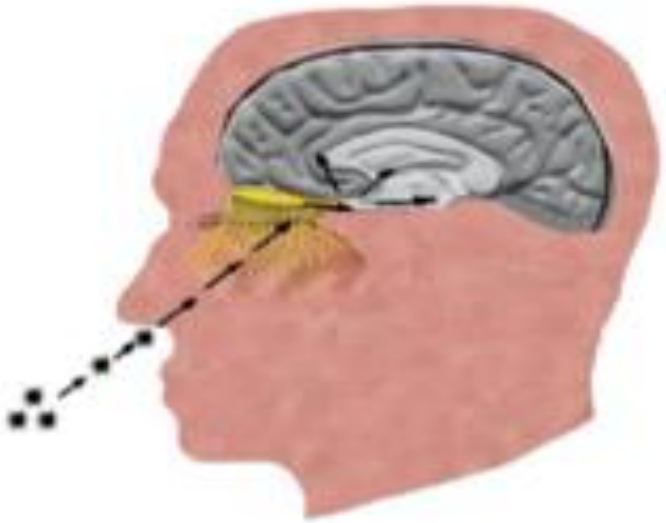
Engineered

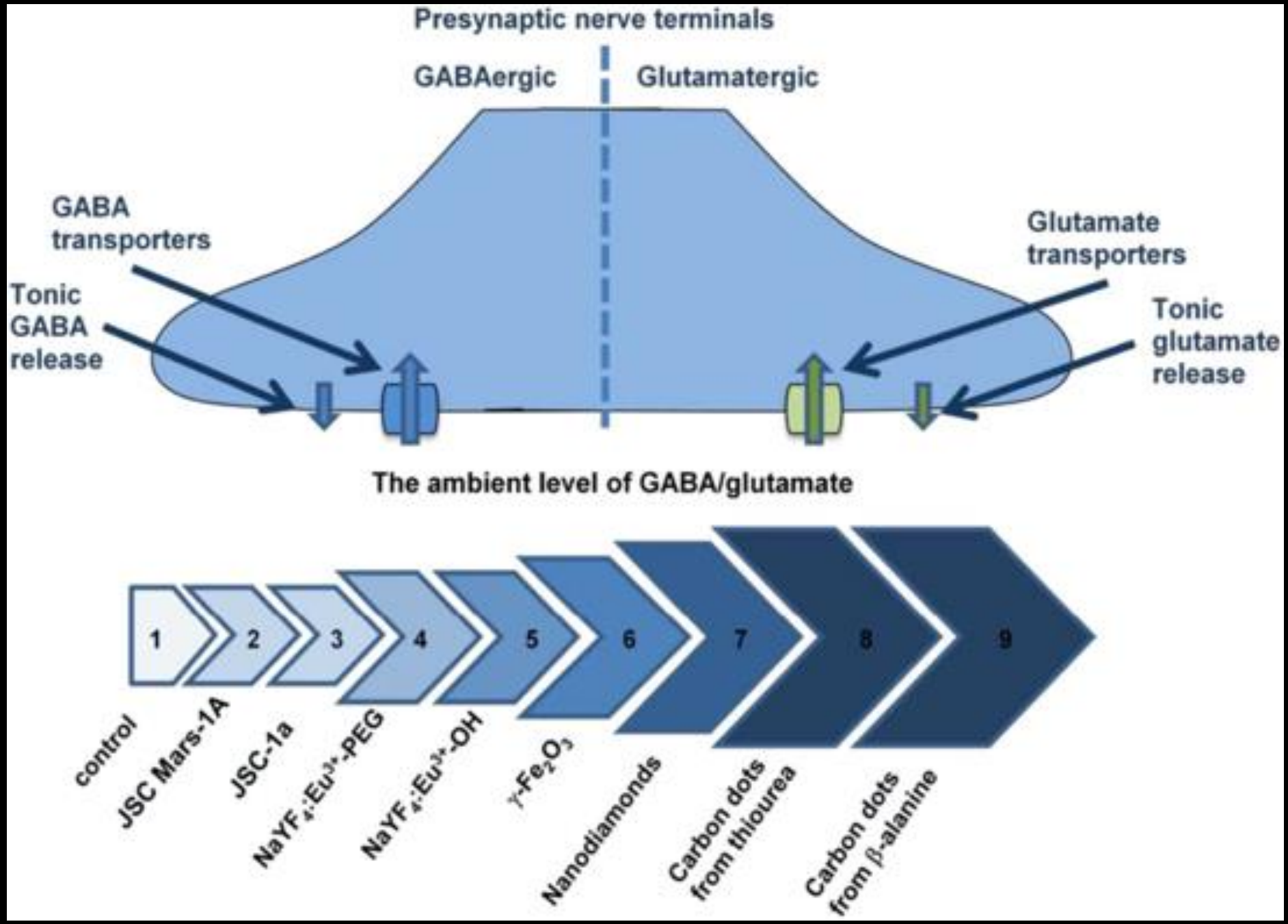
uncoated and surface functionalized particles of different size, shape, composition and surface properties

