Unestablished indications for hyperbaric oxygen therapy

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Abstract

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Unestablished indications are conditions in which systematic clinical use of hyperbaric oxygen treatment (HBOT) is not supported by adequate proof of benefit. HBOT is vulnerable to use in many such conditions for various reasons, perhaps the most important being that a placebo or participation effect may create an impression of efficacy. The systematic use of HBOT in unestablished indications raises ethical concerns about provision of misleading information, giving false hope, and taking payment for therapy of doubtful benefit. Any practice perceived as unethical or unscientific has the potential to draw the wider field into disrepute. Of substantial contemporary relevance is the use of HBOT in treatment of various forms of chronic brain injury; in particular, cerebral palsy in children and the sequelae of mild traumatic brain injury in adults. There are now multiple, randomised, blinded, sham-controlled trials of HBOT in both indications. None of these studies showed benefit of HBOT when compared to sham control, though the sham and HBOT groups often both improved, indicating that a placebo or participation effect influenced outcomes. These results almost certainly explain those of open-label trials (lacking sham controls) in which HBOT frequently seems beneficial. Advocates for HBOT in chronic brain injury claim that the sham treatments (usually 1.3 ATA* pressure exposure whilst air breathing) in the blinded trials are actually active treatments; however, the same dose of oxygen can be achieved at 1 ATA breathing 27% oxygen. To counter this argument, advocates also claim that the extra 0.3 ATA of pressure is somehow independently beneficial, but this notion has limited biological plausibility and there is little supporting evidence. Chronic brain injuries remain unestablished indications at this time and, in our opinion, should not be systematically treated with HBOT.

Key words

Hyperbaric oxygen therapy, hyperbaric research, trauma and stress, central nervous system, children, evidence, ethics, review article

Introduction

Hyperbaric oxygen treatment (HBOT) is a therapeutic modality that has long struggled for credibility within 'mainstream' medicine. In large part, this has been due to a lack of high-quality evidence to support HBOT in its various indications. Thanks to the efforts of practitioners and researchers who recognise the centrality of evidence-based practice for credibility, the last two decades have seen maturation of the evidence base for a limited number of indications, and a concomitant improvement in perceptions of HBOT amongst many of our 'mainstream' colleagues. A tangible manifestation of this was the appearance in 2011 of the first chapter on hyperbaric and diving medicine in an iconic general medicine textbook.[1]

Unfortunately, advocacy for HBOT in indications that are either unsupported by an appropriate evidence base, or that have largely been disproved, threatens the credibility of the field. In particular there is growing controversy around the use of HBOT in treatment of various forms of chronic brain injury and we will return to this specific subject later. This prompted the convening of a session on controversies in hyperbaric medicine at the 2013 tripartite meeting of the South Pacific Underwater Medicine Society (SPUMS), the European Undersea and Baromedical Society (EUBS), and the Southern African Underwater and Hyperbaric Medical Association (SAUHMA). One paper, intended as an overview of the issue of 'unestablished indications', is summarised here.

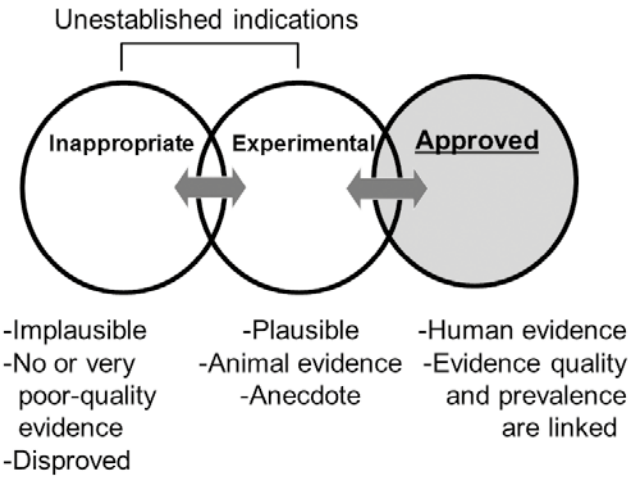
We begin with a brief mention of relevant historical events in the field, and we define an 'unestablished indication' in the modern context. We comment on why HBOT is vulnerable to use in unestablished indications and enumerate the reasons we consider deviation from rational, evidence-based practice to be harmful to the field. Finally, we will discuss cerebral palsy and the sequelae of mild traumatic brain injury (mTBI) as examples of unestablished indications in which the arguments for and against HBOT exemplify important principles.

