The placebo effect and hyperbaric medicine

Deeper into placebo, nocebo and the Hawthorne effect

Randomised, double-blind placebo-controlled trials

- Many advantages, but most importantly:
- The elimination of selection bias (to each arm of st
- T ias b
- R on statistical methods
- Ensure any effect of participation does not bias the result

BUT: Placebo, nocebo and Hawthorne effects can make the result of any study difficult to interpret.

Placebo

From the Latin: placēbō: "I shall please" (Latin verb: placeō, "I please")

"a simulated or otherwise medically ineffectual treatment for a disease or other medical condition intended to deceive the recipient.
Sometimes patients given a placebo treatment will have a perceived or actual improvement in a medical condition, commonly called the **placebo effect**."

Placebo Domino in regione vivorum

Vulgate bible – St. Jerome

Office of the Dead was called 'the placebo'

Placebo singers came to attend the office pretending they knew the deceased in order to share in the feast on offer

These placebos were fakers – not real. Hence placebo as 'fake treatment'

History

18th century. Defined as a "commonplace method or medicine".

1811 it was defined as "any medicine adapted more to please than to benefit the patient", sometimes with a derogatory implication, but not with the implication of no effect. (Kaptchuk 1998)

1903 Richard Cabot said that he was brought up to use placebos, but concluded "I have not yet found any case in which a lie does not do more harm than good".

1961 Henry Beecher found that surgeons he categorized as enthusiasts relieved their patients' chest pain and heart problems more than skeptical surgeons.(Beecher 1995)

1960s placebo controlled trials became the norm in the approval of new medications.

2011 Program in Placebo Studies established at Harvard Medical School.

Comparison of Internal Mammary Artery Ligation and Sham Operation for Angina Pectoris*

E. Grey Dimond, M.D., F.A.C.C., C. Frederick Kittle, M.D. *and* James E. Crockett, M.D.

Kansas City, Kansas

Ligation of the internal mammary arteries as therapy for angina pectoris has received wide attention.[1–9] This report describes an evaluation of the treatment of angina pectoris by ligation of the internal mammary arteries compared with a sham procedure.

Method

This has been carried out in the following manner:

(1) Two cardiologists selected patients who presented an adequate and uniform history classic for angina pectoris.

(2) Each patient had, either at rest or on exercise, a distinctly abnormal electrocardiogram.

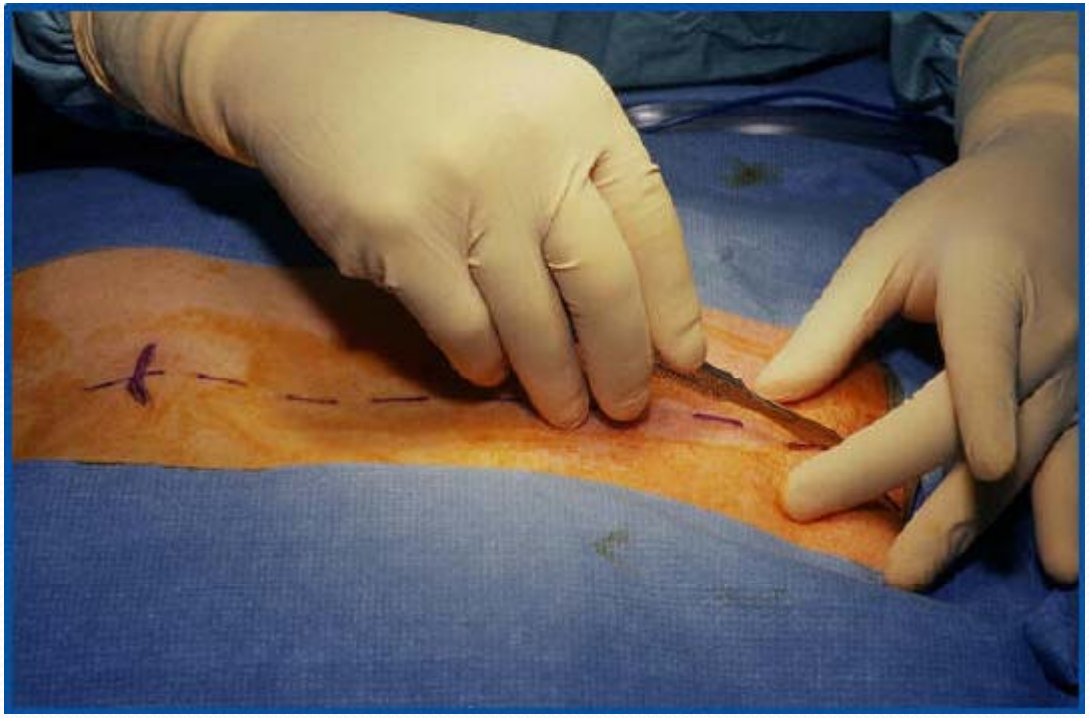
(3) Before operation each patient was exercised to the point of angina under observation, and electrocardiograms were then obtained.

(4) The patients were operated on under local anesthesia. The surgeon, by random sampling, selected those in whom bilateral internal mammary artery and vein ligation (second interspace) was to be

Results

Eighteen carefully selected patients comprised this group. A total of 156 exercise electrocardiograms were obtained. In attempting to evaluate these eighteen patients it was apparent that the two yardsticks, (1) the patient's appraisal of his work capacity, and (2) the changes in the electrocardiogram after exercise, were unrelated. The subjective sensation, angina, was materially lessened in all of the patients immediately following the operation and this improvement was maintained in fifteen of the patients (Chart I). Three patients who were temporarily improved retained this benefit for two days, two weeks and one month, respectively. In the fifteen patients who had sustained benefit (that is, lessened angina) following the surgery, a distinctly abnormal or "positive" electrocardiographic response to exercise could be provoked in thirteen of the fifteen. The

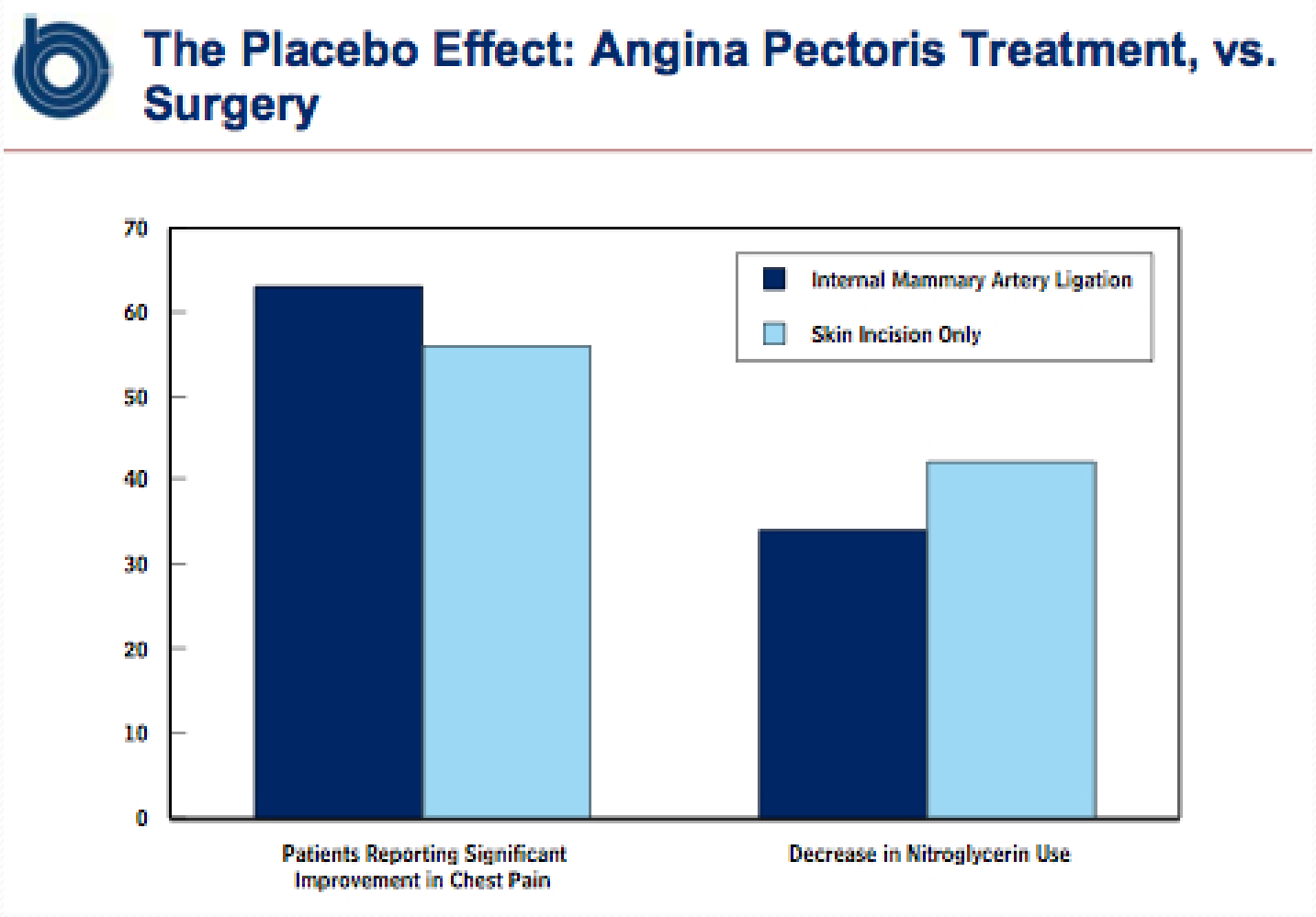
Surgeons randomized patients with stable angina and ECG changes evident on exercise to have MAL or simply the skin incision through which the operation was performed.



