

---

## REVIEW ARTICLE

---

# Hyperbaric Oxygen Therapy: A New Treatment for Chronic Pain?

---

Ainsley M. Sutherland, MD, PhD\*; Hance A. Clarke, MD, PhD\*;  
Joel Katz, PhD\*,<sup>†</sup>; Rita Katznelson, MD\*,<sup>‡</sup>

\**Department of Anesthesia and Pain Management, Toronto General Hospital, University Health Network, Toronto, ON;* <sup>†</sup>*Department of Psychology, York University, Toronto, ON;*

<sup>‡</sup>*Hyperbaric Medical Unit, Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, ON, Canada*

### ■ Abstract

*Background and objective:* Hyperbaric oxygen therapy (HBOT) is a treatment providing 100% oxygen at a pressure greater than that at sea level. HBOT is becoming increasingly recognized as a potential treatment modality for a broad range of ailments, including chronic pain. In this narrative review, we discuss the current understanding of pathophysiology of nociceptive, inflammatory and neuropathic pain, and the body of animal studies addressing mechanisms by which HBOT may ameliorate these different types of pain. Finally, we review clinical studies suggesting that HBOT may be useful in treating chronic pain syndromes, including chronic headache, fibromyalgia, complex regional pain syndrome, and trigeminal neuralgia.

*Database and data treatment:* A comprehensive search through MEDLINE, EMBASE, Scopus, and Web of Science for studies relating to HBOT and pain was performed using the following keywords: hyperbaric oxygen therapy or hyperbaric oxygen treatment (HBOT), nociceptive pain, inflammatory pain, neuropathic pain, HBOT AND pain, HBOT AND headache, HBOT AND fibromyalgia, HBOT AND com-

plex regional pain syndrome, and HBOT AND trigeminal neuralgia.

*Results:* Twenty-five studies examining the role of HBOT in animal models of pain and human clinical trials were found and reviewed for this narrative review.

*Conclusions:* HBOT has been shown to reduce pain using animal models. Early clinical research indicates HBOT may also be useful in modulating human pain; however, further studies are required to determine whether HBOT is a safe and efficacious treatment modality for chronic pain conditions. ■

**Key Words:** review, hyperbaric oxygen therapy, analgesia, animal models, inflammation, nociception, neuropathic pain, fibromyalgia, trigeminal neuralgia, cluster headache, complex regional pain syndromes

### INTRODUCTION

Management of pain, especially when it becomes chronic, is a challenging task requiring a multidisciplinary approach. Currently, most pharmacological, non-pharmacological and interventional modalities achieve only temporary or modest improvements in pain symptoms and often produce intolerable adverse effects which interfere with quality of life and lead to nonadherence. There is a need for new and effective chronic pain treatments that patients can tolerate without significant adverse effects. One such novel treatment is hyperbaric oxygen therapy (HBOT). There is a growing body of evidence to suggest that HBOT is a noninvasive

Address correspondence and reprint requests to: Rita Katznelson, MD, Hyperbaric Medical Unit, Department of Anesthesia and Pain Management, Toronto General Hospital, G PMB 106E, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada. E-mail: rita.katznelson@uhn.ca.

Submitted: February 4, 2015; Revision accepted: March 27, 2015  
DOI: 10.1111/papr.12312

modality with lasting efficacy and minimal side effects that can be used to treat chronic pain conditions.

Hyperbaric oxygen therapy (HBOT) was initially developed to treat decompression sickness, a side effect of deep sea diving. It provides patients with 100% oxygen at pressures greater than atmospheric pressure. HBOT increases partial pressure of oxygen in the alveoli<sup>1</sup> and results in a corresponding increase in the amount of dissolved oxygen carried by the blood which allows oxygenation of ischemic tissue with compromised circulation. HBOT leads to a net gain in oxygen concentration in tissues and subsequently induces neovascularization and angiogenesis, restores tissue homeostasis, and enhances leukocyte function.<sup>2</sup>

Recently, published animal and human studies as outlined below have indicated that HBOT induces an analgesic effect in nociceptive, inflammatory, and neuropathic pain models and may be useful for the treatment of various chronic pain syndromes, although the mechanism is not well understood.

