Emerging indications for hyperbaric oxygen

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Purpose of review
To identify and discuss emerging trends in the therapeutic use of hyperbaric oxygen.

Recent findings
There has been a maturing of the clinical evidence to support the treatment of sudden hearing loss, a wide range of problematic chronic wound states and the prevention and treatment of end-organ damage associated with diabetes mellitus. On the other hand, the controversy continues concerning the use of hyperbaric oxygen therapy (HBOT) to treat sequelae of mild traumatic brain injury. HBOT remains poorly understood by many medical practitioners despite more than 50 years of clinical practice. Pharmacological actions arise from increased pressures of oxygen in the blood and tissues. Most therapeutic mechanisms identified are not the simple result of the reoxygenation of hypoxic tissue, but specific effects on immunological and metabolic pathways by this highly reactive element. HBOT remains controversial despite biological plausibility and a solid clinical evidence base in several disease states.

Summary
Multiple proposals for new indications for HBOT continue to emerge. Although many of these will likely prove of limited clinical importance, some show significant promise. Responsible practitioners remain acutely aware of the need for high-quality clinical evidence before introducing emerging indications into routine practice.

Keywords
diabetes mellitus, hearing loss, hyperbaric oxygenation, wound healing

INTRODUCTION

Hyperbaric oxygen therapy (HBOT) is defined as the therapeutic use of 100% oxygen breathing at pressures greater that one atmosphere absolute (1 ATA or 101.3 kPa). In practice, the routine use of pressures less than 1.5 ATA (152 kPa) is highly unusual and common treatment protocols involve 2.0–2.8 ATA (203–284 kPa) exposures for between 60 and 120 min on a daily or twice daily schedule. These treatments require the use of a compression vessel most commonly referred to as a 'hyperbaric chamber' (Fig. 1).

Exposure to these high oxygen pressures greatly influences the oxygen cascade to the intracellular environment (Fig. 2). Supraphysiologic levels of oxygen produce an array of therapeutic and occasionally toxic effects. The potential therapeutic effects can be classified into three broad groups – the consequences of hydrostatic pressure and the removal of inert gas from the tissues, the pharmacological effects of very high arterial tensions of oxygen and the oxygenation of dysfunctional hypoxic tissues. This approach assists the linking of mechanisms and indications.

Figure 3 and Table 1 indicate some of the accepted indications for HBOT. Indications cross many medical specialties. Unlike other practitioners, hyperbaric physicians are the custodians of a single therapeutic modality used for a wide range of disease states, rather than a suite of related diseases of the same organ system. The consequence is they must persuade colleagues in other specialties that a treatment modality, about which they may know little, is of potential benefit to their patients. This frequently results in a resistance to consider HBOT as a viable medical option and hampers the investigation of novel indications.

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KEY POINTS

- As with most established indications, emerging indications for HBOT are based on anti-inflammatory effects and the modification of metabolic pathways rather than the simple reversal of hypoxia.
- HBOT improves hearing following idiopathic sudden sensorineural hearing loss.
- HBOT exposures may prevent or treat the development of end-organ dysfunction in diabetes mellitus.
- Controversy exists around both the role for HBOT in the late treatment of mild traumatic brain injury and the very possibility of a universally accepted and effective sham exposure.

EMERGING INDICATIONS

The current article considers emerging indications for HBOT based on our appraisal of the literature and experience over the last 12 months to June 2019. We will also reflect briefly on a growing controversy concerning sham-controlled trials involving HBOT.

Idiopathic sudden sensorineural hearing loss

Idiopathic sudden sensorineural hearing loss (ISSHL) is defined as loss of more than 30 decibels (dB) in hearing threshold over at least three contiguous frequencies and which develops over less than 72 h. The annual incidence is 2–20 per 100 000. The cause of ISSHL is unclear, but most authorities believe an inflammatory or hypoxic primary cause is likely. The mainstay of treatment is either oral (OS) or intratympanic steroids (ITS), despite a relatively poor evidence base. The true response rate is poorly defined given the high rate of spontaneous recovery over several weeks (32–65%). HBOT has been used as both an adjunct for first-line treatment and as a salvage approach after the failure of an initial course of steroids.