Results

No difference in the reported rate of improvement in symptoms or use of nitroglycerine

ECG changes were not different before and after



Discussion

- "The frightened, poorly informed man with angina, winding himself tighter and tighter, sensitizing himself to every twinge of chest discomfort, who then comes into the environment of a great medical center and a powerful positive personality and sees and hears the results to be anticipated from the suggested therapy is not the same total patient who leaves the institution with the trademark scar." (Dimond 1960)

Is sham hyperbaric a placebo?

- Common placebos include inert tablets, vehicle infusions, sham surgery and other procedures based on false information.(Lanotte 2005)
- But a compression would cease to be a placebo if we took the position that the procedure had some therapeutic value due to
  - pressure itself
  - minor increases in P_IO_2
  - minor increases in P_IN_2

So placebo treatment seems simple…

- You randomise subjects to receive your real treatment or an inert/ineffective alternative
- You blind everyone you can
- Any difference in outcome must be due to:
  - the effect of the real treatment plus placebo
  - versus placebo effect alone

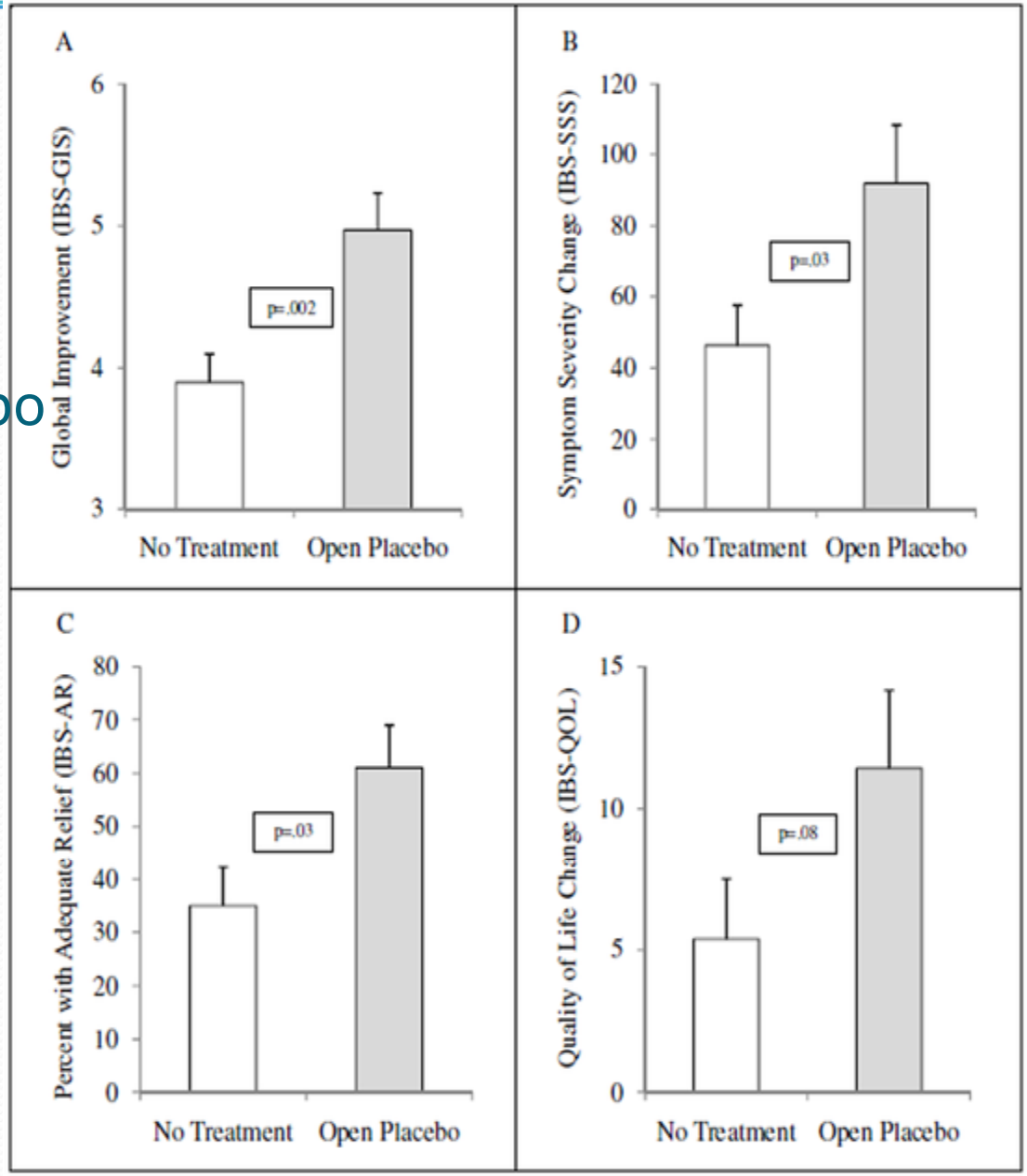
But is it that simple?

- Placebos can also have a surprisingly positive effect on a patient who knows that the given treatment is without any active drug, as compared with a control group who knowingly did *not* get a placebo.(Kaptchuk 2010)

- Tested whether open-label placebo (non-deceptive and non-concealed administration) is superior to a no-treatment control with matched patient-provider interactions in the treatment of irritable bowel syndrome (IBS).