## LITERATURE SEARCH METHODS

The present article reviews the basic science and clinical evidence in support of HBOT for managing various chronic pain conditions. In the first section, we review basic science evidence showing that HBOT exerts antinociceptive, anti-inflammatory, and antineuropathic effects in animal models of pain and nociception. In the second section, we review the available clinical evidence for the efficacy of HBOT in humans with a variety of chronic pain conditions, including headache, fibromyalgia, complex regional pain syndrome, and trigeminal neuralgia. A comprehensive search through MEDLINE, EMBASE, Scopus, and Web of Science for studies relating to HBOT and pain was performed using the following keywords: nociceptive pain, inflammatory pain, neuropathic pain, HBOT AND pain, HBOT AND headache, HBOT AND fibromyalgia, HBOT AND complex regional pain syndrome, and HBOT AND trigeminal neuralgia.

## RESULTS

### Antinociceptive Effects of HBOT in Animals

HBOT has been shown to inhibit nociception in murine models of pain. The abdominal constriction test measures the number of abdominal constrictions (ie., lengthwise stretches of the torso with concave arching

of the back) mice display in response to painful intraperitoneal (IP) injection of acetic acid.<sup>3</sup> In one study, mice were treated with HBOT with 100% oxygen at 3.5 atmospheres absolute (ATA) or with a mixture of 70% nitrous oxide (N<sub>2</sub>O) and 30% O<sub>2</sub> at 1.0 ATA for 60 minutes prior to IP injection of acetic acid.<sup>4</sup> The number of abdominal constrictions each treatment group displayed was compared to those of control mice sham-treated with air at 1.0 ATA, and the degree of antinociception was calculated as the percentage decrease in the number of abdominal constrictions vs. control. Exposure to HBOT resulted in a decrease in nociceptive response by 80–95% for up to 90 minutes after exposure to HBOT. In comparison, N<sub>2</sub>O resulted in at least 70% antinociception up to 15 minutes after exposure and fell to 20% by 30 minutes.<sup>4</sup>

The same study demonstrated that the antinociceptive effect of HBOT was mediated by a neural nitric oxide (NO)-dependent release of opioid peptide.<sup>4</sup> HBOT has been previously shown to increase the pO<sub>2</sub> and tissue NO concentration in the cerebral cortex.<sup>5</sup> As such, the authors examined whether NO played a role in HBOT-induced analgesia in the mice. Systemic administration of naltrexone, an opioid antagonist, and intracerebroventricular (ICV) administration of neural nitric oxide synthase (NOS) inhibitors prior to 60-minute HBOT antagonized the antinociceptive effects of HBOT.<sup>4</sup> Central (ICV) pretreatment with antiserum against the opioid peptide dynorphin, but not  $\beta$ -endorphin or methionine-enkephalin, also reduced the antinociceptive effects of HBOT.<sup>4</sup> These results suggest a key role for supraspinal neural NO and endogenous opioids in HBOT-induced analgesia. Further evidence for the role of NO in HBOT-induced analgesia was demonstrated in a separate study in which HBOT-induced analgesia was attenuated by ICV and intrathecal (IT) pretreatment with L-NAME, an inhibitor of NOS, and by antisense nucleotides against neuronal NOS.<sup>6</sup>

HBOT-induced, NO-dependent release of endogenous opioids appears to involve dynorphin and activation of  $\kappa$ - and  $\mu$ -opioid receptors in the spinal cord in addition to supraspinal sites.<sup>7</sup> IT administration of  $\kappa$ - and  $\mu$ -selective opioid antagonists, but not a  $\delta$ -selective opioid antagonist, prior to HBOT antagonized the antinociceptive effects of a brief 11-minute treatment with HBOT in mice. IT pretreatment with rabbit antiserum against dynorphin, but not against  $\beta$ -endorphin or methionine-enkephalin, also attenuated the antinociceptive effect of HBOT in a murine model of

acute nociceptive pain (the acetic acid abdominal constriction test). These results indicate that the HBOT-induced antinociception involves the release of neuronal dynorphin and activation of  $\kappa$ - and  $\mu$ -opioid receptors in the spinal cord.<sup>7</sup>