Based largely on a Cochrane systematic review published in 2012, the Undersea and Hyperbaric Medical Society added ISSHL to their list of indications for HBOT (Table 1) [4,5]. They recommend treatment start within 14 days of onset. Although encouraging, the review gave only cautious endorsement to the routine use of HBOT and suggested a clinically meaningful improvement in hearing had not been proven at that time. Little work had been done on the use of HBOT as a salvage treatment. The past year has seen the publication of a number of studies designed to better establish the place of HBOT [6▪,7▪,8▪▪,9▪,10].

Hyperbaric oxygen therapy as salvage treatment

Sun 2018 reviewed the records of 104 patients with ISSHL and treated initially with intravenous lidocaine once (0.2 g in 10 ml) and methylprednisolone 80 mg daily for the first 3 days, then 40 mg for 3 further days [6▪]. If response was inadequate at day 10, they were given either intratympanic methylprednisolone (2 mg every 3 days to day 18) or HBOT (daily for 90 min at 2.0 ATA for 3 weeks). These groups were compared with those who declined salvage treatment. There was no demonstrated advantage for HBOT or ITS over control patients, although the ITS group was more likely to show some degree of recovery than the HBOT group (4/31 versus 2/32, $P = 0.37$). Salvage strategies were of little effect. Almosnino *et al.* [7▪] reported a matched control retrospective study including 36 patients who failed to recover with primary steroid therapy and were given a salvage treatment of either ITS or ITS and HBOT. The combination therapy was numerically

FIGURE 1. Examples of a monoplace (L) and multiplace (R) chamber for the delivery of hyperbaric oxygen therapy. Reproduced by courtesy of M. Bennett.