What is an unestablished indication?

The history of hyperbaric medicine dates back centuries to the 'hyperbaric spas' or 'air baths' of Europe; an era in which exposure to mildly elevated pressures of air was advocated for treatment of a wide variety of ills.[2] This tradition of intuitive and speculative practice was continued into the 20th century with arguably the most conspicuous example set by

* **Footnote:** 1 ATA = 101.3 kPa. Since all the trials described in this article report the pressure used in ATA, these units rather than kPa will be used here.

Figure 1
Three categories of potential indications for HBOT (see text for explanation)



an anesthesiologist in the United States, Orval Cunningham, who ran a practice based on exposure of patients to hyperbaric air, which he used to 'treat' a variety of disease processes. The bizarre zenith of his activities came with the construction of a large and luxuriously appointed residential chamber perhaps best described as a 'hyperbaric hotel'. While quaint and perhaps even funny, the Cunningham saga provided an early example of how unconventional practice can attract the derision of conventional colleagues. Cunningham himself was deregistered following repeated refusal to provide any evidence to back up his claims of benefit from hyperbaric treatment and his residential chamber was closed. After his death, the facility was dismantled for scrap, and these events were announced to the medical world in a *JAMA* news column under the banner headline "*Useless tank to become useful tanks*".[3] This article, among other things, stated:
"*The tank here referred to was originally constructed some 13 years ago by the late Dr Orval J Cunningham of Kansas City, Mo, for the purpose of instituting his preposterous pressure treatment for diabetes, pernicious anemia, and carcinoma*."[3]

In relation to the project's funding by a wealthy industrialist the author asked:
"*Why do people of great wealth who are unacquainted with scientific fact and apparently unwilling to consult scientific authority so frequently support strange notions in the field of medical care?*"[3]

We will return to the issue of harm to the field later, but it is obvious that this characterisation of hyperbaric therapy as "*preposterous*" and a "*strange notion*" in one of the world's most influential medical journals could only have been extremely damaging to the efforts of anyone trying to advance the modality in a rational manner.

Thankfully there are few practitioners as overtly unconventional as Cunningham in the present era, though there is little doubt that unestablished indications are being systematically treated with HBOT. This, of course, begs the question 'what defines an unestablished indication'? We categorise the potential indications for HBOT into three groups (Figure 1), each of which is characterised by several descriptors.

'Approved indications' are supported by human evidence of efficacy, and the quality of the supporting evidence should reflect the prevalence of the disease in question. Thus, not all approved indications require support by high-quality, large randomised trials. Sporadic, rare, and catastrophic diseases such as necrotising fasciitis are a good example. Such conditions are difficult to study in randomised trials, and the evidence quality bar may consequently be set lower than would be the case for a prevalent indication like 'problem' wounds.

An obvious point of contention in application of this model is who determines whether an appropriate standard of evidence has been met for an indication to be 'approved'? The Undersea and Hyperbaric Medical Society (UHMS), an independent and responsible scientific society, has approached the problem by convening a standing committee of experts who periodically review the available evidence and make determinations on the status of new or existing 'approved' indications.[4] This process does not eliminate potential for contentious decisions, but it seems a pragmatic solution to a difficult problem. The double-ended arrows in Figure 1 are intended to indicate that this process of regular review ensures no indication is immutably categorized in the face of emerging evidence. Thus, for example, an 'experimental' indication can become 'approved' if sufficient evidence emerges to justify this.