Kaptchuk 2010

Widespread improvements in placebo over no treatment

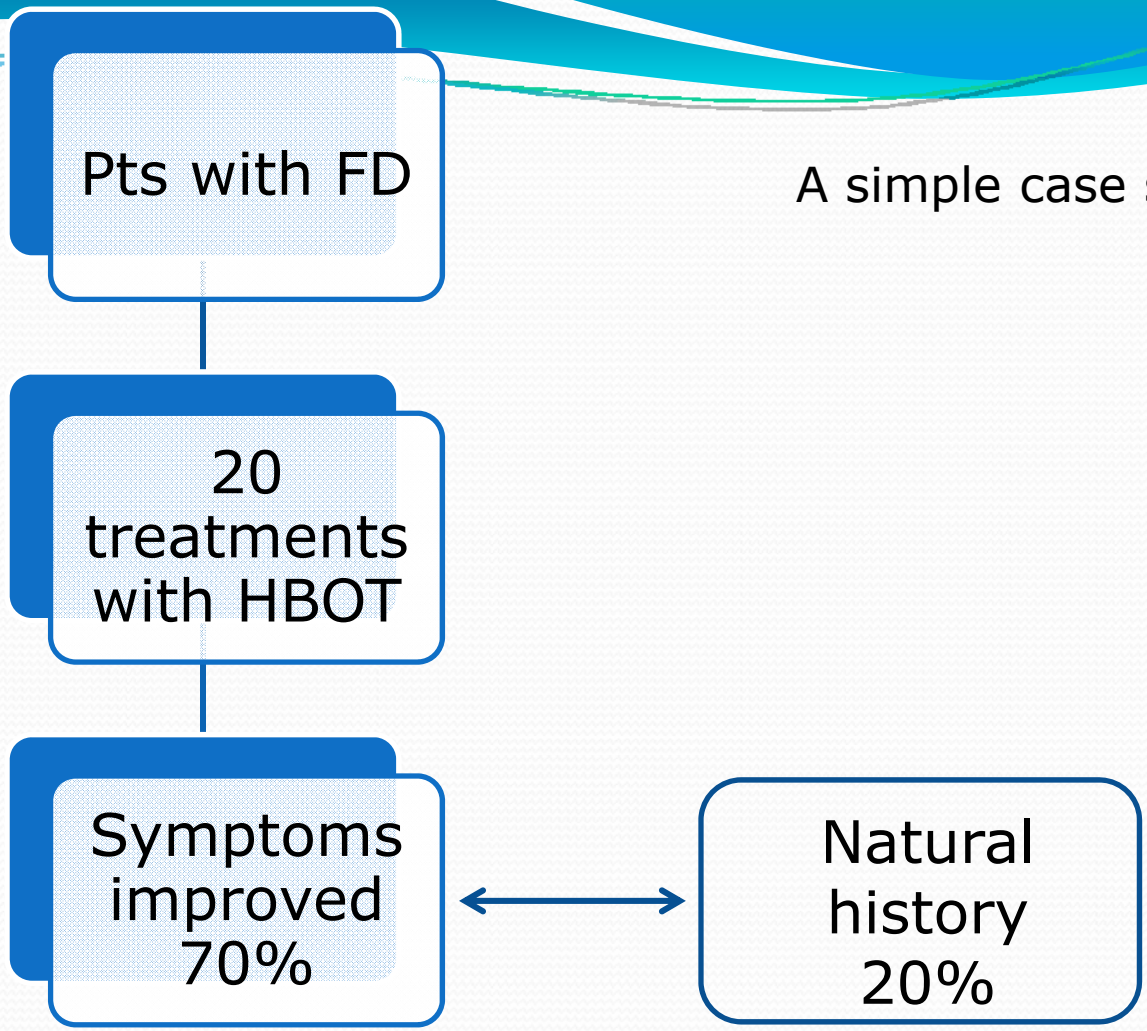


Imagine an experiment…

To investigate the efficacy of HBOT for the treatment of "Feldmeier Disease"

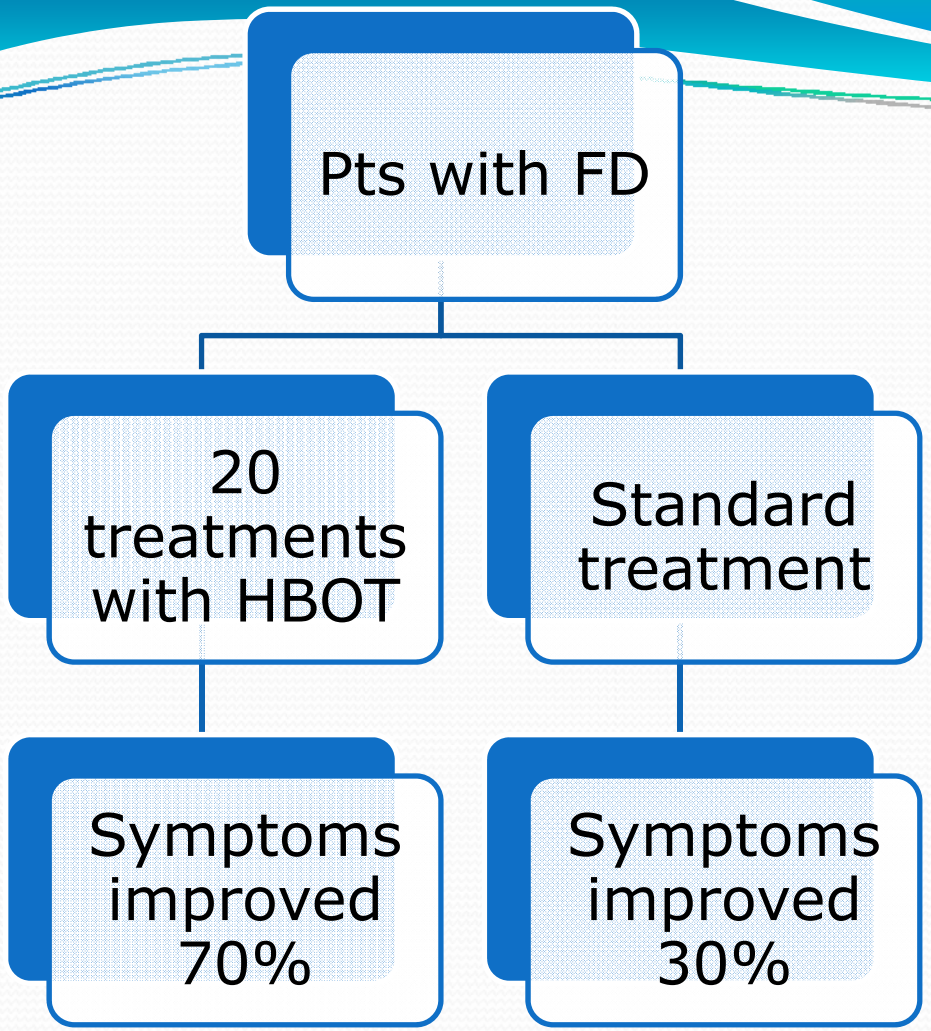
A chronic, incurable central neurological disease with generally intractable symptoms and signs

A simple case series



Conclusion: HBOT seems to improve symptoms of FD *OR* there is a placebo/participation effect

A non-random cohort



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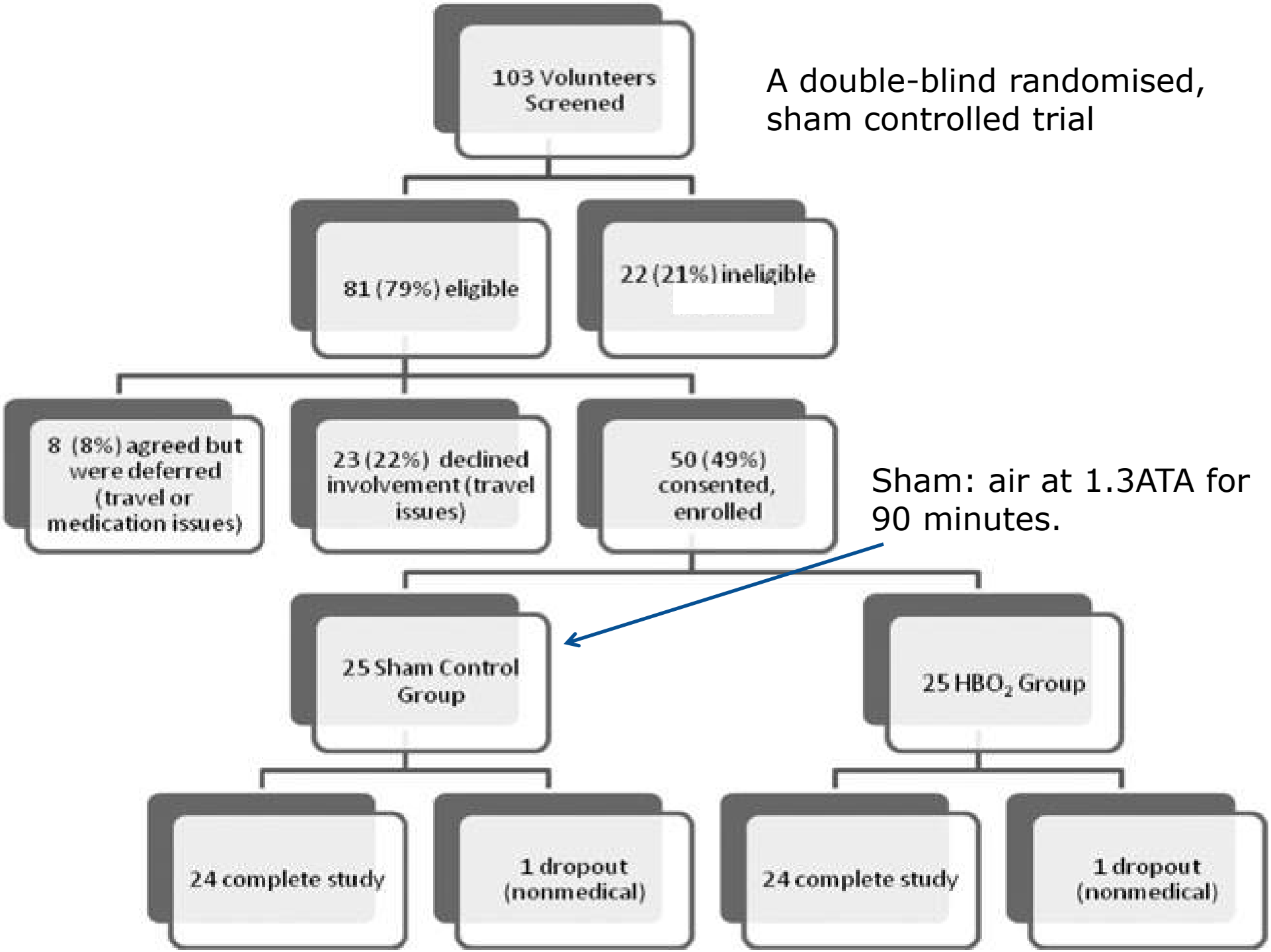