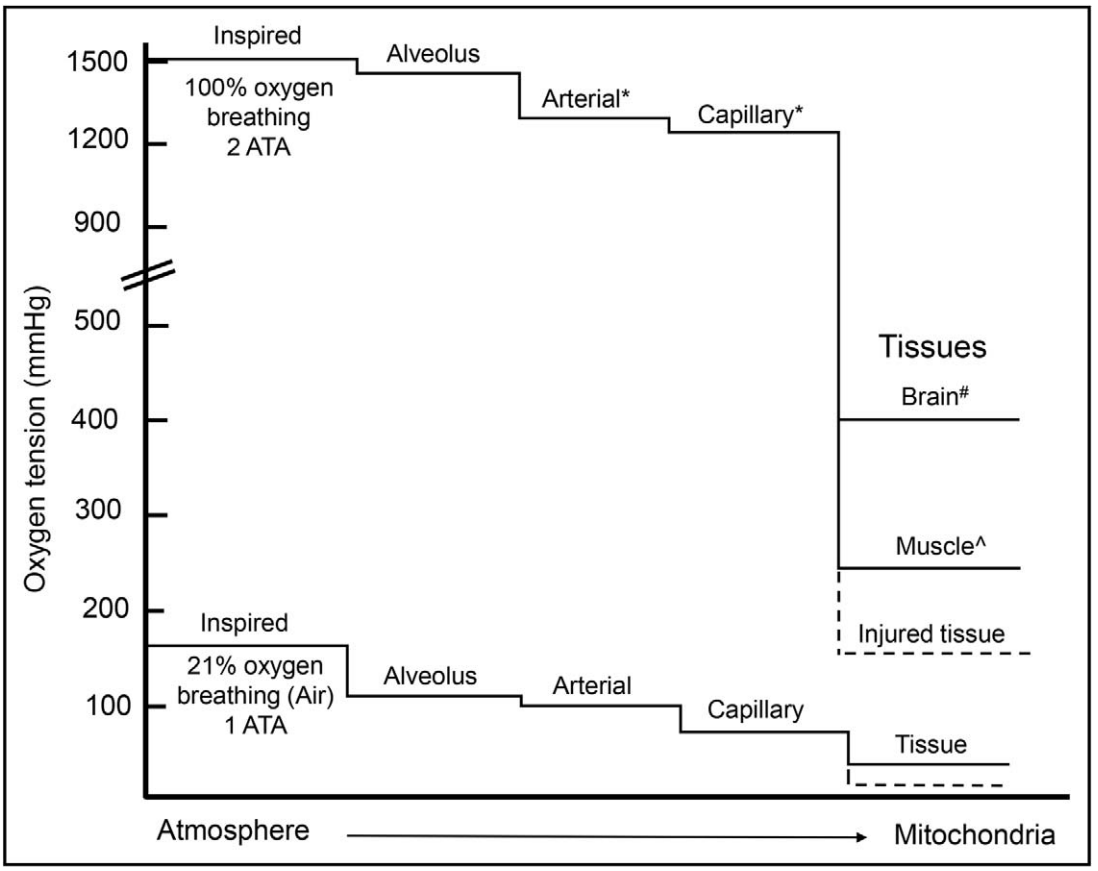

FIGURE 2. The oxygen cascade during air and hyperbaric oxygen breathing (100% at 2 ATA). *, #, ^ Refer to [1–3], respectively.

superior to ITS alone (33% recovery to 'serviceable hearing' with ITS versus 42% with ITS and HBOT), but not statistically significant ($P > 0.05$). Authors of both these underpowered studies concluded that HBOT did not have a clear role in salvage treatment and more work was needed.

Hyperbaric oxygen therapy as early treatment

Chi 2018 performed a randomised trial comparing the acute treatment of ISSHL using a combination including either oral steroids and pentoxyfylline and intravenous dextran with the same treatment and HBOT starting on day eight (10 treatments at 2.5 ATA for 90 mins, twice daily) [8▪▪]. Although there was no difference in the proportion with useful hearing recovery at day 13, at day 180 those in the HBOT group were more likely to have complete or partial recovery (80 versus 47%, $P = 0.04$). Xie *et al.* [9▪] retrospectively reviewed 178 patients treated acutely in their facility with adjuvant HBOT (mean interval to first treatment 7.8 days). All patients were treated with either oral steroids, 'blood flow promoters' and vitamin B complex. HBOT was at 2.5 ATA for 60 min twice daily (mean 17 sessions). The overall recovery rate (complete + partial) was a rather disappointing 37.1%. Multivariate analysis suggested both more profound hearing loss on presentation and longer times to the first HBOT (5.6 days in those who recovered and 9.1 in those who did not) were associated with a poor prognosis.

These studies reinforce the impression there may be some benefit from the addition of HBOT to steroids in the acute setting. There does not seem to be any advantage in the use of HBOT as a salvage therapy and if HBOT is to be used it should be instituted as early as practicable. Unfortunately considerable heterogenicity remains across comparative clincial studies and it seems only a large, multicentred, randomized trial will prove powerful enough to identify those most likely to benefit from the adjunctive use of HBOT. This conclusion is supported by a recent review of comparative trials [10].

Enhancement of healing

HBOT is indicated for enhancement of healing in selected problem wounds (Table 1). Most relevant evidence pertains to lower limb wounds in diabetic