'Experimental indications' are typically those in which there is a plausible biological rationale for application of HBOT and perhaps some supportive animal evidence or human anecdote. However, there is insufficient human evidence to achieve 'approval'.

'Inappropriate indications' are typically those with little face validity or biological rationale, and little or no supporting evidence. This categorisation would also be applied to well-researched indications which may have once seemed plausible, but in which the overwhelming weight of available evidence is unsupportive.

As indicated in Figure 1, the 'experimental' and 'inappropriate' indications collectively constitute what we refer to as 'unestablished indications'. Such indications may, of course, continue to be studied if it is deemed justified. However, we strongly believe that HBOT should not be represented as a proven treatment in these conditions. Nor should medical

practitioners systematically treat unestablished indications with HBOT outside the context of research, or (in our opinion) receive payment for such treatment.

Why is HBOT vulnerable to use in unestablished indications?

There are a variety of reasons why HBOT is frequently utilised in treatment of unestablished indications. Firstly, the status of oxygen as a drug, and the regulations around who may administer it are uncertain or ambiguous in some countries. It is not uncommon to find so-called 'hyperbaric medicine units' owned by members of non-medical craft groups (like former commercial divers) who see nothing wrong with applying their recompression chamber operational experience to the medical field. Such people may enter into relationships of convenience with local doctors for the purposes of billing state-sponsored funding agencies, but the doctors sometimes know even less about hyperbaric medicine than the chamber operators. Not surprisingly, these scenarios often result in particularly bizarre claims of efficacy. A relatively recent example from New Zealand resulted in a full-page newspaper advertisement claiming efficacy for HBOT in around 100 medical conditions, many of which were spelled incorrectly.

Secondly, oxygen is easily marketed to the general public as being essential for life. In this paradigm, HBOT is portrayed simplistically as 'more of a good thing'. The mainstream public are vulnerable to such claims and levels of knowledge about these matters are poor. A recent brochure extolling the virtues of an oxygen café in Brisbane, Australia claimed that oxygen levels in the atmosphere of a typical large city hover around 12–16%, and that this is even lower in buildings. One of the present authors was contacted by a television station researcher to check the veracity of the claim!

Thirdly, the application of HBOT is technical and dramatic. It usually takes place in a positive, supportive and affirming clinical environment; and it requires considerable commitment from highly motivated patients who are invariably hopeful of a good effect. This is a perfect collection of circumstances for the emergence of a substantial placebo or participation effect and under such circumstances it is not surprising that HBOT often appears to work. This is particularly so for problems where outcomes are subjective, amenable to psychological manipulation, or where the results of confirmatory investigations can be easily misinterpreted. Under these circumstances it is not surprising that well-meaning practitioners may earnestly believe that they are achieving good results for their patients. Perhaps not surprisingly, there is a substantial body of emerging evidence that a placebo effect might be responsible for apparent improvement in particular unestablished indications and we will return to this issue later in consideration of chronic brain injuries.

Finally, desperate patients with chronic or progressive problems are frequently willing to 'try anything', and it is not difficult to convince such patients to try HBOT. This gives rise to several of the ethical concerns we have about systematic and remunerated treatment of unestablished indications.

What are the concerns about treatment of unestablished indications for HBOT?

We have two major concerns with the treatment of unestablished indications using HBOT. The first relates to the ethics of unintentional (or intentional) exploitation of vulnerable patients that we alluded to in the final point above. Given the (at best) uncertain benefit from HBOT in treatment of unestablished indications, any insinuation of benefit is potentially misleading. Similarly, the acceptance of payment for unproven therapy when the patient has unrealistic or unfounded expectations is widely regarded as unethical. For example, in a standards document, the College of Physicians and Surgeons of Saskatchewan specifically states:
"*It is unethical to engage in or to aid or abet in treatment which has no scientific basis, may be dangerous, may deceive the patient by giving false hope, or which may cause the patient to delay in seeking proper care until his or her condition becomes irreversible.*"[5]
The ethics of exposing patients to a therapy with risks when the benefit is unknown or even unlikely are highly questionable.