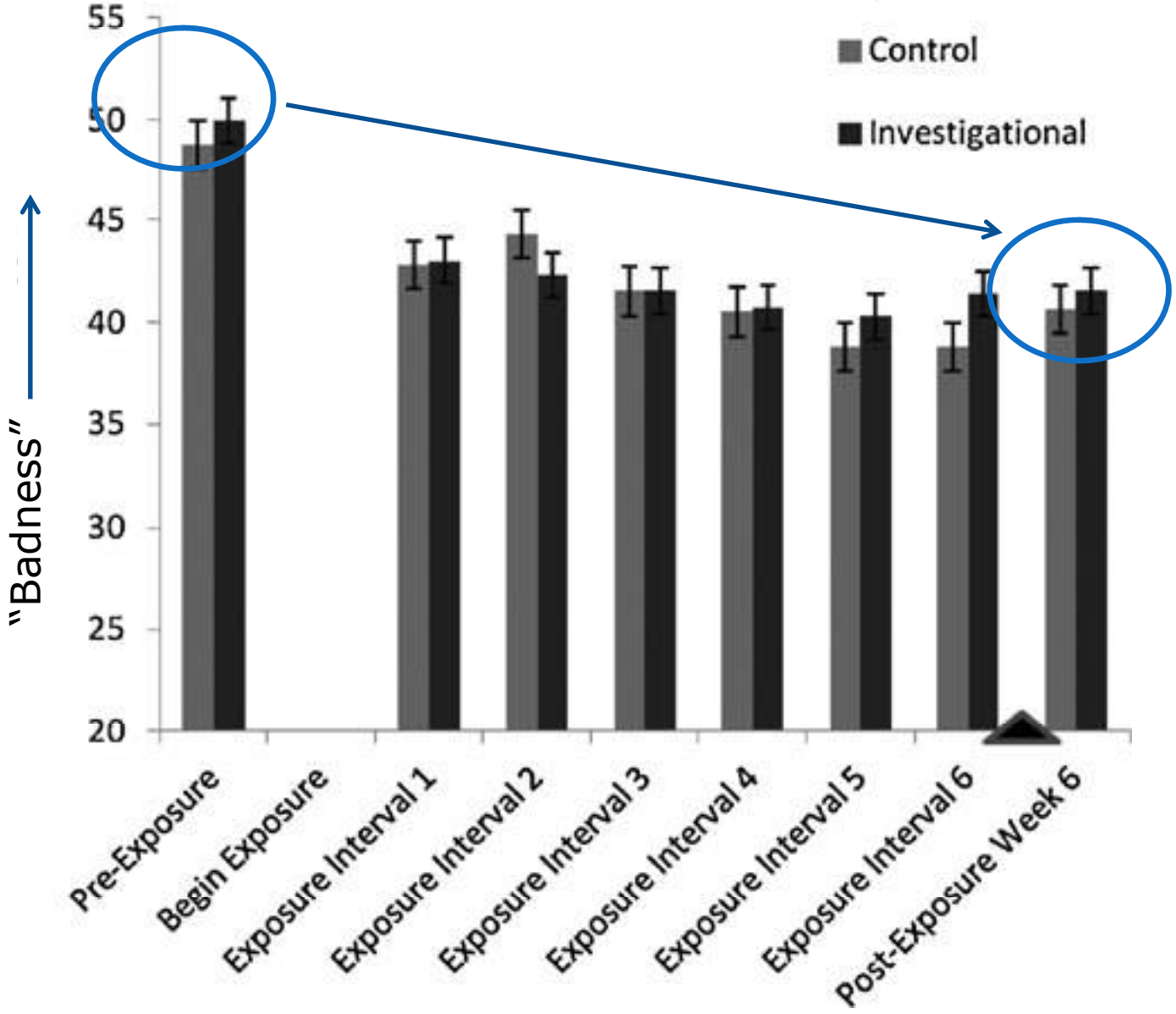
A double-blind randomised, sham controlled trial

Sham: air at 1.3ATA for 90 minutes.

Major outcome one

Δ pre-exposure to 6 weeks P<0.05 both groups

No difference between groups



Potential conclusions

1. HBO works to alleviate the symptoms of FD, and so does the sham therapy

2. Neither HBOT nor the sham work. The improvement shown here represents a placebo or participation effect

JOURNAL OF NEUROTRAUMA 29:2606–2612 (November 20, 2012)

DOI: 10.1089/neu.2012.2549

Original Articles

The Effect of Hyperbaric Oxygen on Symptoms after Mild Traumatic Brain Injury

George Wolf,[1] David Cifu,[2–4] Laura Baugh,[1,5] William Carne,[3,4,6] and Leonardo Profenna[1]

Abstract

In this single-center, double-blind, randomized, sham-controlled, prospective trial at the U.S. Air Force School of Aerospace Medicine, the effects of 2.4 atmospheres absolute (ATA) hyperbaric oxygen (HBO_2) on post-concussion symptoms in 50 military service members with at least one combat-related, mild traumatic brain injury were examined. Each subject received 30 sessions of either a sham compression (room air at 1.3 ATA) or HBO_2 treatments at 2.4 ATA over an 8-week period. Individual and total symptoms scores on Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT®) and composite scores on Post-traumatic Disorder Check List-Military Version (PCL-M) were measured just prior to intervention and 6 weeks after completion of intervention. Difference testing of post-intervention means between the sham-control and HBO_2 group revealed no significant differences on the PCL-M composite score ($t = -0.205$, $p = 0.84$) or on the ImPACT total score ($t = -0.943$, $p = 0.35$), demonstrating no significant effect for HBO_2 at 2.4 ATA. PCL-M composite scores and ImPACT total scores for sham-control and HBO_2 groups revealed significant improvement over the course of the study for both the sham-control group ($t = 3.76$, $p = 0.001$) and the HBO_2 group ($t = 3.90$, $p = 0.001$), demonstrating no significant HBO_2 effect. Paired t-test results revealed 10 ImPACT scale scores in the sham-control group improved from pre- to post-testing, whereas two scale scores significantly improved in the HBO_2 group. One PCL-M measure improved from pre- to post-testing in both groups. This study showed that HBO_2 at 2.4 ATA pressure had no effect on post-concussive symptoms after mild TBI.