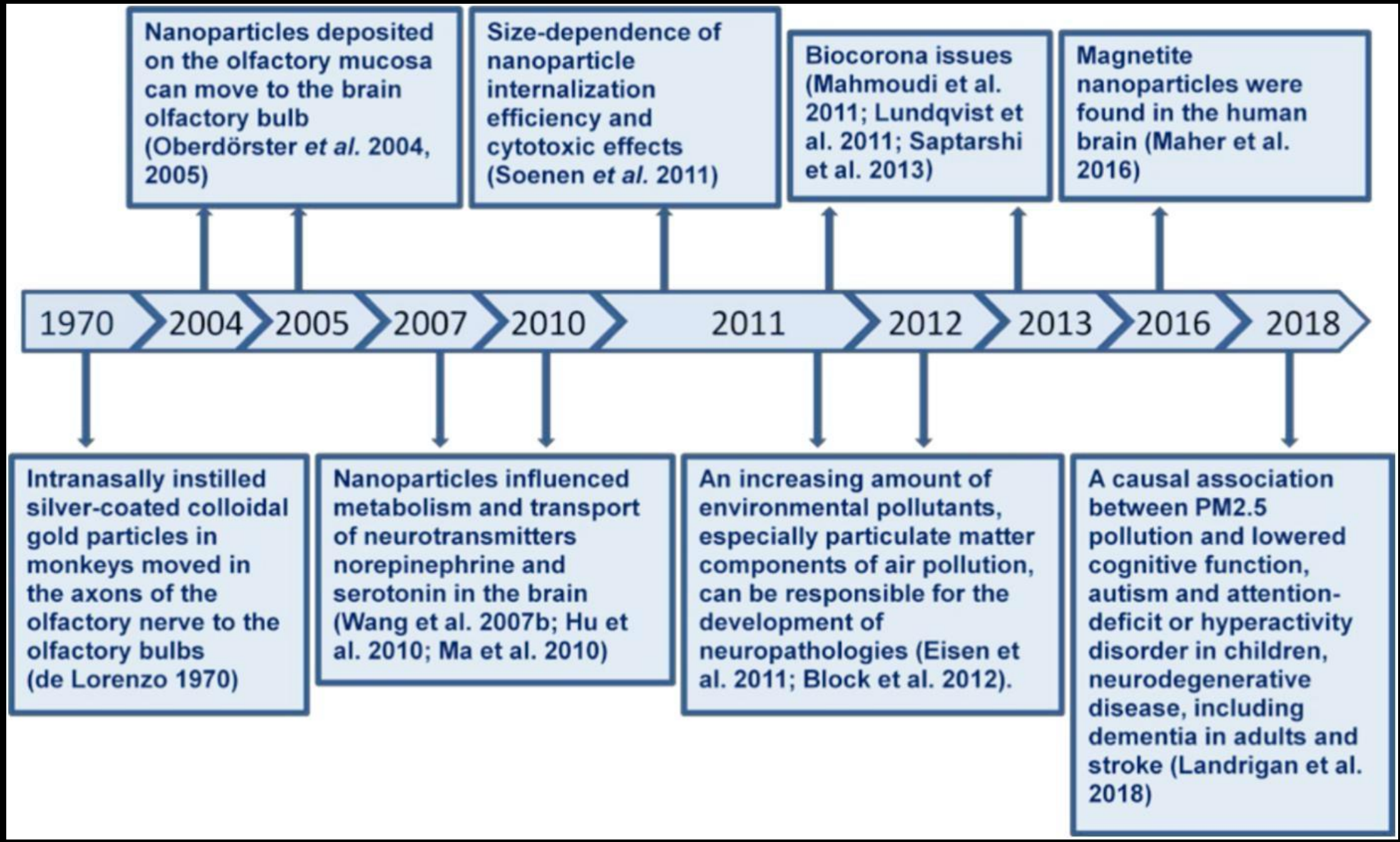
Planetary

Lunar and Martian dust

B




Presynaptic nerve terminals
GABAergic
Glutamatergic
GABA transporters
Tonic GABA release
Glutamate transporters
Tonic glutamate release
The ambient level of GABA/glutamate
1
2
3
4
5
6
7
8
9
control
JSC Mars-1A
JSC-1a
NaYF4:Eu3+-PEG
NaYF4:Eu3+-OH
γ-Fe2O3
Nanodiamonds
Carbon dots from thiourea
Carbon dots from β-alanine


Nanoparticles deposited on the olfactory mucosa can move to the brain olfactory bulb (Oberdörster *et al.* 2004, 2005)
Size-dependence of nanoparticle internalization efficiency and cytotoxic effects (Soenen *et al.* 2011)
Biocorona issues (Mahmoudi et al. 2011; Lundqvist et al. 2011; Saptarshi et al. 2013)
Magnetite nanoparticles were found in the human brain (Maher et al. 2016)
1970
2004
2005
2007
2010
2011
2012
2013
2016
2018
Intranasally instilled silver-coated colloidal gold particles in monkeys moved in the axons of the olfactory nerve to the olfactory bulbs (de Lorenzo 1970)
Nanoparticles influenced metabolism and transport of neurotransmitters norepinephrine and serotonin in the brain (Wang et al. 2007b; Hu et al. 2010; Ma et al. 2010)
An increasing amount of environmental pollutants, especially particulate matter components of air pollution, can be responsible for the development of neuropathologies (Eisen et al. 2011; Block et al. 2012).
A causal association between PM2.5 pollution and lowered cognitive function, autism and attention-deficit or hyperactivity disorder in children, neurodegenerative disease, including dementia in adults and stroke (Landrigan et al. 2018)

MICROBIOTA

ORIGINAL ARTICLE

Changes in the gut microbiota during and after commercial helium–oxygen saturation diving in China

Yuan Yuan,[1] Guosheng Zhao,[2] Hongwei Ji,[3] Bin Peng,[1] Zhiguo Huang,[3] Wei Jin,[3] Xiaoqiang Chen,[4] Haitao Guan,[5] Guangsheng Tang,[4] Hui Zhang,[3] Zhenglin Jiang[1]

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/oemed-2019-106031).

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Correspondence to
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Received 14 June 2019
Revised 28 August 2019
Accepted 2 September 2019

ABSTRACT

Objectives The influence of commercial helium–oxygen saturation diving on divers' gut microbiotas was assessed to provide dietary suggestion.

Methods Faecal samples of 47 divers working offshore were collected before (T1), during (T2) and after (T3) saturation diving. Their living and excursion depths were 55–134 metres underwater with a saturation duration of 12–31 days and PaO_2 of 38–65 kPa. The faecal samples were examined through 16S ribosomal DNA amplicon sequencing based on the Illumina sequencing platform to analyse changes in the bacteria composition in the divers' guts.

Results Although the α and β diversity of the gut microbiota did not change significantly, we found that living in a hyperbaric environment of helium–oxygen saturation decreased the abundance of the genus *Bifidobacterium*, an obligate anaerobe, from 2.43%±3.83% at T1 to 0.79%±1.23% at T2 and 0.59%±0.79% at T3. Additionally, the abundance of some short-chain fatty acid (SCFA)-producing bacteria, such as *Fusicatenibacter*, *Faecalibacterium*, rectale group and *Anaerostipes*, showed a decreased trend in the order of before, during and after diving. On the contrary, the abundance of species, such as *Lactococcus garvieae*, *Actinomyces odontolyticus*, *Peptoclostridium difficile*, *Butyricimonas virosa*, *Streptococcus mutans*, *Porphyromonas asaccharolytica* and *A. graevenitzii*, showed an increasing trend, but most of them were pathogens.

Conclusions Occupational exposure to high pressure in a helium–oxygen saturation environment decreased the abundance of *Bifidobacterium* and some SCFA-producing bacteria, and increased the risk of pathogenic bacterial infection. Supplementation of the diver diet with probiotics or prebiotics during saturation diving might prevent these undesirable changes.

Key messages

What is already know
- Saturation divers ar hyperoxic and hype relatively long time physiological and r may impact human
- The appropriate die alleviate many of th metabolic concerns and performance of

What are the new fir
- Helium–oxygen sat 134 metres of dept and β diversity of th However, the abund *Bifidobacterium* an acid (SCFA)-produci that of some patho during and after div saturation diving m homoeostasis and i pathogen infection.