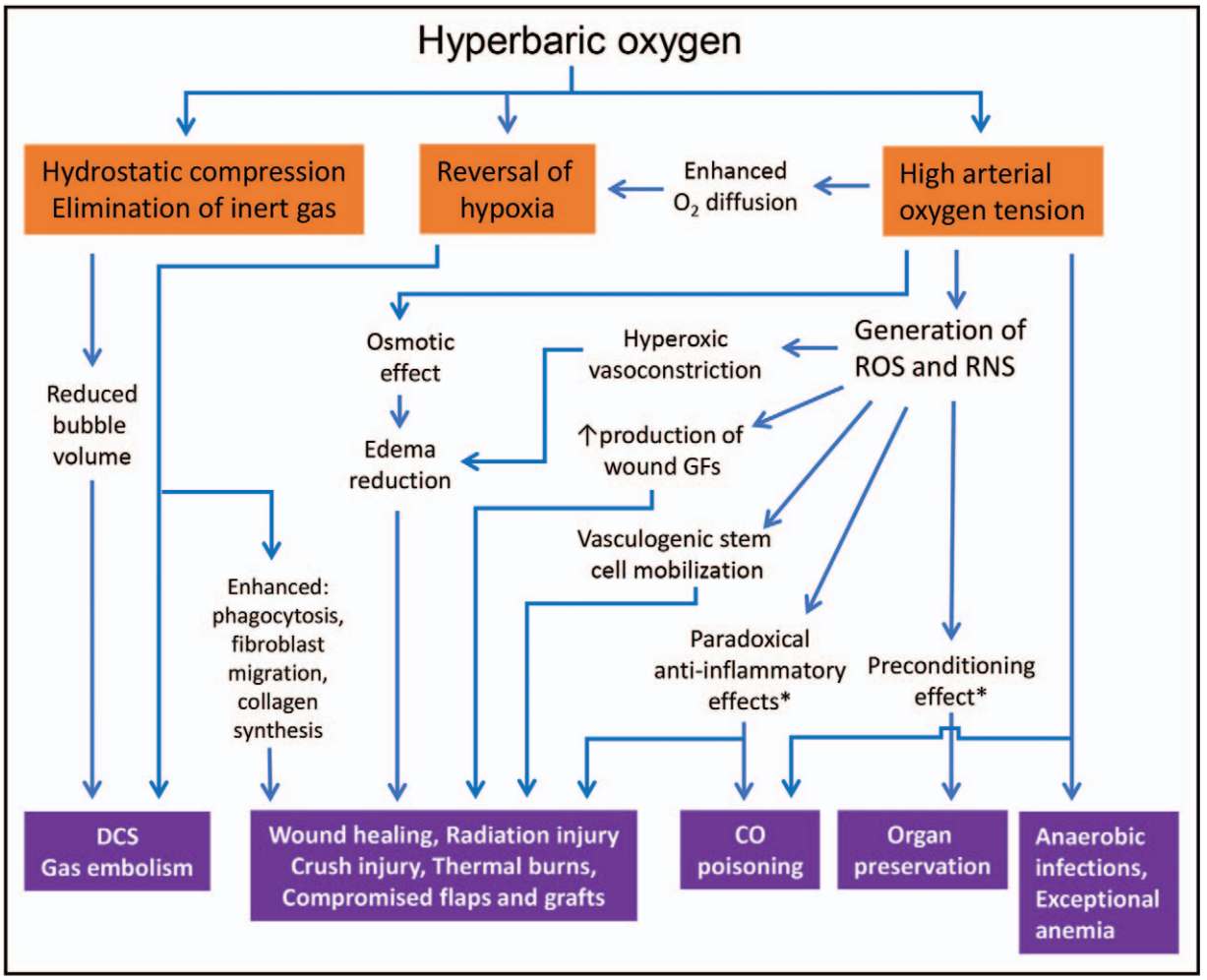

FIGURE 3. The three principal therapeutic mechanisms of hyperbaric oxygen therapy and linkage to some common indications. *Includes induction of multiple reactive species including heat shock proteins and haemoxygenase-1.

patients, and two recent studies further address this issue. One demonstrating a benefit [11▪▪] and the other finding no benefit except in a strict per protocol analysis [12▪▪]. Since the emphasis of this review is 'emerging indications' these controversies around an indication considered 'established' are not discussed further.

Other recent studies have focused on nondiabetic wounds of various types. In the most important human study, 74 patients with venous lower limb ulcers underwent 1 month of optimal wound care. In 31 the ulcers failed to reduce in size by more than 50% and these patients were then randomized to receive 30 HBOT treatments (80 min at 2.4 ATA) or 30 sham HBOT exposures in addition to continuation of wound care [13▪]. There was no between-group difference in the proportion of ulcers completely healed at 12 weeks after randomization, but the percentage ulcer area reduction was greater in the HBOT group (mean 95 versus 54% reduction). Unfortunatley, like many human investigations in this area, this study was small and underpowered for its primary outcome measure (complete healing).

In a nonrandomized study of patients with peripheral wounds attributed to thromboangiitis obliterans, 97 patients were treated with conventional therapies including wound care, acetylsalicylic acid, clopidogrel, pentoxifylline, and iloprost [14▪]. Forty-seven also received HBOT (median 34 treatments for 90 min at 2.4 ATA). In follow-up at 10 months, fewer patients underwent major amputations in the HBOT group (two of 47 patients versus 13 of 50 in the non-HBOT group), and the proportion of patients exhibiting complete healing of wounds favored the HBOT group (21 of 47 versus 11 of 50). Interpretation of these findings are limited by the design of the study.