As the opioid receptor antagonist naltrexone has been shown to block the antinociceptive effects of HBOT in mice, presumably by inhibiting the release of endogenous opioids,<sup>4,8,9</sup> the next logical approach was to determine whether repeated exposure, and tolerance, to exogenous opioids would similarly inhibit the antinociceptive effects of HBOT in mice. To test this hypothesis, mice were repeatedly injected with subcutaneous (SC) fentanyl, a  $\mu$ -selective opioid receptor agonist, IP (-)-U50488H, a  $\kappa$ -selective agonist, or SC morphine sulfate ( $\mu$  and  $\kappa$ ) over 4 days to induce opioid tolerance.<sup>10</sup> Control, opioid-naïve, mice were injected with saline according to the same schedule. On day 5, opioid-tolerant and control mice were exposed to HBOT at 3.5 ATA for 30 minutes. Mice were then injected with IP acetic acid and evaluated using the abdominal constriction test. HBOT produced 72% antinociception in opioid-naïve mice. Mice tolerant to morphine, fentanyl, or (-)-U50488H all had significantly reduced antinociceptive responses to HBOT, indicating that tolerance to exogenous opioid receptor agonists inhibits the analgesic effects of HBOT.<sup>10</sup> As tolerance to both fentanyl and (-)-U50488H almost completely abolished the antinociceptive effects of HBOT, it may be that the functional loss of either the  $\mu$ - or  $\kappa$ -opioid receptor is able to completely antagonize HBOT antinociception. The authors suggest that the reduced antinociceptive effect of HBOT in opioid-tolerant mice may be due to cross-tolerance; where repeated use of a drug causes decreased responsiveness to that drug and also to other drugs,<sup>10</sup> including endogenous opioids. This may have implications for the treatment of pain with HBOT in patients on chronic opioid therapy.

Repeated treatment with HBOT results in a two-phase antinociceptive response.<sup>8</sup> Mice treated with four daily 60-minute HBOT sessions at 3.5 ATA had 90–95% suppression of abdominal constrictions that lasted up to 6 hours after the last HBOT session. When the mice underwent abdominal constriction testing at later time points, the antinociceptive effect of HBOT was no longer evident at 12 hours, began to reappear at 24 hours after the last HBOT treatment, peaked 5 days post-treatment, and lasted for up to 2 weeks post-treatment. The authors distinguished these phases as the early and late phases of antinociception. In agreement

with their previous work, the authors demonstrated that early-phase antinociception is attenuated by inhibitors of NO and endogenous opioids. Late-phase antinociception was also inhibited by up to 80% by ICV administration of L-NAME and naltrexone at the time of HBO treatment. However, ICV administration of L-NAME or naltrexone 2 weeks after HBO treatment had no effect on the late-phase antinociceptive response. These results indicate that the development of late-phase antinociception is dependent on early NO and opioid receptor activation, but that the final downstream step in the antinociceptive pathway is NO- and opioid receptor independent.<sup>8</sup>

### Anti-Inflammatory Effects of HBOT in Animals

Hyperbaric oxygen therapy may play a role in inhibiting the inflammatory response following injury and associated inflammatory pain. An early study in rats demonstrated that HBOT decreased paw edema following injury, indicating that HBOT reduced inflammation, but pain behavior in the rats was not measured.<sup>11</sup> To assess whether HBOT has a role in limiting both inflammation and pain, a subsequent study measured paw edema and mechanical paw withdrawal thresholds (MPWT), a pain behavior measurement, in rats injected with 1% carrageenan into their hind paws.<sup>12</sup> Paw edema and MPWT were compared between rats treated with HBOT at 2.4 ATA for 90 minutes and untreated control rats one hour after carrageenan injection. The results showed that HBOT significantly decreased paw edema and mechanical hyperalgesia for up to 5 hours in an acute inflammatory pain condition.<sup>12</sup>