How might this impact on policy or clinical practice in the foreseeable future?
- A diet supplemented with probiotics, such as species from *Bifidobacterium*, or prebiotics that can stimulate gut *Bifidobacterium* and SCFA-producing bacteria might promote the health of saturation divers.

redox homoeostasis, immunological function and haematological variables.[1–6] Furthermore, satura-

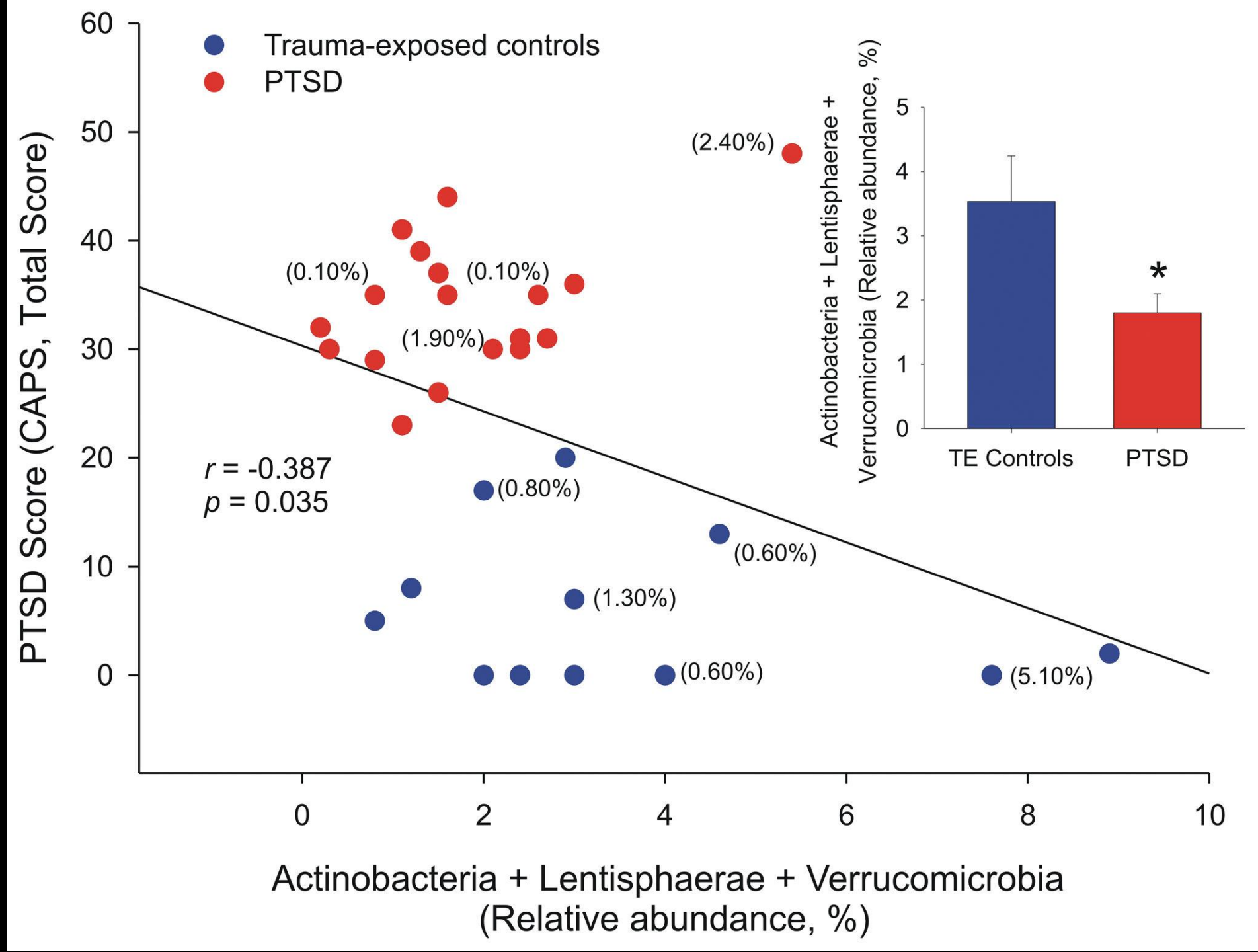
How might this impact on policy or clinical practice in the foreseeable future?
- A diet supplemented with probiotics, such as species from *Bifidobacterium*, or prebiotics that can stimulate gut *Bifidobacterium* and SCFA-producing bacteria might promote the health of saturation divers.

Psychosom Med. Author manuscript; available in PMC 2018 Oct 1.
Published in final edited form as:
Psychosom Med. 2017 Oct; 79(8): 936–946.
doi: 10.1097/PSY.0000000000000512

PMCID: PMC5763914
NIHMSID: NIHMS889683
PMID: 28700459

The Microbiome in Posttraumatic Stress Disorder and Trauma-Exposed Controls: An Exploratory Study

Sian M.J. Hemmings, PhD,[1,†] Stefanie Malan-Muller, PhD,[1,†] Leigh L. van den Heuvel, MMed (Psych),[1] Brittany A. Demmitt, BS,[2,3] Maggie A. Stanislawski, MS,[4,5] David G. Smith, BS,[6] Adam D. Bohr, PhD,[3,7] Christopher E. Stamper, MS,[7] Embriette R. Hyde, PhD,[8] James T. Morton, BS,[9] Clarisse A. Marotz, MS,[8] Philip H. Siebler, BS,[7] Maarten Braspenning, Ir,[10] Wim Van Criekinge, PhD, Ir,[11] Andrew J. Hoisington, PhD,[12,13] Lisa A. Brenner, PhD,[13,14,15,16] Teodor T. Postolache, MD,[13,16,17] Matthew B. McQueen, ScD,[3,7] Kenneth S. Krauter, PhD,[2,3] Rob Knight, PhD,[8,9,18] Soraya Seedat, MD, PhD,[1] and Christopher A. Lowry, PhD[7,13,15,16,19,20,*]


Trauma-exposed controls
PTSD
PTSD Score (CAPS, Total Score)
Actinobacteria + Lentisphaerae + Verrucomicrobia (Relative abundance, %)
r = -0.387
p = 0.035
(2.40%)
(0.10%)
(0.10%)
(1.90%)
(0.80%)
(0.60%)
(1.30%)
(0.60%)
(5.10%)
Actinobacteria + Lentisphaerae + Verrucomicrobia (Relative abundance, %)
TE Controls
PTSD
*

SCIENTIFIC REPORTS

OPEN

Study of the impact of long-duration space missions at the International Space Station on the astronaut microbiome

Received: 6 March 2019
Accepted: 17 June 2019
Published online: 09 July 2019

Alexander A. Voorhies[1], C. Mark Ott[2], Satish Mehta[2], Duane L. Pierson[2], Brian E. Crucian[2], Alan Feiveson[2], Cherie M. Oubre[2], Manolito Torralba[1], Kelvin Moncera[1], Yun Zhang[1], Eduardo Zurek[1] & Hernan A. Lorenzi[1]

Over the course of a mission to the International Space Station (ISS) crew members are exposed to a number of stressors that can potentially alter the composition of their microbiomes and may have a negative impact on astronauts' health. Here we investigated the impact of long-term space exploration on the microbiome of nine astronauts that spent six to twelve months in the ISS. We present evidence showing that the microbial communities of the gastrointestinal tract, skin, nose and tongue change during the space mission. The composition of the intestinal microbiota became more similar across astronauts in space, mostly due to a drop in the abundance of a few bacterial taxa, some of which were also correlated with changes in the cytokine profile of crewmembers. Alterations in the skin microbiome that might contribute to the high frequency of skin rash/hypersensitivity episodes experienced by astronauts in space were also observed. The results from this study demonstrate that the composition of the astronauts' microbiome is altered during space travel. The impact of those changes on crew health warrants further investigation before humans embark on long-duration voyages into outer space.