Key words: hyperbaric oxygen; post-concussive syndrome; traumatic brain injury

Conclusions…

- "both groups improved more than would be expected (at) 6 months"
- "Given that HBO_2, in this controlled study, demonstrates no therapeutic value, requires long treatment series, is expensive, exposes patients to potential side effects, and has limited availability, clinical usage is not warranted…"

- NOT: *"Both the mild air and traditional HBO_2 treatments work"*

Boussi-Gross 2013

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial

Rahav Boussi-Gross, Haim Golan, Gregori Fishlev, Yair Bechor, Olga Volkov, Jacob Bergan, Mony Friedman, Dan Hoofien, Nathan Shlamkovitch, Eshel Ben-Jacob, Shai Efrati

Published: November 15, 2013 • DOI: 10.1371/journal.pone.0079995

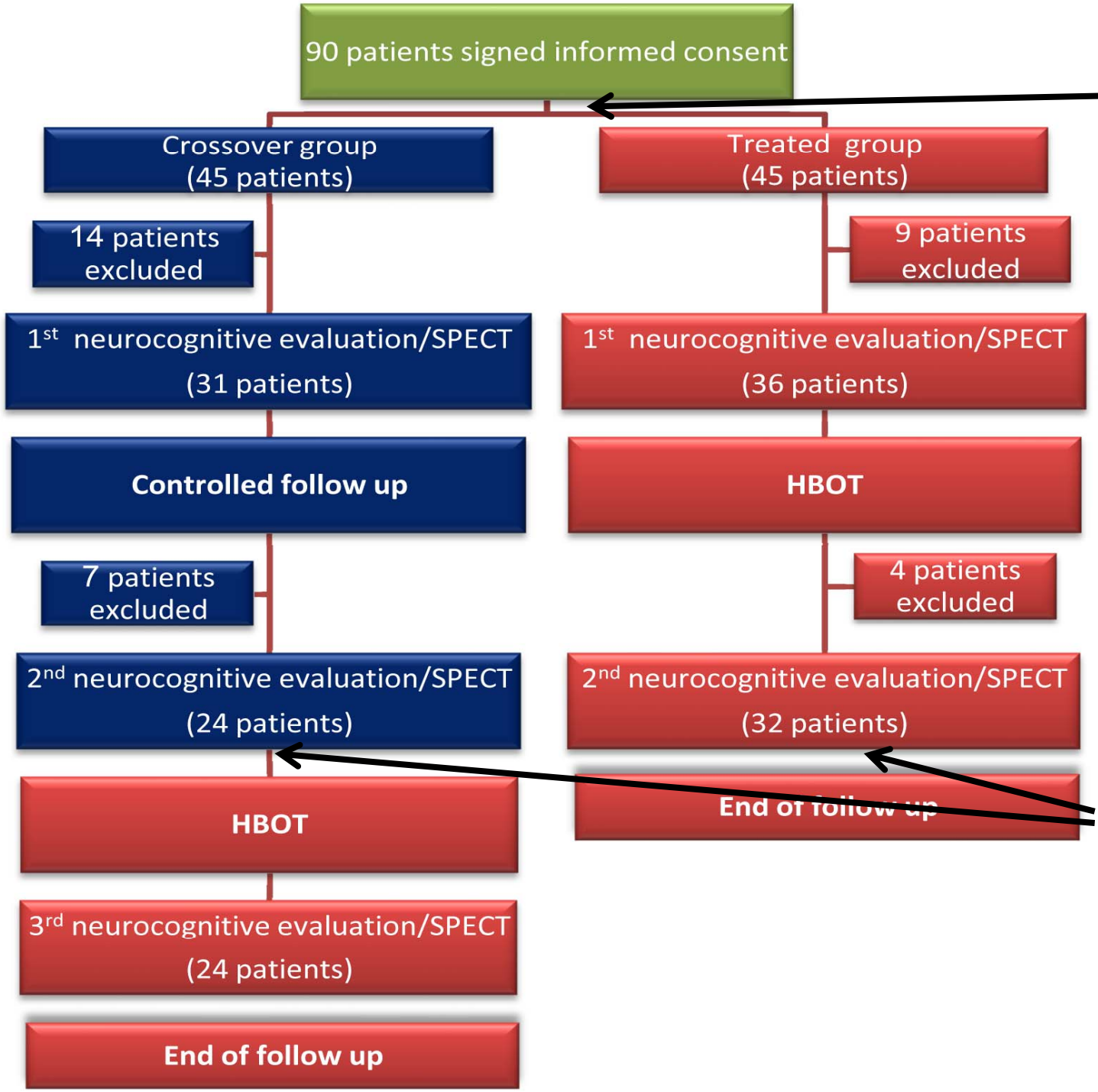
Abstract

Background

Traumatic brain injury (TBI) is the leading cause of death and disability in the US. Approximately 70-90% of the TBI cases are classified as mild, and up to 25% of them will not recover and suffer chronic neurocognitive impairments. The main pathology in these cases involves diffuse brain injuries, which are hard to detect by anatomical imaging yet noticeable in metabolic imaging. The current study tested the effectiveness of Hyperbaric Oxygen Therapy

Question the use of 'sham' HBOT

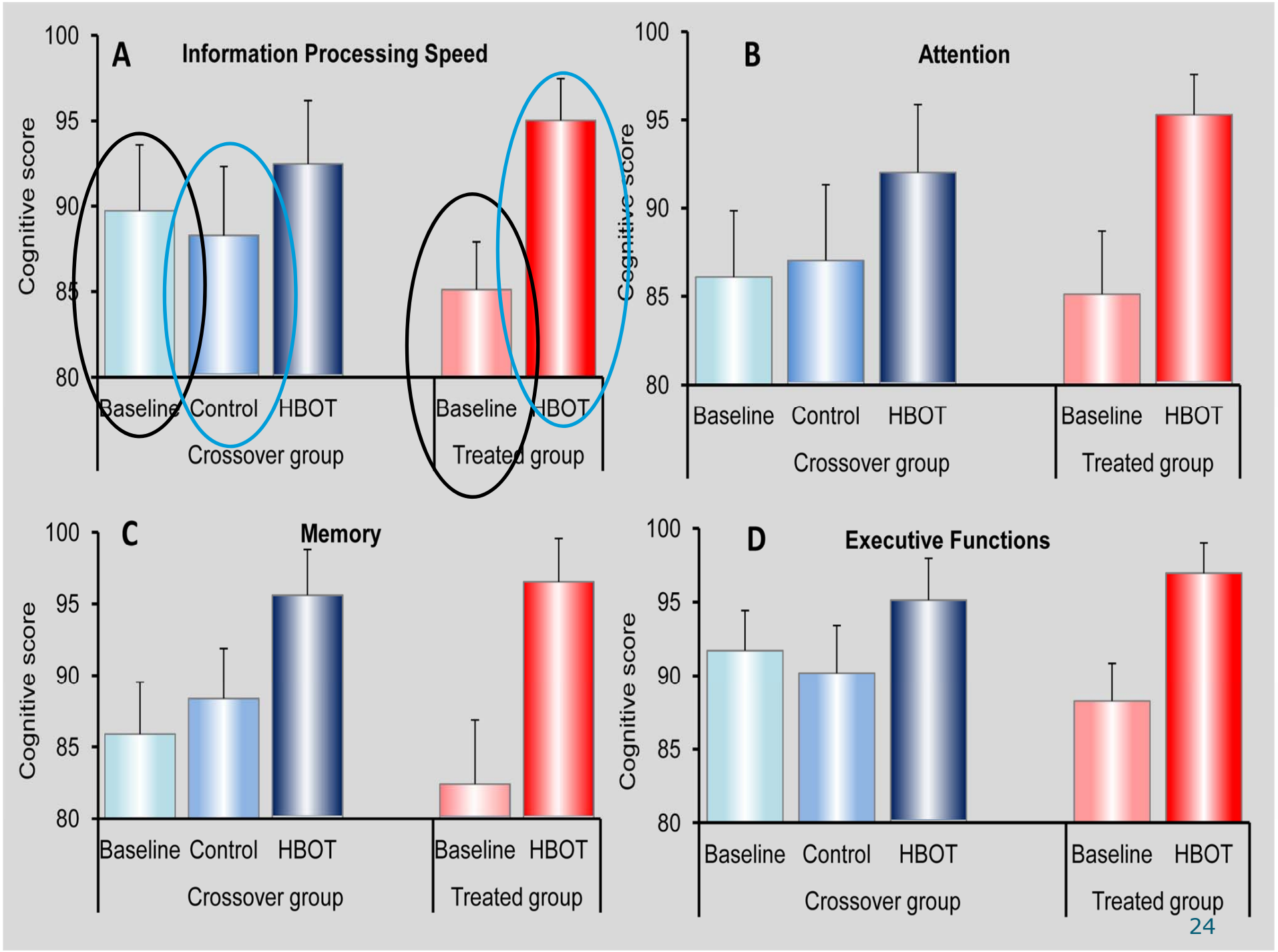
- Even trivial pressure exposures may produce therapeutic effects
- It is not possible to design a truly inert sham exposure in a chamber
- Therefore it is unhelpful and misleading to do so