The second concern relates to the perception that treatment of unestablished indications creates among our mainstream medical colleagues. The use of HBOT in indications where there is little biological rationale let alone convincing human evidence creates the very real risk that hyperbaric physicians come to be seen as 'alternative medicine' practitioners (or worse). The 'Cunningham experience' described earlier in this article exemplified the derision that indiscriminate non-evidence-based practice attracts, and there have been more recent examples.

Experienced hyperbaric physicians will remember the 1987 Gabb and Robin article in *Chest* which famously labelled HBOT "*a therapy in search of diseases*".[6] In support of their thesis, these authors cited a typical long list of indications claimed by enthusiastic advocates (similar to the one that we earlier described from a New Zealand newspaper), and predictably proclaimed that "*the broad range of conditions speaks for itself*".

In 2013, the Federal Drug Administration became concerned enough about claims relating to HBOT in unestablished indications that it saw fit to issue a communication entitled "*Hyperbaric oxygen therapy: don't be misled*."[7] Although the communication was targeted against claims of efficacy in treating unestablished indications like autism, AIDS, cancer, stroke and depression rather than the approved indications, many readers will have neither grasped the distinction nor advanced beyond the pejorative title.

Thus, over the years, advocates for HBOT in unestablished indications have attracted ridicule in prominent journals like *JAMA* and *Chest*, and provoked admonishment from the FDA. This sort of negative attention from the mainstream medical community is damaging. We confidently predict that virtually all contemporary hyperbaric physicians will have struggled in the promotion of HBOT to at least some of their colleagues; usually based on the latter harbouring suspicions of the field as 'alternative' or lacking in evidence. Conspicuous promotion of HBOT for treatment of unestablished indications reinforces such prejudices, and almost certainly makes it less likely that patients who would benefit from treatment of approved indications will be referred.

Contemporary issues

In recent years, the use of HBOT for the treatment of various forms of chronic neurological injury has been at the forefront of debate over unestablished indications. The evolution of the debate and the related research it has stimulated illuminates many of the issues we have discussed above and we provide a summary of it here. This account is, of necessity, relatively superficial and readers are encouraged to read the various references and judge relative merits for themselves.

The 'HBOT in chronic brain injury debate' first came to prominence in relation to cerebral palsy (CP) in children. Based on anecdotal observation of alleged improvement in behavioural and motor parameters, a number of enthusiasts promoted HBOT treatment for CP during the 1990s. The explanations offered for the alleged benefits focussed on unproven and vague concepts described in terms like the activation of 'dormant' or 'idling' neurons lying adjacent to areas of previous damage. There were also reports of putative improvements in cerebral blood flow patterns on SPECT scanning in association with HBOT treatments (vide infra).

The first definitive study was published in 2001.[8] This was a randomised, sham-controlled study of 111 children who received either 40 HBOT treatments at 1.75 ATA for one hour, or 40 air exposures at 1.3 ATA. Follow up was at three months after treatment. Both groups improved in respect of all outcome measures; most notably motor function, but there was no difference between the groups. The authors ascribed the general improvement to a placebo or participation effect, as did an independent scientific advisory committee.[9] This study created a storm of controversy which included emergence of the argument that 1.3 ATA of air is actually an active treatment. HBOT advocates opined that the study merely compared one active dose of oxygen with another, and that 1.3 ATA of air cannot be used as a sham control. We will address this issue in more detail later.