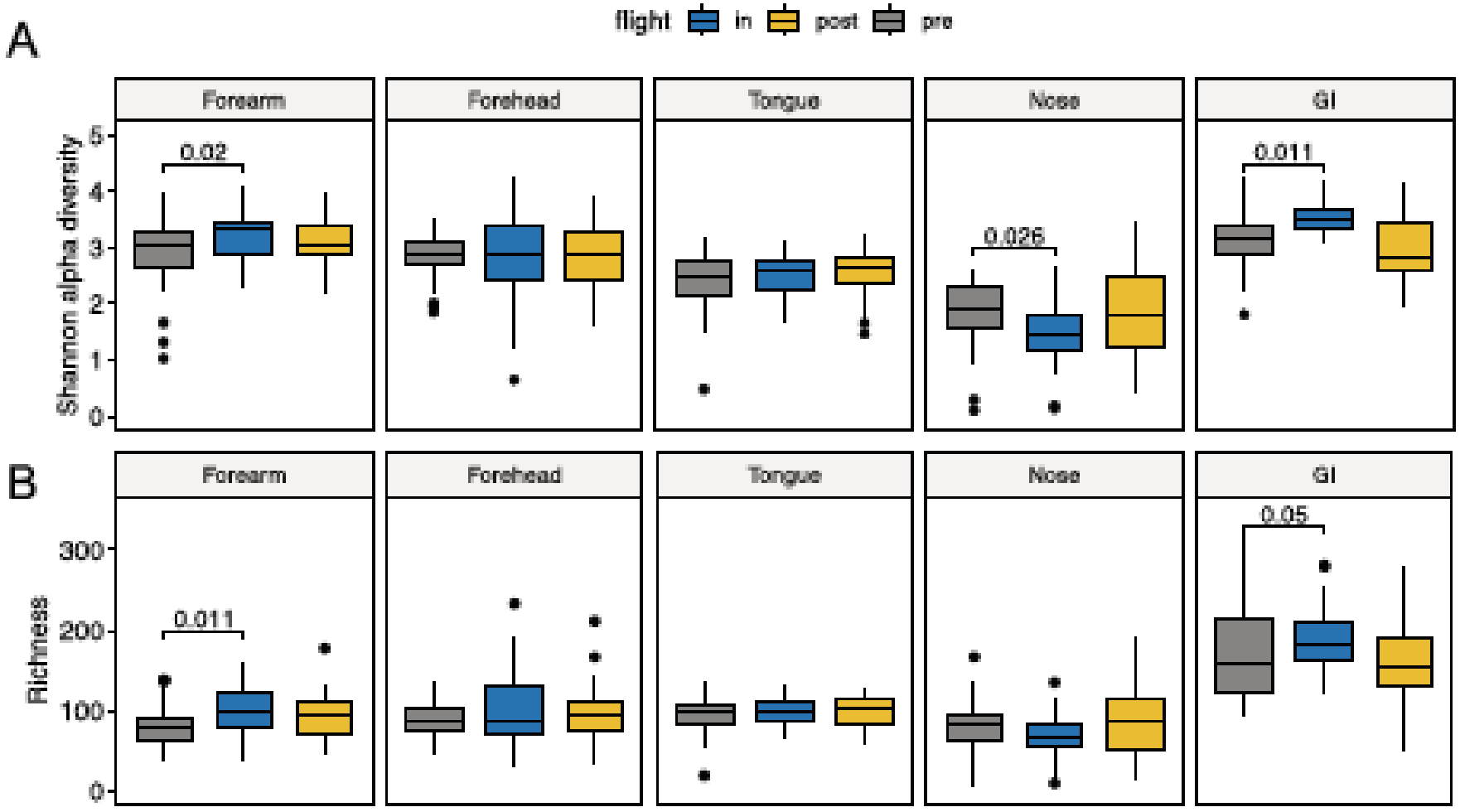


Figure 3. Changes in alpha diversity and richness of the astronauts' microbiome. Boxplots depicting changes in Shannon alpha diversity (**A**) and Richness (**B**) of the five human microbiomes surveyed in this study during a mission to the ISS. Significant linear mixed-effects model p-values are depicted using mission stage Preflight as baseline.

NUTRITION :