Randomised

No blinding

RCT ends here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Original Articles

The Effect of Hyperbaric Oxygen on Symptoms after Mild Traumatic Brain Injury

J Head Trauma Rehabil
Vol. 29, No. 1, pp. 11–20

The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms

Neurorehabilitation and Neural Repair
http://nnr.sagepub.com/

Randomized, Sham-Controlled, Feasibility Trial of Hyperbaric Oxygen for Service Members With Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention

William C. Walker, Laura Manning Franke, David X. Cifu and Brett B. Hart
Neurorehabil Neural Repair published online 26 December 2013
DOI: 10.1177/1545968313516869

Is sham hyperbaric a placebo?

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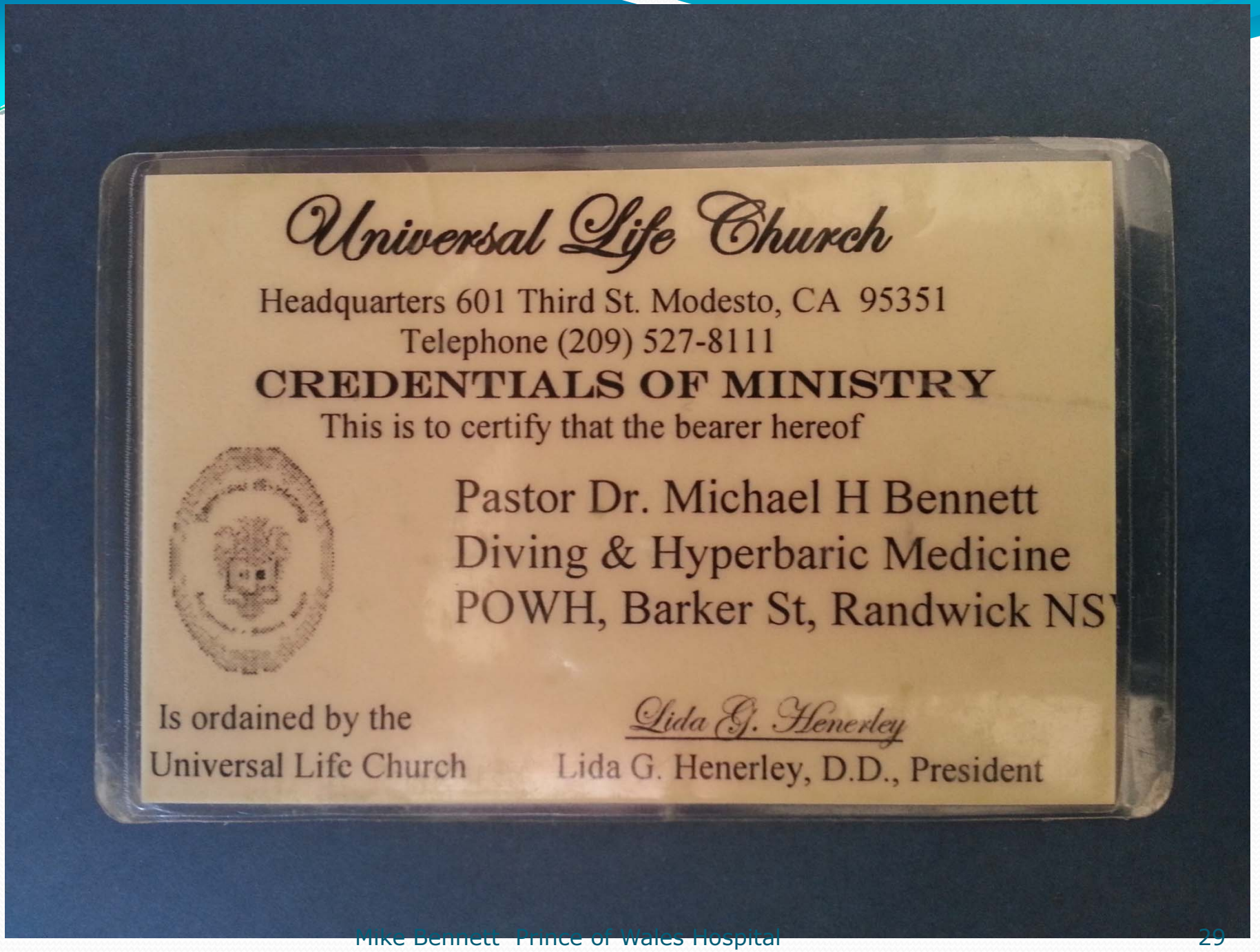
Summary of HBOT dose/response

Everything should be made as simple as possible, but not simpler. Einstein

Occam's Razor: No more things should be presumed to exist than are absolutely necessary, i.e., the fewer assumptions an explanation of a phenomenon depends on, the better the explanation.

(William of Occam)

izquotes.com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Lida G. Henerley, D.D., President

Supporting evidence

- Experience in acute mountain sickness
- Elzion 2000
  - Brain slices behaviour at 10MP (about HPNS)
- Hanlo 1997
  - Hydrocephalus and myelination
- Berman 2013
  - Malignant hypertension
- Johnson 2012
  - Malignant Hypertension

What is the mechanism?

- Placebo response is simply the patient response that cannot be attributed to an investigational intervention
- There are multiple possible components of a measured placebo effect.
  - Altered levels of hormones or endorphins
  - Expectancy effects
  - Regression to the mean
  - Flawed trial methodology

Levine 1978

Blinded RCT of post-op dental extraction pain
Pain assessed by VAS (0-10)

Patients in this figure are those given placebo at T_1 and naloxone at T_2.

Patients either responded to placebo or they did not.

When given naloxone the pain increased in both groups.

Conclusion: Placebo acting through opiate receptors.