There have also been several recent in-vivo studies or reviews whose results suggest that HBOT may be worth trialing in related clinical scenarios.

Two randomized controlled animal studies in different animal models (dogs, diabetic rabbits)

Table 1. Indications accepted for routine treatment with hyperbaric oxygen therapy by the Undersea and Hyperbaric Medical Society 2019 [4]

1. Air or gas embolism (includes diving-related, iatrogenic, and accidental causes)
2. Carbon monoxide poisoning (including poisoning complicated by cyanide poisoning)
3. Clostridial myositis and myonecrosis (gas gangrene)
4. Crush injury, compartment syndrome, and acute traumatic ischemias
5. Decompression sickness
6. Enhancement of healing in selected problem wounds
7. Exceptional blood loss (where transfusion is refused or impossible)
8. Intracranial abscess
9. Necrotizing soft-tissue infections (e.g., Fournier's gangrene)
10. Osteomyelitis (refractory to other therapy)
11. Delayed radiation injury (soft-tissue injury and bony necrosis)
12. Skin grafts and flaps (compromised)
13. Thermal burns
14. Idiopathic sudden sensorineural hearing loss

found that bone ingrowth around osseointegrated implants was enhanced by HBOT [15,16]. Differences were significant at 4 weeks in both models but only in the dog model at 8 weeks. Failure rates for primary dental implants are low, but these results may encourage a clinical trial in scenarios with a higher failure risk, such as implant retreatment in sites that have previously failed [17].

A systematic review of 13 in-vivo studies of HBOT in anastomotic healing of colorectal resections in rats found that HBOT improved bursting pressure and/or wound hydroxyproline levels in both normal and ischemic anastomoses [18▪]. HBOT may therefore help prevent anastomotic leak in colorectal surgery. Such leaks are infrequent at around 5% of anterior resections [19] and it would be difficult to conduct an adequately powered human study. Nevertheless, HBOT could be studied clinically with a focus on high-risk patients.

A recent study of healing in surgical incisions in healthy dogs showed no benefit of HBOT and wound care over wound care alone [20]. This reinforces that HBO is not advocated for healing enhancement in uncomplicated wounds that have established momentum toward healing.

Diabetic management

Diabetic foot ulcers (DFU) are an established indication for HBOT. There is a well documented fall in blood glucose levels with HBOT, and while the mechanism remains unclear, researchers have demonstrated an increase in insulin sensitivity [21]. The anti-inflammatory effect of HBOT, mediated through the production of reactive oxygen and nitrogen species (Fig. 2) is comparable with treatment with corticosteroids – without the negative side effects of the latter (immunosuppression and hyperglycemia). The chronic state of inflammatory hypoxia induced by diabetes mellitus and the ability of HBOT to modify this state suggests HBOT may be of benefit in the management of diabetes mellitus and other chronic diseases [22]. Encouraging clinical data support this suggestion. Fife *et al.* [23] reported the use of HBOT in a group of patients with renal failure and DFU. Of 835 patients, 76% showed improved renal function after treatment.

Harrison 2018 notes that DFU and diabetic kidney disease (DKD) have microvascular endothelial disease as a common underlying feature and this group has investigated the potential for HBOT to positively influence DKD in both an animal model and the clinical setting [24▪▪]. Using the emerging technique of 'metabolomics' in a group of 17 patients treated for DFU, Harrison identified a suite of changes in urinary metabolites following HBOT (2.4 ATA for 90 min, 30 treatments). Their data support the concept that HBOT can reduce biomarkers of renal injury, oxidant stress, and mitochondrial dysfunction in patients receiving HBOT for DFU. Furthermore, the activation of molecular chaperones such as heat shock proteins and hemoxygenase-1 play a role in the attenuation of oxidative damage in tissues (Fig. 3).