A second, randomised, sham-controlled study in CP patients was published in 2012.[10] In this case, 49 children were randomised to receive 40 HBOT treatments at 1.5 ATA or 40 exposures at 1.5 ATA breathing an inspired fraction of oxygen of 14% (equivalent inspired PO_2 to 21% oxygen at 1 ATA). The notable feature of this design is the elimination of any therapeutic effect of increased inspired PO_2 in the sham controls. Follow up was out to six months post treatment. There were no improvements in motor function scores, but this study did find significant improvement in a disability inventory in both groups, but (once again) no difference between the groups.

Table 1
Key characteristics of the US military studies of HBOT for mild traumatic brain injury (mTBI); note that the Navy study was designed to factor out any effect of elevated inspired PO_2 in the control group; 1 ATA = 101.3 kPa

Service	Sessions	Control	HBOT
Army[14]	40	Air, 1.2 ATA	100% O_2, 1.5 ATA
Air Force[15]	30	Air, 1.3 ATA	100% O_2, 2.4 ATA
Navy[16–18]	40	10.5% O_2, 2.0ATA	100% O_2, 2.0 ATA
			75% O_2, 2.0 ATA

A second related area of recent interest has been the use of HBOT in chronic mild traumatic brain injury (mTBI). This has received much attention in the USA where large numbers of affected servicemen and women have returned from overseas conflicts. In 2013, Harch and colleagues published a series of 16 returned servicemen with sequelae of mTBI who all received 40 HBOT treatments at 1.5 ATA.[11] These patients exhibited improvements in various neuro-cognitive tests, and improvements in regional cerebral blood flow measured by SPECT scans. A second observational study in 63 mTBI patients treated similarly reported a common subjective perception of benefit but no clinically important changes on more objective neurocognitive testing.[12] A small subset of these patient had SPECT and CT angiographic studies which, as in the Harch series,[11] demonstrated an apparent improvement of regional cerebral blood flow after HBOT.

Several studies under the aegis of the US military (approximately corresponding to one per service) were subsequently undertaken in response to strong lobbying for systematic use of HBOT in veterans with mTBI. Whilst it is beyond the scope of this paper to describe these studies in detail, some trial characteristics are germane. The methodologies are summarised in an article by Weaver et al[13] and in the individual papers themselves.[14–18] All three were randomised, double blinded, sham-controlled trials, but with variation between studies in both treatment and sham protocols (Table 1).

The outcome measures in all studies included symptom inventories and neuropsychological testing. Results are reported at one month for the Army study; at one and six weeks for the Air Force Study, and immediate post-treatment,

one week and three months for the Navy study. The results for all three studies were presented at the Undersea and Hyperbaric Medical Society annual meeting in 2013, and have now been published.[14–18] None of the studies demonstrated any benefit for HBOT when compared to the sham protocol. In the Army and Air Force studies both sham and HBOT groups improved more than expected, but there was no difference between the groups. As was the case in the cerebral palsy trials previously discussed, the various authors considered a placebo effect most likely to account for parallel improvements in both sham (control) and HBOT patients.

These outcomes have disappointed enthusiasts.[19] It is notable the negative results contrast sharply with those reported from two recent studies of HBOT (versus standard care) in chronic stroke and mTBI that used an open-label, randomised design with no blinded sham hyperbaric exposures.[20,21] These studies demonstrated benefit when patients randomised to receive HBOT were compared to those randomised not to receive it. Not surprisingly, their authors have devoted considerable effort to explaining the different results in comparison to those of the US military mTBI studies.[19–21] They focus particularly on the contention that the US military sham exposures were actually effective treatments, and that this accounted for the equivalent results when sham and HBOT groups were compared.