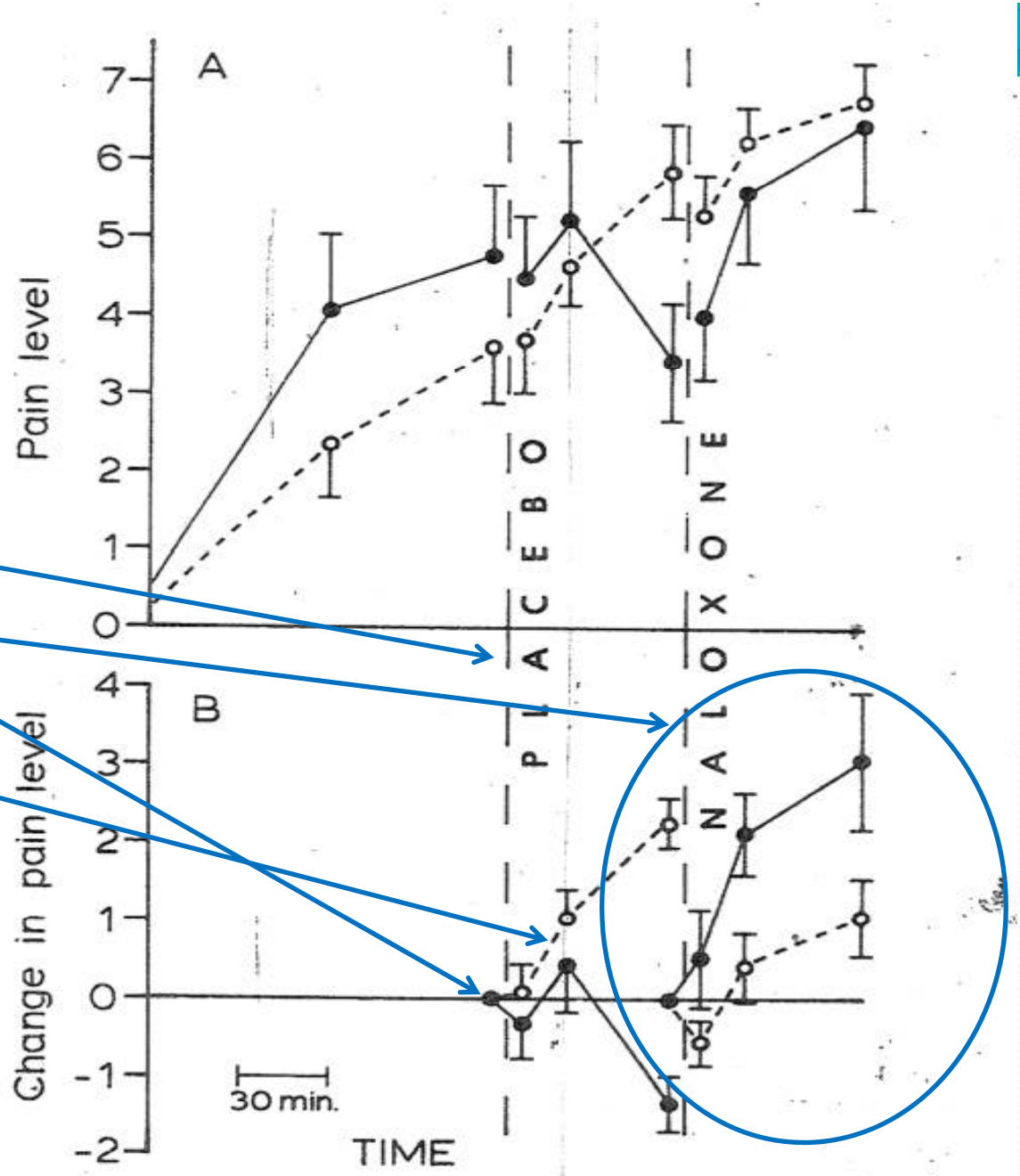


Fig. 3—Differential effect of naloxone on placebo responders and nonresponders.

Mike

A Phase I Study of Low-Pressure Hyperbaric Oxygen Therapy for Blast-Induced Post-Concussion Syndrome and Post-Traumatic Stress Disorder

Paul G. Harch,[1] Susan R. Andrews,[2] Edward F. Fogarty,[3] Daniel Amen,[4] John C. Pezzullo,[5] Juliette Lucarini,[6] Claire Aubrey,[6] Derek V. Taylor,[4] Paul K. Staab,[1] and Keith W. Van Meter[1]

- J of Neurotrauma 2012
- 16 patients: 40 1hr treatments at 1.5ATA
- Improvements in symptoms, neuro exam, IQ (+15pts), delayed and working memory; QoL etc…
- SPECT – diffuse improvements in regional CBF

SPECT changes

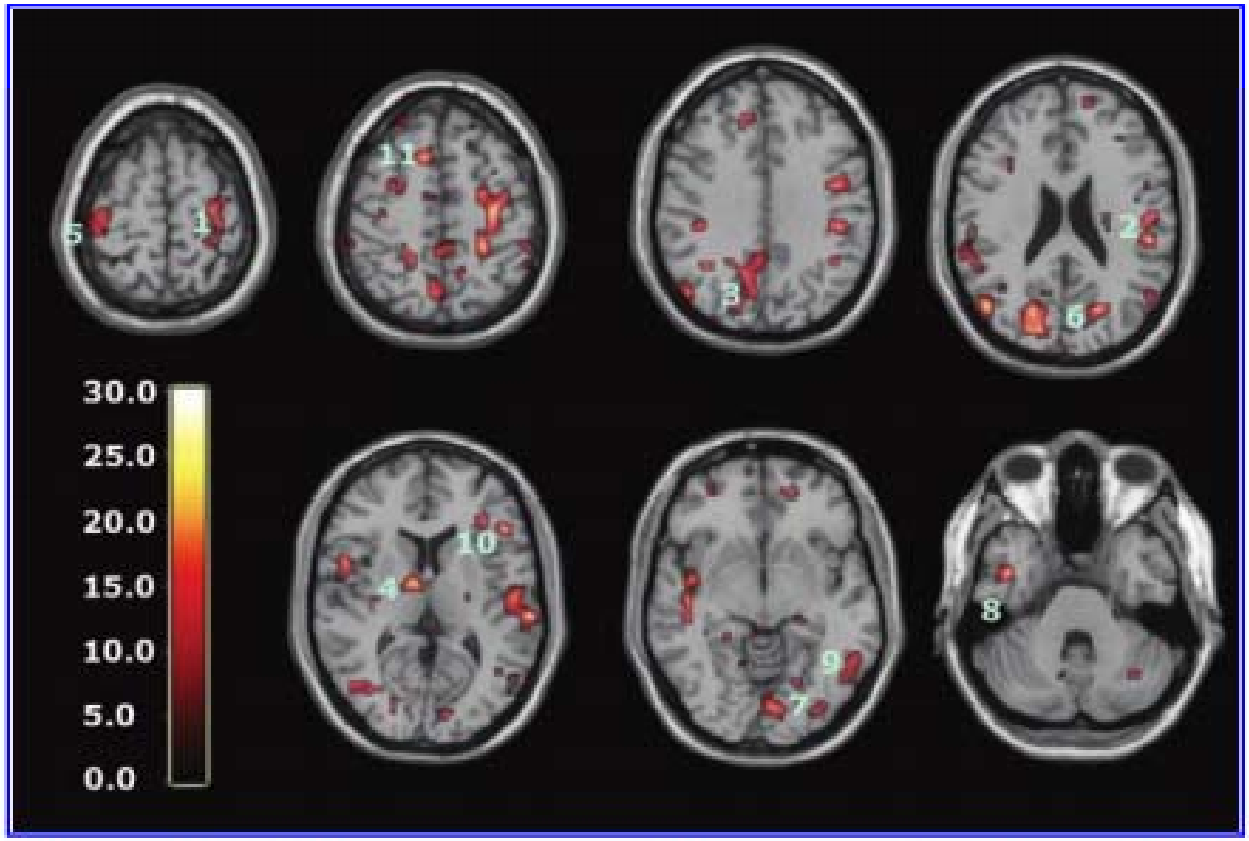
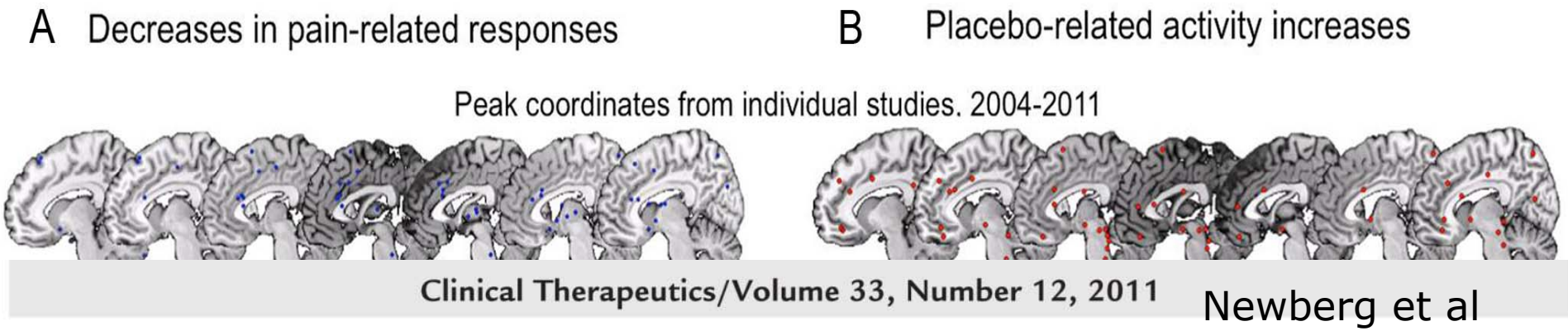


FIG. 2. Fusion of significant single photon emission computed tomography (SPECT) clusters after 1 HBOT with standard reference MRI T1 transverse image. Numbers correspond to the top 11 significant clusters at the $p < 0.001$ level labeled in Table 9, numerically in order from highest T value to lowest. Significant clusters incidentally occurring on the same slices are also depicted. (Color bar shows relative amplitude of rCBF improvement; rCBF, regional cerebral blood flow; HBOT, hyperbaric oxygen therapy; MRI, magnetic resonance imaging).