Irawan 2018 published clinical data supporting this concept [25▪]. In a nonrandom cohort of 30 patients treated for DFU, half received a standard treatment approach with insulin and intravenous empiric antibiotics, while the other had the same and a course of HBOT at 2.4 ATA for 90 min daily for 10 days. After completion of HBOT, the percentage of glycosylated hemoglobin (HbA1c) was lower in both groups, but significantly more so with HBOT ($9.7 \pm 2.5\%$ in standard group versus $7.1 \pm 1.2\%$ with HBOT, $P < 0.001$) and leukocyte counts were lower with HBOT, although not statistically significantly so (11 000 versus 8800/μl, $P = 0.18$). Irawan concludes that HBOT can assist in reducing glycemic and inflammatory levels and that perhaps short courses of HBOT are useful in this setting.

Both these clinical reports, along with encouraging animal models concerning bone growth, muscle oxidative capacity and the prevention of hyperglycemia in diabetes mellitus [16,26,27], suggest there is a strong case for further investigation and ultimately for well powered randomized controlled trials in these patients to determine the place of HBOT in the prevention and treatment of end-organ dysfunction associated with diabetes mellitus.

Mild traumatic brain injury

No emerging indication for HBOT is as controversial as treatment of the cognitive and dysthymic sequelae of mild traumatic brain injury (mTBI), often referred to as 'postconcussion syndrome'. Open label investigations of HBOT almost invariably report benefit, whereas three randomized sham-controlled blinded studies showed no outcome differences between true and sham HBOT interventions (studies summarized by Mitchell and Bennett [28]). Notably, in two of these studies both true and sham HBOT groups appeared to benefit from the intervention, which both study's authors attributed to a placebo or participation effect. Recently, one small sham-controlled, blinded exploratory study showed a subtle benefit for HBOT that did not persist after 6 months and would probably not have reached significance if statistical adjustment had been made for the hundreds of comparisons calculated [29].

Enthusiasts for HBOT have countered that typical approaches to conducting blinded sham hyperbaric treatments, such as breathing air at minimally elevated pressures (usually 1.2 or 1.3 ATA), are actually 'active treatments'. They rationalize the results of sham-controlled studies, in which patients allocated to true and sham HBOT improve equally, as indicating a therapeutic benefit. In the sham arm this is attributed to one or more of minimally increased inspired tensions of oxygen or nitrogen, or to the pressure increase itself. It is far more plausible to us that any apparent benefit is the result of a placebo or participation effect associated with the complex and prolonged ritual of hyperbaric therapy. This effect could be particularly powerful when open label designs are adopted to evaluate HBOT in conditions like mTBI where psychological wellbeing may influence perceptions of benefit [29].

The impetus for HBOT in mTBI arises from an understandable motivation to improve outcomes for affected military veterans in the USA. Unfortunately, the undisputed moral mandate for this cause has to some extent overwhelmed objective consideration of the available scientific evidence. This was exemplified in a recent report from the veterans affairs evidence-based synthesis program which acknowledged the weak evidence in support of HBOT, but which nevertheless suggested the use of HBOT was 'reasonable' where other treatment modalities had failed [30]. We consider this position inappropriate on the basis that it effectively justifies any unproven intervention to treat conditions where the highest quality trials indicate no benefit [31].

CONCLUSION

With the expansion of knowledge concerning the pharmacological actions of hyperbaric oxygen over the last 20 years, the field seems at the cusp of a significant paradigm shift. We are moving on from the concept that delivery of 100% oxygen at pressure simply enables us to re-oxygenate hypoxic tissue to a deeper understanding of the very complex metabolic and immunological consequences. HBOT is not over when the patient exits the chamber. This is evident from the well established protection from ischemia-reperfusion phenomena through the prolonged suppression of neutrophil activation in response to endovascular damage, to the mobilization of vasculogenic stem cells from the bone marrow and the upregulation of antioxidant capacity.

While we will continue to treat poorly healing hypoxic wounds into the foreseeable future, we are also likely to develop effective short courses of HBOT to protect against expected future insults and still others to modulate chronic inflammatory disease states.

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Conflicts of interest

The authors have no conflicts of interest, financial or otherwise, to declare in relation to this work.

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- ■■ of outstanding interest

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