In a rat model of arthritis, HBOT was shown to be as effective as aspirin in decreasing inflammation and mechanical hypersensitivity.<sup>13</sup> Carrageenan was injected into the left knee joint of rats to induce an arthritic condition. The next morning, rats were treated with either HBOT at 2.4 ATA for 90 minutes, intraperitoneal injection of 150 mg/kg of aspirin in solution or IP injection of saline for controls. Both the HBOT-treated and aspirin-treated groups had significantly smaller paw diameters (less inflammation) and higher MPWTs (less mechanical sensitivity) than the control group.<sup>13</sup>

### HBOT Effects on Animal Models of Neuropathic Pain

Hyperbaric oxygen therapy has shown promising results in animal models of neuropathic pain. Chronic

constriction injury (CCI) of the sciatic nerve is a commonly used animal model of nerve injury and neuropathic pain in which loosely constrictive ligatures are placed around the sciatic nerve.<sup>14</sup> HBOT improved blood flow, decreased edema, and prevented cellular damage in rats with a CCI that subsequently underwent HBOT, but pain behavior was not examined.<sup>15</sup> In a subsequent study, Thompson et al. examined whether HBOT was associated with less pain behavior in rats, as measured by decreased MPWT following CCI or L5 spinal nerve ligation. Rats were treated with HBOT at 2.4 ATA for 90 minutes for 14 days beginning 3 days post-L5 ligation, or 5 days post-CCI. MPWT was measured every day of treatment and for 5 days after treatment. Animals treated with HBOT after either type of nerve injury displayed less mechanical hypersensitivity than those that did not receive treatment with HBOT.<sup>16</sup> The CCI group responded to treatment sooner than did the L5 spinal nerve ligation group and the treatment effect lasted longer.<sup>16</sup> However, it is difficult to interpret the results as the CCI animals had 2 extra days to recover before HBOT therapy was initiated.

HBOT has been shown to decrease injury-induced inflammation. Li et al. tested the hypothesis that HBOT reduced CCI-induced neuropathic pain behaviors in rats by decreasing production of the pro-inflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$ . Compared to untreated controls, rats treated with HBOT at 2.4 ATA for one hour daily for 7 days following CCI showed a lower cold allodynia response, and a higher threshold for mechanical allodynia, indicating reduced neuropathic pain behaviors in response to nerve injury.<sup>17</sup> Injured rats treated with HBOT also showed decreased TNF- $\alpha$  protein content in their sciatic nerves compared to control rats, suggesting that HBOT led to decreased inflammation following nerve injury, and this may be responsible for the attenuation of neuropathic pain.<sup>17</sup>

A subsequent study examining the effect of HBOT on the attenuation of neuropathic pain in rats measured changes in the phosphorylation of proteins thought to be involved in the development of neuropathic pain.<sup>18</sup> Consistent with previous studies, treatment with HBOT at 3.0 ATA daily for 7 days starting 30 minutes after CCI-induced sciatic nerve injury reduced the severity and duration of thermal hyperalgesia and mechanical allodynia in rats, behavioral indicators of neuropathic pain.<sup>18</sup> In contrast, neither high pressure nor pure oxygen alone reduced neuropathic pain behavior following CCI. In a second arm of the study, the authors showed that HBOT administered for 3 days 2 weeks after nerve

injury attenuated neuropathic pain behavior by a transient decrease in thermal hyperalgesia and mechanical allodynia. A longer and later course of HBOT, from post-CCI days 14–21 resulted in long-lasting inhibition of thermal hyperalgesia and mechanical allodynia for at least 2 weeks after the last HBO treatment.<sup>18</sup>

To elucidate the HBOT-induced biochemical changes responsible for the attenuation of neuropathic pain behavior in rats, Gu et al. extracted protein from rat spinal cord following CCI and treatment with HBOT. Daily HBOT initiated 30 minutes after nerve injury and continued for 7 days, inhibited expression of c-Fos and activation of astrocytes in the dorsal horn compared to rats not treated with HBOT post-CCI.<sup>18</sup> In addition, HBOT post-CCI inhibited the phosphorylation of the NR1 and NR2B NMDA receptor subtypes, extracellular signal-regulated kinases (ERK), calmodulin-dependent kinase II (CaMKII), cyclic adenosine monophosphate (cAMP) response element-binding (CREB) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in rat spinal cord.<sup>18</sup> These NMDA receptors and downstream signaling molecules have a well-characterized role in neural plasticity and neuropathic pain. The results suggest that HBOT may inhibit neural activation as well as NMDA receptor activation and signaling after nerve injury, possibly leading to attenuation of neuropathic pain behaviors in rats.<sup>18</sup>