The argument that a low-pressure air sham exposure is an effective treatment (and, therefore, an inappropriate control) is poorly supported. No-one has objectively demonstrated that exposure to 1.3 ATA of air is either neuroprotective or capable of resurrecting chronically 'idling' neurons in an injured brain. Moreover, there is no body of basic science evidence suggesting that small elevations in inspired pressures of oxygen and nitrogen (or small elevations of pressure itself) would be expected to exert a relevant therapeutic effect. 'Explanations' of the mechanisms underpinning the alleged efficacy of low-pressure air are rarely more sophisticated than the observation that there is a very modest elevation of the arterial PO_2 when breathing air at 1.3 ATA, and that this has effects on completely different (usually pulmonary) pathologies in unrelated settings.[20,21] We have seen no cogent arguments to explain why this, of itself, would improve a chronic brain injury. Known effects of higher dose HBOT (such as stem cell mobilisation and effects on nitric oxide synthase) are often cited in the context of these debates, but to our knowledge such effects have never been demonstrated at these minimally elevated oxygen tensions.

One significant problem in relation to the 'active air sham' argument is that the same inspired PO_2 achieved breathing air at 1.3 ATA could also be achieved by breathing 27% oxygen at 1 ATA, without the risks and costs of hyperbaric exposure. This begs an obvious question. If proponents of HBOT for chronic TBI believe that a 1.3 ATA air sham is actually an active treatment, why do they not simply treat TBI patients with 27% oxygen at room pressure (or at least test this intervention; something they have all avoided doing to this point)?

A cynic might suggest this has much to do with the respective billing potential of the two modalities, but the response from advocates is that the putative neuro-rehabilitative effect of air at 1.3 ATA depends not only on the elevated arterial PO_2 but also on the small elevation of ambient pressure.[19] To our knowledge, this argument is unsupported by any data demonstrating neuroprotective or neuro-rehabilitative benefit from exposure to pressure alone, and the notion lacks biological plausibility. Advocates attempt to address this concern by quoting the transduction of small pressure changes by certain cells in marine invertebrates,[22] and by citing pressure effects on mammalian neurons[23] revealed in studies whose outcome measures had nothing to do with neuro-rehabilitation and whose methods involved exposure to far greater pressures than 1.3 ATA.

This is sloppy citation and poor science, yet it is tenaciously promoted because the notion that pressure is a key contributor to the apparent benefit accrued from air at 1.3 ATA is crucial to two arguments advanced by those promoting HBOT for mTBI. The first, introduced above, is that even if air at 1.3 ATA is as effective as higher doses of HBOT, the hyperbaric approach cannot be replaced by breathing the equivalent PO_2 (27% O_2) at room pressure because the patient would not receive the alleged 'benefit' of pressure. The second is that the assumed benefit of pressure alone allows a circular argument which conveniently invalidates the randomised sham-controlled trials that show no benefit from HBOT in chronic brain injury,[8,10,14–16] including those designed to exclude any elevation of inspired PO_2 in the sham groups.[10,16] Essentially, this argument holds that while proper blinding of controls cannot be achieved without some pressure exposure, any pressure increase means the controls are receiving an active treatment rather than an inactive sham. If one was to accept this argument, it would make sham-controlled trials virtually impossible to conduct – thus justifying the inferior non-blinded cross-over designs employed in recent studies of stroke and mild TBI as 'the best we can do'.[20,21]

Based on present evidence, we reject the argument that pressure per se is an active treatment in mTBI. We acknowledge the small increase in inspired PO_2 to 0.27 ATA that occurs when air is breathed at 1.3 ATA, but we consider there is no convincing evidence for a neuro-rehabilitative effect of this dose of oxygen. On that background, we reiterate the fact that without exception, every randomised sham-controlled (blinded) study of HBOT in chronic brain injury to date has demonstrated equivalent improvement in patients receiving both HBOT and sham. Importantly, these include two studies designed to exclude any elevation of inspired PO_2 in the sham groups.[10,16] The corollary is that unless the reader truly believes small increases in ambient pressure or the inspired PN_2 alone can restore function to the

chronically injured human brain (notions that are currently unsupported by evidence), the appropriate interpretation of the sham-controlled study results is that there is no true therapeutic effect of HBOT in chronic brain injury. We are puzzled that advocates for HBOT in mTBI cite these studies as proof that the shams are not inert.[21]