Well Being
Anti-Oxydant
Microbiota
Chelation

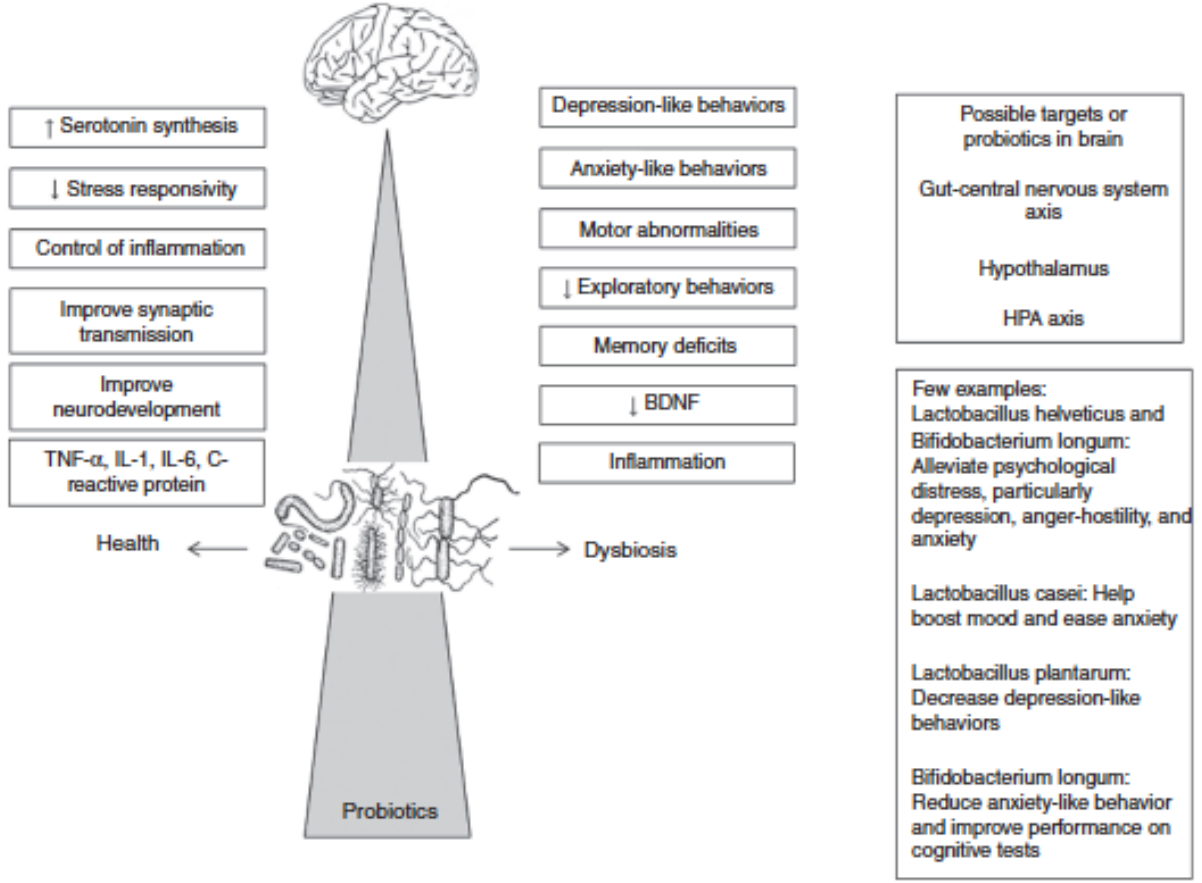


Figure 1: Schematic representation of gut-brain axis and microbiota in mood disorders.

DE GRUYTER Rev. Neurosci. 2017; aop

Adiel C. Rios, Pawan Kumar Maurya, Mariana Pedrini, Maiara Zeni-Graiff, Elson Asevedo, Rodrigo B. Mansur, Andrea Wieck, Rodrigo Grassi-Oliveira, Roger S. Mcintyre, Mirian A.F. Hayashi and Elisa Brietzke*

Microbiota abnormalities and the therapeutic potential of probiotics in the treatment of mood disorders

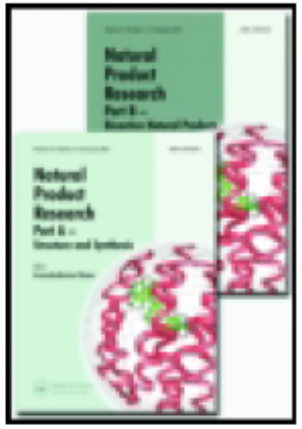
DOI 10.1515/revneuro-2017-0001
Received January 5, 2017; accepted March 8, 2017

Abstract: Major depressive disorder (MDD) and bipolar disorder (BD) are among the leading causes of burden and disability worldwide. Despite intensified research efforts to improve the treatment options and remission rates in mood disorders, no disease modifying treatment exists for these disorders. Accumulating evidence implicates the involvement of the gut microbiota in processes relevant to etiopathology of central nervous system-based disorders. The objective of this article was to critically evaluate the evidence supporting the link between gastrointestinal microbiota and mood disorders and to discuss the potential benefits of using probiotics in the treatment of MDD and BD. The concept of psychobiotics, which is bacterial-based interventions with mental health benefit, is emerging in the field. On the other hand, while probiotics might potentially represent a significant advance, specific roles of microbiota in the pathophysiology of mood disorders still need further investigation along with intervention studies.

Keywords: bipolar disorder; major depression disorder; microbiome; microbiota; mood disorders; probiotics.

Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are mood disorders and are among the leading causes of burden and disability worldwide (Collins et al., 2011). Notwithstanding the progress in drug development, most individuals receiving treatment for a mood disorder



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Natural Product Research

Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: http://www.tandfonline.com/loi/gnpl20

A red orange extract modulates the vascular response to a recreational dive: a pilot study on the effect of anthocyanins on the physiological consequences of scuba diving

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To cite this article: C. Balestra, F. Cimino, S. Theunissen, T. Snoeck, S. Provyn, R. Canali, A. Bonina & F. Virgili (2015): A red orange extract modulates the vascular response to a recreational dive: a pilot study on the effect of anthocyanins on the physiological consequences of scuba diving, Natural Product Research, DOI: 10.1080/14786419.2015.1107062