Another study demonstrated that HBOT before or after CCI attenuated mechanical allodynia and thermal hyperalgesia and decreased expression of spinal neuronal NOS (nNOS) and inducible NOS (iNOS).<sup>19</sup> Rats were treated with one course of HBOT at 2.5 ATA for 60 minutes either 12 hours pre-CCI or 12 hours post-CCI. HBOT pretreatment was more effective in reducing mechanical allodynia and thermal hyperalgesia than HBOT post-CCI. Multiple HBOT treatments were not performed in this study, so it is not possible to compare these results with previous studies of multiple HBOT treatments postnerve injury. Spinal cord tissue was harvested 28 days post-CCI and HBOT treatment, and nNOS-, eNOS-, and iNOS-positive neurons were quantified. CCI resulted in an increase in the numbers of nNOS and iNOS, but not eNOS-positive neurons compared to untreated control rats and sham-operated rats. Pre-CCI treatment with HBOT and post-CCI HBOT resulted in significantly decreased numbers of both nNOS- and iNOS-positive neurons compared to injured, but non-HBOT-treated rats.<sup>19</sup> These results conflict with the previously discussed studies demonstrating the antinociceptive effects of HBOT mediated

through nitric oxide (NO)-dependent release of opioid peptide, and with studies demonstrating that NOS and NO mediate the analgesic effects of morphine.<sup>20</sup> These conflicting results on the effect of HBOT and NO-induced pain or analgesia may reflect the varied roles of NO subtypes play in different tissues.

Further work showed that HBOT may ameliorate allodynia following sciatic nerve crush injury in rats through an opioid receptor-dependent mechanism,<sup>9</sup> similar to that previously described in acute pain models in mice.<sup>4,7-10,21</sup> Rats underwent surgical sciatic nerve crush injury or a sham operation. Allodynia was measured by mechanical withdrawal threshold (MWT). Seven days after surgery the rats were treated with HBOT at 3.5 ATA for 60 minutes or with room air at 1.0 ATA. One group of rats also had a cannula inserted into the right lateral cerebral ventricle that was used to infuse naltrexone into the ventricles 24 hours before HBOT and for 7 days thereafter. HBOT had an anti-allodynic effect in rats with sciatic nerve crush injury. This effect was counteracted by cerebroventricular administration of naltrexone. These results suggest, that as in animal models of acute pain, HBOT may mediate relief of neuropathic pain by CNS opioid receptor-mediated mechanisms.<sup>9</sup> The study did not investigate the role of NO in mediating the opioid receptor-dependent response.

More recently, in a study of HBOT-mediated reduction of neuropathic pain behaviors in rats, HBOT inhibition of allodynia, oxidative stress, and spinal astrocyte activation after CCI of the sciatic nerve were quantified.<sup>22</sup> Rats underwent CCI or a sham operation and then received HBOT at 2.0 ATA, 2.5 ATA, or a control condition with room air for 60 minutes every day for 7 days starting on postoperative day 1. Allodynia was measured using MWT and thermal withdrawal latency (TWL) testing daily immediately after removal from the HBOT chamber and at 1, 2, and 3 hours after HBOT. Blood was collected from the tail veins for measurement of methane dicarboxylic aldehyde (MDA) and superoxide dismutase (SOD) as indices of oxidative stress response immediately after and 1 hour post-HBOT. Lumbar spinal cord samples were harvested on postoperative day 7 for quantitation of glial fibrillary acidic protein activation in the spinal cord dorsal horns of L4-L6 segments.