Based on the available evidence and applying the principle of Occam's razor, we believe the most plausible explanation for the results of sham-controlled studies in chronic brain injury is a substantial placebo or participation effect. Given the demonstrated efficacy of cognitive rehabilitation therapy in TBI,[24] it seems very plausible that at least some sequelae of chronic brain injury may improve when highly motivated patients are given a dramatic prolonged course of treatment in a stimulating, positive, and optimistic clinical environment. It follows that we are not surprised by a recent non-blinded, non-randomised study in cerebral palsy comparing patients treated with: conventional methods; air at 1.3 ATA; HBOT at 1.5 ATA; and HBOT at 1.75 ATA, which found that all 'hyperbaric' groups (including air at 1.3 ATA) improved more than conventionally treated controls.[25] The authors stated: "*The very important difference observed in treated vs. controlled children can only be a genuine beneficial effect of HBO$_2$ therapy*." It is extraordinary that the reviewers allowed this conclusion to be published because it is patently unjustifiable. Indeed, we believe that studies investigating HBOT in chronic brain injury that do not include a sham control group are deeply flawed.

Before concluding this discussion it is appropriate to mention SPECT scan detection of positive changes in regional cerebral blood flow (rCBF) following HBOT for mTBI.[11,12,21] These changes are sometimes cited as proof of an HBOT effect that cannot be due to placebo. In fact, it has been shown that rCBF as measured by SPECT may be influenced by cognitive therapy for mTBI and a placebo effect on SPECT results would therefore not be surprising.[24] Indeed, SPECT changes in response to placebo have been demonstrated,[26,27] with one analgesic study concluding: "*CBF changes appeared to correlate with the perception of pain or pain relief and not to the actual treatment administered per se*."[26] The literature contains many high-quality references to placebo-induced changes in rCBF measured by other functional brain imaging techniques, and these are arguably relevant to SPECT. For example, functional magnetic resonance imaging has demonstrated that placebo analgesia causes decreased brain activity in pain-sensitive brain regions.[28] We accept that such results cannot be extrapolated directly to brain injury, but equally, we do not think that changes in SPECT scans following HBOT for mTBI constitute a convincing argument against placebo effects.

In the broader context of 'unestablished indications' the object lesson arising from the chronic brain injury saga is that there are some prevalent conditions in which HBOT may appear to work when observational evidence is considered in isolation. Different conclusions may be drawn if sham-controlled studies are undertaken. Uncritical interpretations of observational data or data from trials without blinded sham controls[25,29] could result in massive expenditure on an expensive time-consuming 'therapy' that may, in fact, only work through a placebo effect. This should be of concern to all hyperbaric physicians who base their practice on evidence, and who are striving to build collaborations with sceptical mainstream colleagues.

We conclude this paper with an acknowledgement that research is ongoing in this area. Our commentary is based on the current state of the field, and we accept that evidence in respect of some of the 'unestablished indications' discussed here may evolve to a point where we revise our opinions in either of the directions indicated in Figure 1. In respect of chronic brain injuries, after multiple sham-controlled studies in which controls and HBOT subjects improved equally, any argument in support of HBOT now hinges on acceptance of the theory that the control intervention (air breathed at 1.2–1.3 ATA) is an active treatment with equivalent effects to higher doses of hyperbaric oxygen. We are unable to find either plausible explanations or substantive evidence to support this hypothesis. We accept that the matter has not been definitively studied and indeed, for this reason, we consider the current claims of therapeutic benefit across an extraordinary range of hyperbaric exposures to be premature, and most likely a misinterpretation of a placebo effect. As hyperbaric physicians there is nothing we would appreciate more than new, evidenced-based indications for HBOT, but we owe it to ourselves, the field and our patients not to actively promote unproven or ineffective therapy.

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