To link to this article: http://dx.doi.org/10.1080/14786419.2015.1107062

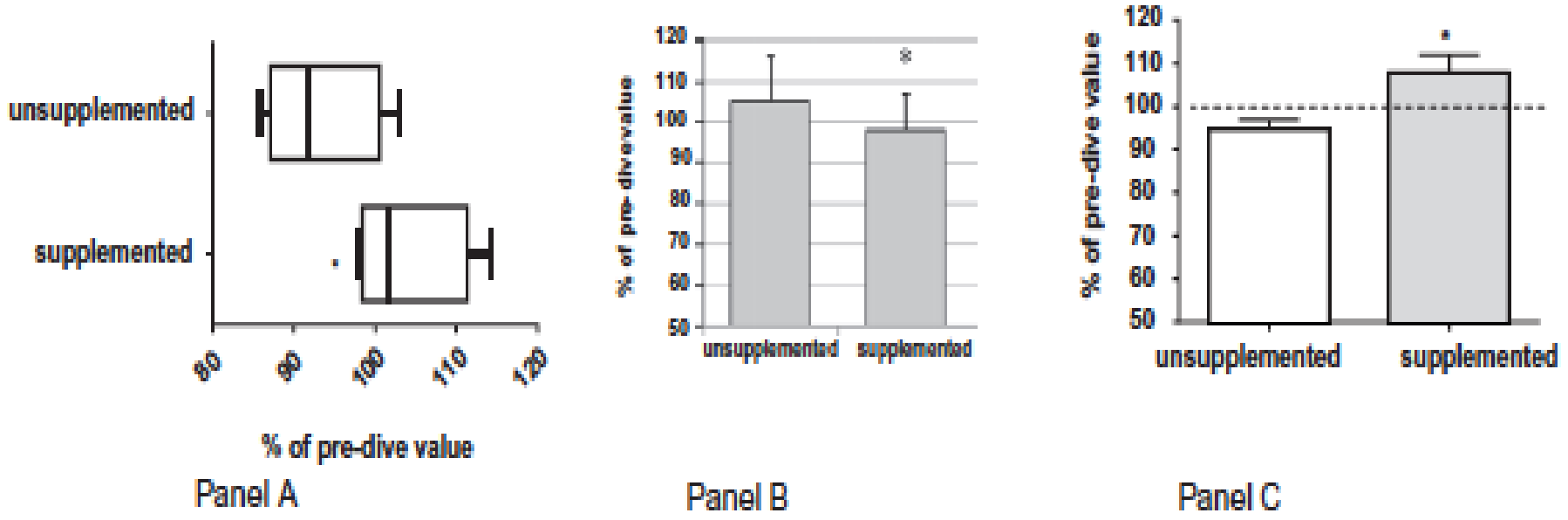
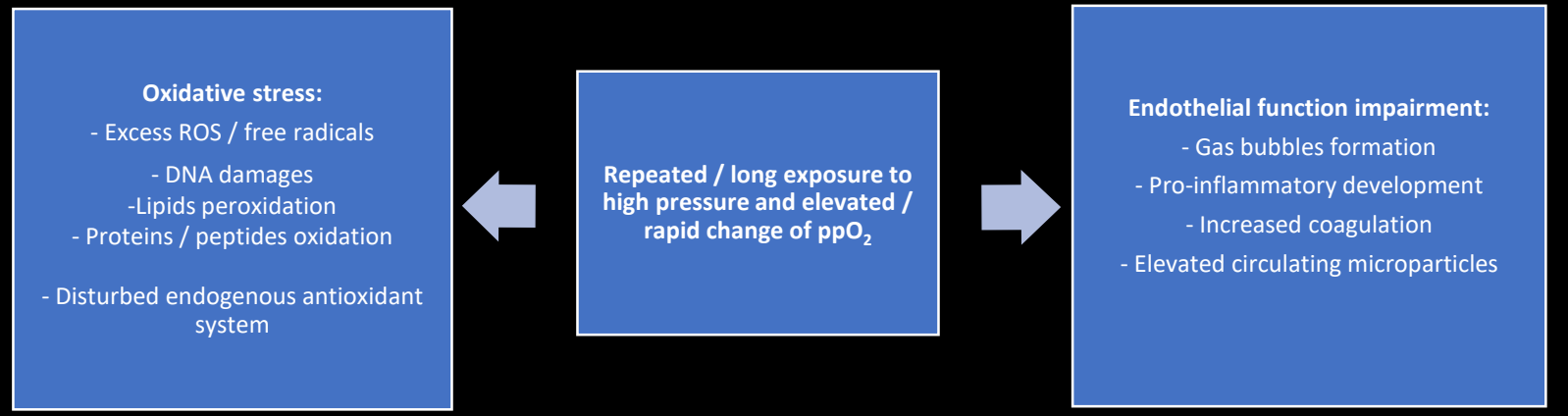


Figure 1. Panel A: HTC changes (as % of pre-dive value) after diving and effect of the administration of 400 mg ROC. Panel B: Extracellular water measured by multifrequency bioimpedance changes (as % of pre-dive value) after diving and effect of the administration of 400 mg ROC. Panel C: FMD changes (as % of the initial value) after diving and effect of the administration of 400 mg ROC. *$p < 0.05$ according to Mann–Whitney *U*-test vs. unsupplemented.