Rats with CCI of the sciatic nerve demonstrated brief hyperallodynia immediately after removal from the HBOT chamber.<sup>22</sup> This hyperallodynic response faded by 1 hour, and it was shown that a single HBOT

treatment inhibited mechanical and thermal allodynia for up to 2 hours after HBOT on days 1-5. Rats with sciatic CCI that underwent HBOT at 2.0 or 2.5 ATA had increased MDA levels immediately post-HBOT that decreased by 1 hour and decreased SOD activity immediately post-HBOT that increased one hour post-HBOT. The authors suggest that the brief hyperallodynia seen after HBOT with 2.0 ATA or 2.5 ATA may be due to increased oxidative stress following HBOT, as measured by increased MDA, which aggravates nerve injury temporarily, but resolves as antioxidant SOD levels increased.<sup>22</sup>

After 5 days of HBOT, a prolonged anti-allodynic response developed that was sustained for more than 24 hours.<sup>22</sup> This finding is consistent with previous work that demonstrated a two-phase antinociceptive response to acute pain with HBOT,<sup>8</sup> but it conflicts with other reports that demonstrated an immediate decrease in neuropathic pain behaviors following a single treatment with HBOT.<sup>17,19</sup> The authors suggest that HBOT produces an antinociceptive response by inhibiting astrocytes in the spinal dorsal horn as sciatic nerve CCI increased astrocyte activation in the dorsal horn, and HBOT inhibited this activation.<sup>22</sup>

## HYPERBARIC OXYGEN THERAPY IN TREATMENT OF HUMAN PAIN

There is a body of evidence supporting the use of HBOT to decrease inflammation and pain behaviors in rodents. However, level 1 evidence for the clinical utility of HBOT in treating different types of human pain conditions is lacking. Preliminary results suggest that HBOT may be useful in treating chronic headache, fibromyalgia, complex regional pain syndrome, and trigeminal neuralgia, but, to date, large-scale randomized, controlled trials (RCT) have not been conducted.

### Headache

Several studies have examined the efficacy of HBOT in the treatment and prevention of migraine and cluster headaches. Five randomized control trials (RCTs) examined the use of HBOT for treatment and prevention of migraine.<sup>23-27</sup> Bennett et al. summarized the findings from these trials in a 2008 systematic review.<sup>28</sup> All the trials were found to be of moderate to low methodological quality, and although they were RCTs, they were underpowered and enrolled only a total of 103 patients (between 8 and 40 per study). Two of the

studies used a crossover design.<sup>25,27</sup> Four of the trials treated patients with a single HBOT treatment of 60 minutes,<sup>24–27</sup> while one trial treated patients with 30 minutes of HBOT on 3 consecutive days.<sup>23</sup> Together, they provide some evidence that HBOT is efficacious in relieving an acute migraine attack, but not in preventing future attacks.<sup>28</sup>

Di Sabato et al. studied the efficacy of HBOT in terminating active cluster headache attacks (CH) in 13 patients.<sup>29</sup> They compared the effect of a 30-minute session of HBOT at 2.4 ATA with normal air at 1 ATA beginning 5 minutes after the onset of a CH attack in 7 and 6 patients, respectively. HBOT-treated patients had significantly shorter CH durations compared to the average time of their previous attacks. Patients treated with normal air did not show a significant difference in the duration of their attacks compared to their previous attacks.<sup>29</sup> In addition, three of seven patients who received HBOT reported no further attacks in the two-month follow-up period. In patients who were treated with normal air subsequent, CH attacks were not prevented.<sup>29</sup>

Despite these promising results, interpretation of the data is limited by the small sample size and data comparing the duration of attacks between the two groups were not presented.<sup>29</sup>

In a later study, the same authors suggested that the analgesic effects of HBOT in CH may be negatively correlated with the concentration of substance P in the nasal mucosa of HBOT-treated patients<sup>30</sup> based on a prior hypothesis that trigeminal C fibers may be involved in the pathogenesis of CH<sup>31</sup> through the release of neuropeptides such as substance P.