Is the persistent post concussion improvement with HBOT a placebo or not?

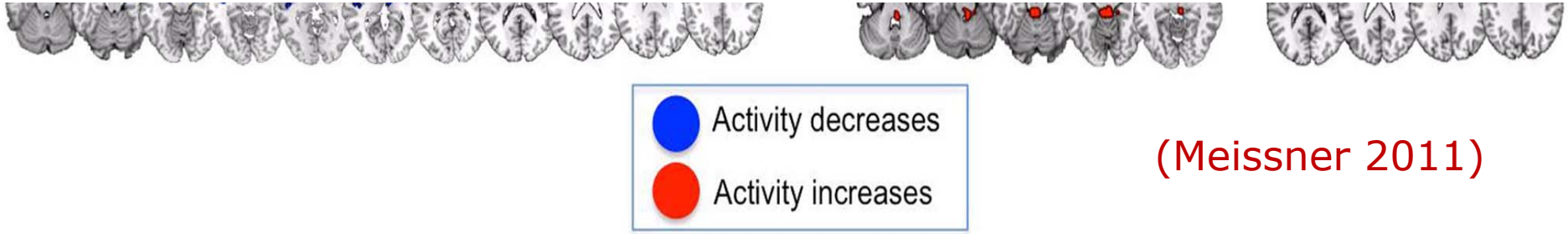
- “The imaging results in Harch's patients show clearly that we are not dealing with a pure placebo effect (unless anyone wants to argue that "placebo" effects manifest as changes in brain blood flow).”



Clinical Therapeutics/Volume 33, Number 12, 2011

Newberg et al

Double-Blind, Placebo-Controlled, Randomized Pilot Study of Cerebral Blood Flow Patterns Employing SPECT Imaging in Dental Postsurgical Pain Patients With and Without Pain Relief



(Meissner 2011)

Placebo-related neuroimaging changes in multiple studies 2004 to 2011. The top down activation of endogenous analgesic activity via the descending modulatory system represents an integral part of the mechanisms of placebo analgesia.

FUNCTIONAL NEUROIMAGING CHANGES WITH PLACEBO

Nocebo

- Latin for "I shall harm”. A harmless substance that creates harmful effects in a patient who takes it. The **nocebo effect** is the negative reaction experienced by a patient who receives a nocebo.

Hawthorne effect

First reported following a research programme investigating methods of increasing productivity in the Western Electrical Company's Hawthorne Works in Chicago during the 1920s and 30s

Hawthorne effect

- A form of reactivity whereby subjects improve or modify an aspect of their behaviour in response to the fact that they know that they are being studied, not in response to any particular experimental manipulation.

- The original studies investigated productivity in response to changes in the workplace – but whatever changes were made always resulted in improvements that then faded away (e.g. in response to both increasing and decreasing illumination).

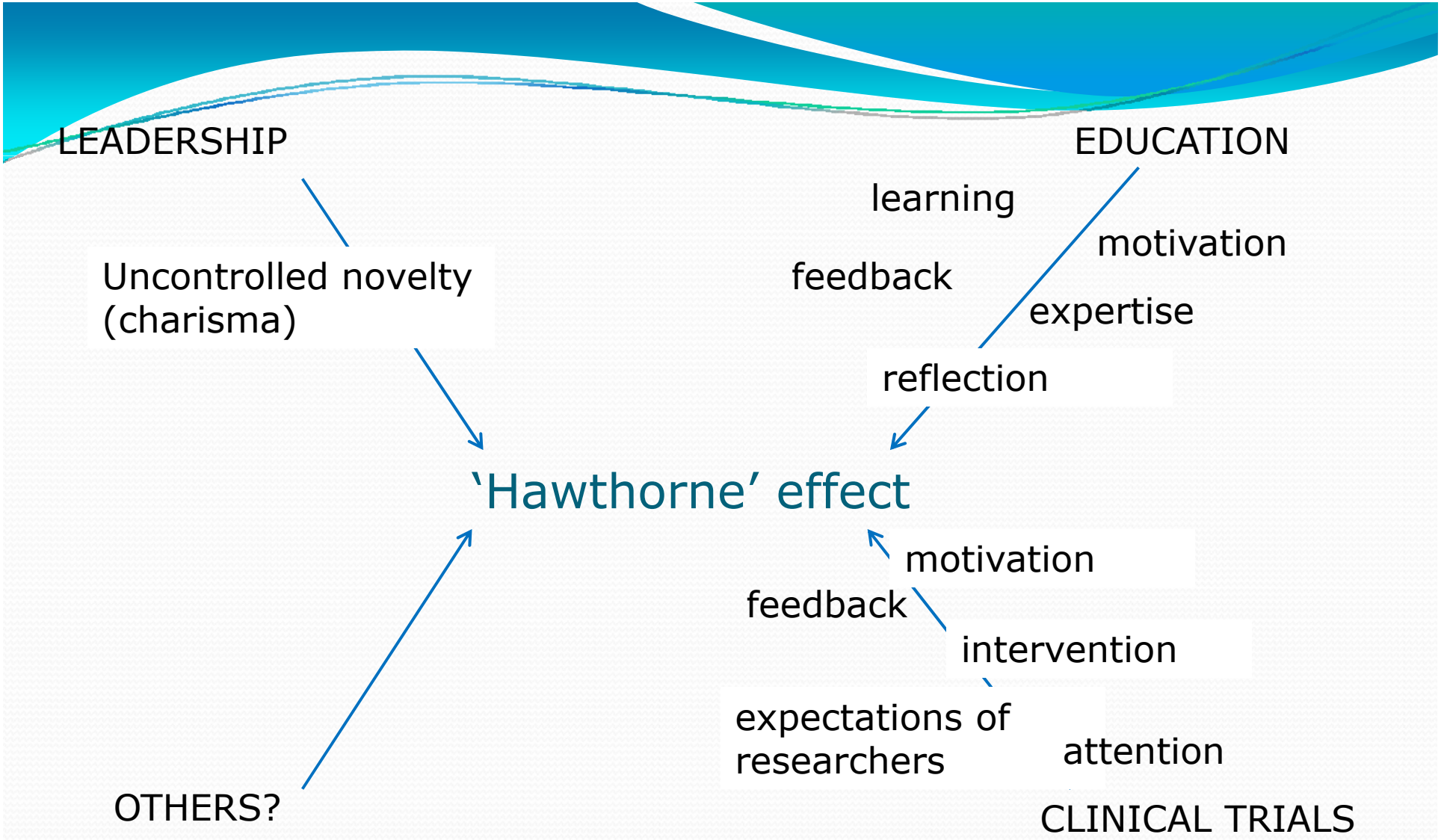
- Concept has been extended to treatment response in clinical trials. The mechanism is unclear.

Implications for HBOT

- The Hawthorne Effect should not affect assessment of the difference between intervention and control.
- May result in an inflated estimate of effect size in routine clinical settings by over-estimating response in both groups.
- If a treatment is equally ineffective as the control, then both groups may improve, BUT
- If a trial is unblinded, the Hawthorne effect may bias the results in favour of the 'active' treatment arm – whether or not it is 'truly' effective.

Adair 1984

- An experimental effect depends on the participants' interpretation of the situation.
- It is not awareness per se, nor special attention per se, but participants' interpretation that must be investigated in order to discover if/how the experimental conditions interact with the participants' goals. This can affect whether participants believe something, if they act on it or do not see it as in their interest, etc.
- the most important (though not the only) aspect of this is how the participants interpret the situation. Interviewing them (after the "experiment" part) would be the way to investigate this.



There is an absence of a comprehensive catalogue of the ways in which human awareness sometimes affects the outcomes of experiments on human participants

Bottom line

- Only RCTs can reliably infer causation
- There is no substitute for rigorous trial methodology
- Always consider alternative explanations for both anticipated and unanticipated results AND modify trial procedures to minimise any misinterpretation before you start
- Use Occam's razor (*lex parsimoniae*) to interpret findings.

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