Diving potential risks and mitigation

Diving procedures

Acclimatization, biological defences

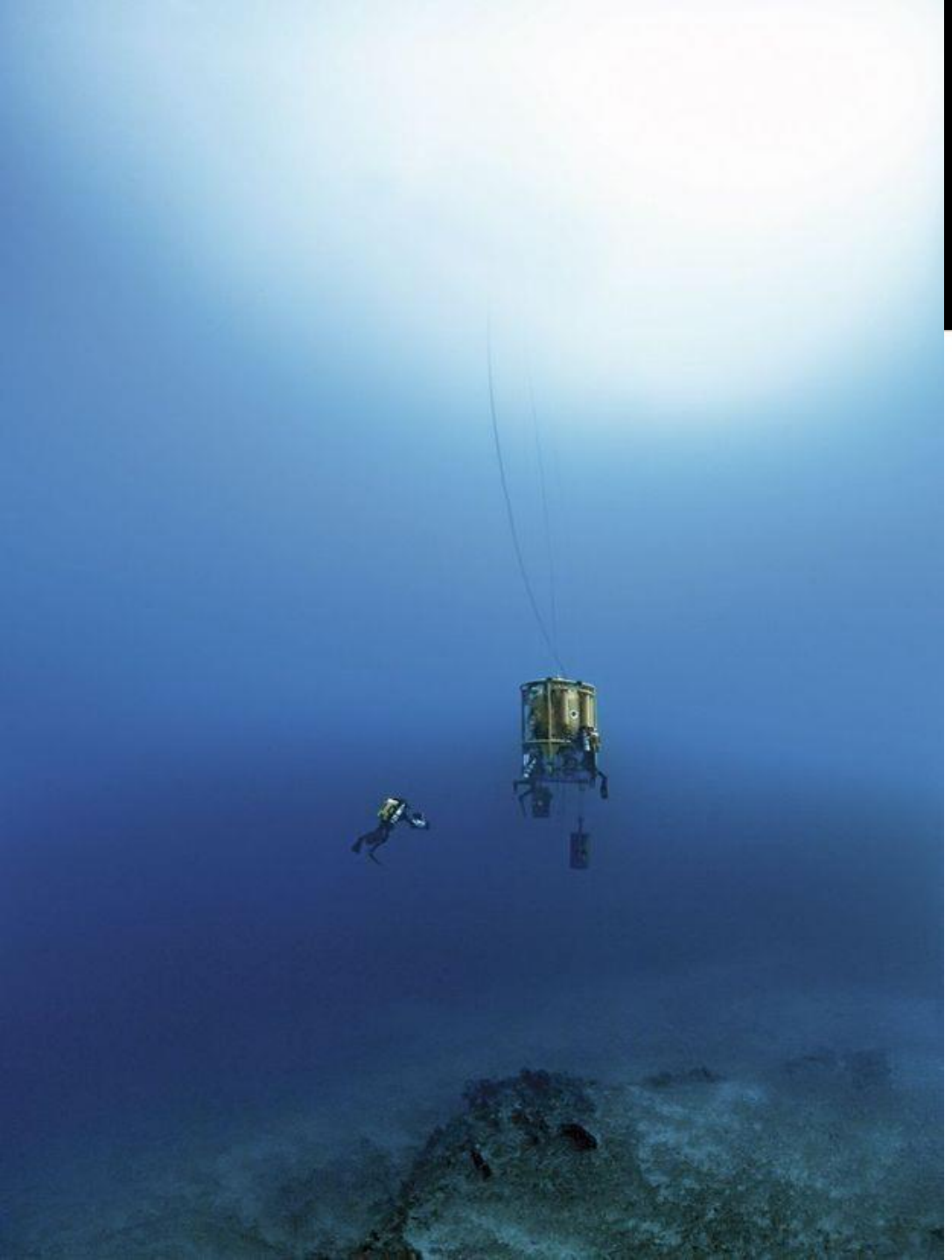


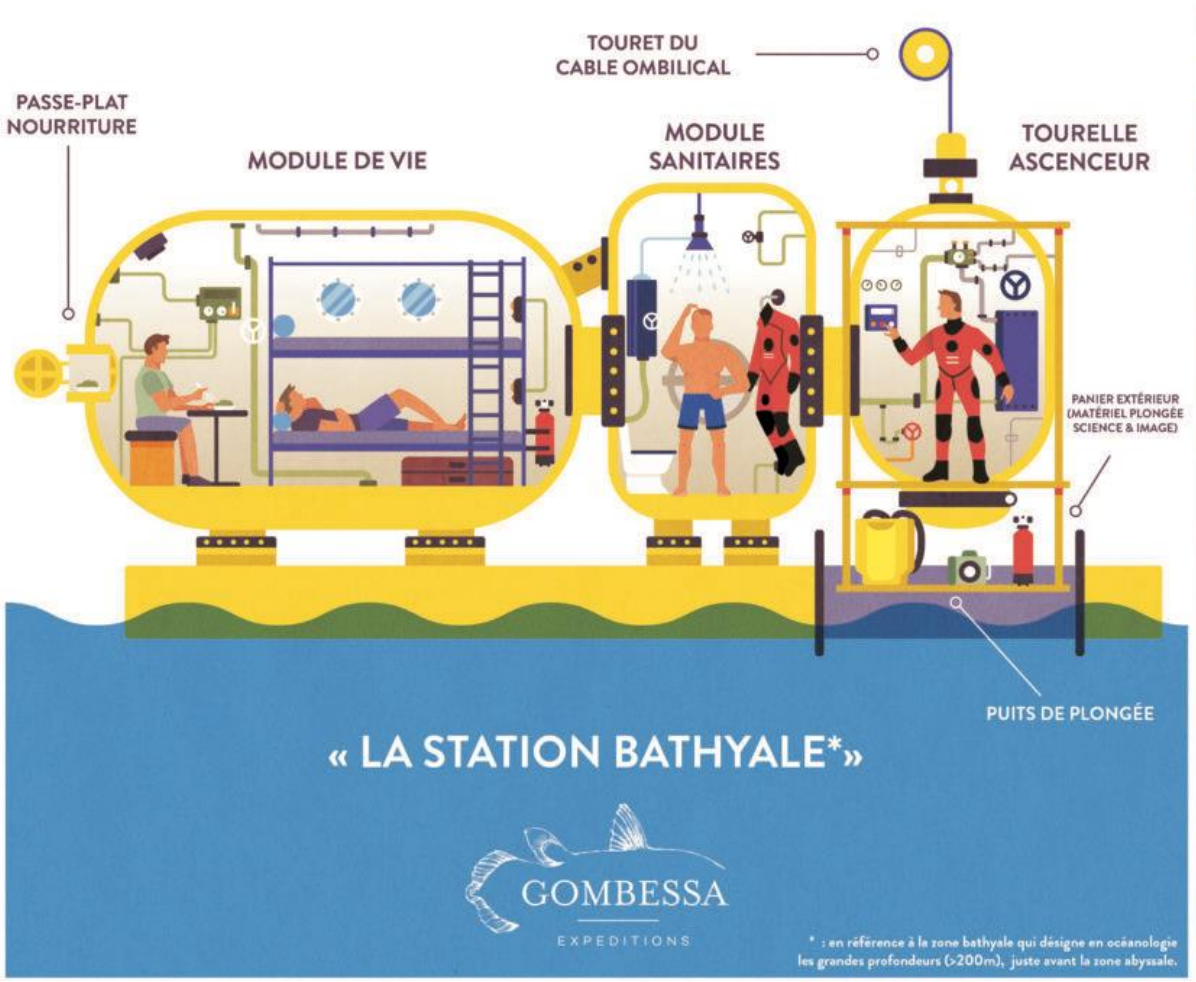

DUKE
DUKE
ATLANTIS II

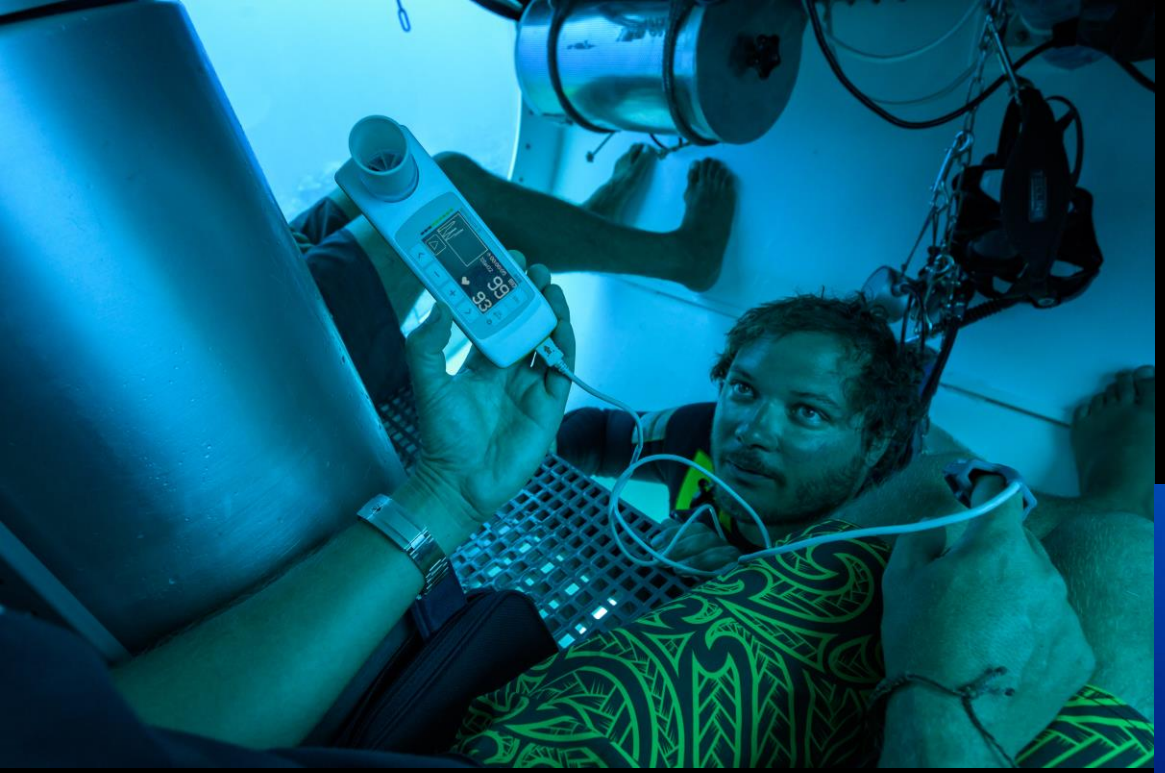

686 m.
2250 ft

Theo Mavrostomos

Gombessa V (Mediterranean Planet)







Under The Pole (Capsule Project)

Conclusions

-We are facing a new moment in Diving Pathophysiology understanding

-Saturation diving research papers have never been so many since the last few years. We understand today that :

Depth of 180-225 msw seems to be the starting level of HPNS and the effects have not shown to alter Divers significantly according to actually accepted and tested procedures.

Deeper diving may be possible considering a multifactorial approach needing more investigations.

Online version at http://www.minervamedica.it

Minerva Anestesiologica 2019 October;85(10):1129-37
DOI: 10.23736/S0375-9393.19.13618-8

EXPERT'S OPINION

Diving physiopathology: the end of certainties? Food for thought

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ABSTRACT

Our understanding of decompression physiopathology has slowly improved during this last decade and some uncertainties have disappeared. A better understanding of anatomy and functional aspects of patent foramen ovale (PFO) have slowly resulted in a more liberal approach toward the medical fitness to dive for those bearing a PFO. Circulating vascular gas emboli (VGE) are considered the key actors in development of decompression sickness and can be considered as markers of decompression stress indicating induction of pathophysiological processes not necessarily leading to occurrence of disease symptoms. During the last decade, it has appeared possible to influence post-dive VGE by a so-called "preconditioning" as a pre-dive denitrogenation, exercise or some pharmacological agents. In the text we have deeply examined all the scientific evidence about this complicated but challenging theme. Finally, the role of the "normobaric oxygen paradox" has been clarified and it is not surprising that it could be involved in neuroprotection and cardioprotection. However, the best level of inspired oxygen and the exact time frame to achieve optimal effect is still not known. The aim of this paper was to reflect upon the most actual uncertainties and distil out of them a coherent, balanced advice towards the researchers involved in gas-bubbles-related pathologies.

(*Cite this article as:* Balestra C, Germonpré P, Rocco M, Biancofiore G, Kot J. Diving physiopathology: the end of certainties? Food for thought. Minerva Anestesiol 2019;85:1129-37. DOI: 10.23736/S0375-9393.19.13618-8)

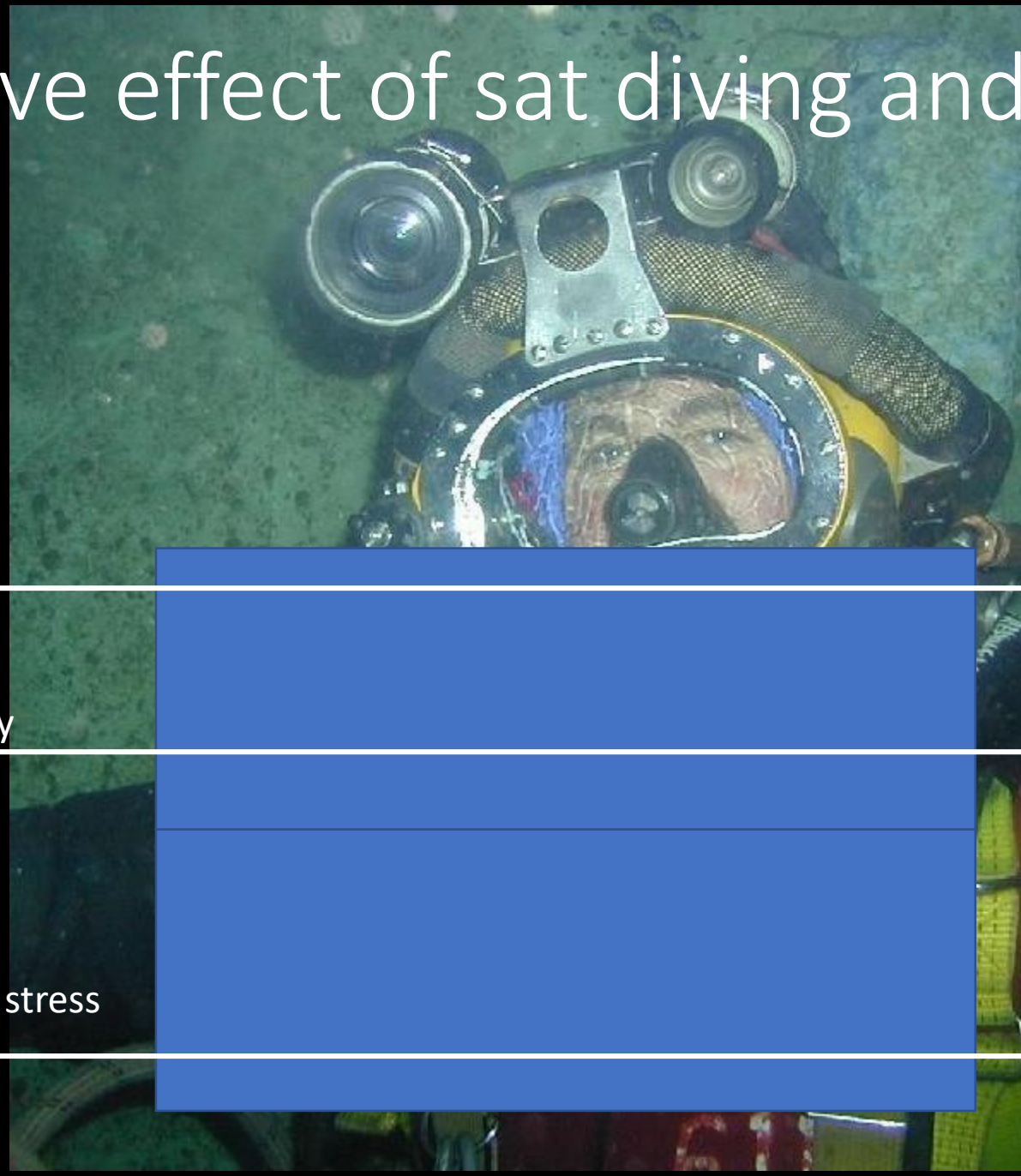
KEY WORDS: Diving; Decompression sickness; Physiopathology.

A few more tips on stress hardiness

The Four A's

Avoid the stressor
Alter the stressor
Adapt to the stressor
Accept the stressor

Cumulative effect of sat diving and stress



PTSD like symptoms

Clinical brain inflammation

Additional stress/anxiety

Sub clinical brain inflammation

Sat diving and oxidative stress

Objectives for next years

- Identify pertinent bio markers
- Monitor these bio markers to evaluate divers' recovery - preparation
- Base sat exposure (depth and frequency) on measured recovery status

FOCUS ????

Auto reference…self referencing


YOUR ATTENTION
I THANK YOU
FOR
memegenerator.net