The authors enrolled 14 patients in an active phase of CH attacks to receive either 30 minutes of HBOT treatment at 2.5 ATA, or sham treatment in a hyperbaric chamber with room air. Randomization and blinding procedures were not specified.<sup>30</sup> After HBOT or sham treatment, nasal mucosa samples were fixed and stained with antisubstance P antibody, and immunoreactivity to substance P was qualitatively evaluated using an arbitrary density score of 1–20. The observer was blinded to the patient's group. The authors state that the substance P density scores of those patients treated with HBOT were lower than those who received sham treatment, although no statistical analysis is provided.<sup>30</sup> The authors state that the patients who were treated with HBOT had a transient improvement of their CH meaning either disappearance, or at least a 50% diminution, of symptoms.<sup>30</sup>

In further work by Di Sabato et al., the authors examined the effect of HBOT on chronic CH and serotonin binding to mononuclear cells.<sup>32</sup> Ten chronic CH patients were exposed to fifteen 30-minute sessions of HBOT at 2.5 ATA, while 4 chronic CH patients were exposed to room air in the hyperbaric chamber. The number of attacks per week and indomethacin use was compared between the 2 groups. The HBOT group had significantly less attacks per week and consumed less indomethacin than the sham group.<sup>32</sup>

To determine the effect of HBOT on serotonin binding to mononuclear cells, blood was drawn before and after 15 sessions of HBOT or sham treatment<sup>32</sup> to quantitate <sup>3</sup>H-labeled 5HT binding to mononuclear cells before and after treatment. Unfortunately, the data are highly variable, to the point where the authors admit statistical tests that are insignificant.<sup>32</sup>

This data suggest that HBOT may be useful in terminating a cluster headache, although, as in migraine, it is somewhat impractical and resource intensive to bring patients who are suffering from a fairly brief, episodic headache into a hospital or clinic for HBOT. A more practical application may be in treating chronic CH headache, where HBOT has shown some promise,<sup>32</sup> but further study with a more robust study design is required before HBOT becomes accepted practice.

### Fibromyalgia

Fibromyalgia is a chronic pain syndrome characterized by widespread pain, low energy, and mood and sleep disturbance.<sup>33</sup> It has been proposed that local hypoxia may cause degenerative changes in muscle leading to chronic pain.<sup>34,35</sup> By raising oxygen tension in the body, hyperbaric oxygen therapy was proposed as an adjunct to pharmacologic treatment by improving muscle oxygenation in fibromyalgia, thus restoring aerobic metabolism and correcting local tissue hypoxia and acidosis.<sup>36</sup>

In 2004, an RCT testing this hypothesis in 50 patients who met the 1990 diagnostic criteria of the American College of Rheumatology (ACR) for fibromyalgia<sup>37</sup> demonstrated a decrease in pain scores and tender points.<sup>36</sup> In this study, 26 patients received fifteen 90-minute HBOT sessions at 2.4 ATA over 3 weeks, while 24 control patients breathed air at 1 ATA (sham treatment) for 90 minutes for fifteen sessions. The number of tender points, pain threshold as measured by algometer and VAS pain score was recorded for each patient before the first HBOT or sham session, and after the fifteenth. There was a significant decrease in the

number of tender points and pain threshold in the HBOT group compared to the sham treatment group as early as after the first HBOT session that persisted after the 15th session.

### Complex Regional Pain Syndrome

HBOT may be useful in treating CRPS. A double-blind, randomized, placebo-controlled study was designed to assess whether HBOT was superior to placebo in treating patients with post-traumatic CRPS of the wrist.<sup>38</sup> Seventy-one patients were randomized into a treatment group of ( $n = 37$ ) that received fifteen daily 90-minute HBOT sessions at 2.4 ATA or a control group ( $n = 34$ ) that received fifteen daily 90-minute sessions in the hyperbaric chamber with normal air. Patients were blinded to which group they were in. Only the treating physician was aware whether patients were receiving HBOT or room air for safety reasons. Patients were evaluated prior to treatment, after the 15 sessions were completed, and after 45 days. The physician evaluating patients before and after therapy was blinded to the treatment group.

The CRPS patients who received HBOT were shown to have significantly lower VAS scores after the 15th treatment and at 45 days post-treatment ( $P < 0.001$ ). In contrast, the control group did not show a significant improvement in pain scores compared to baseline pain scores prior to sham treatment. Wrist extension, but not flexion, was significantly improved in the HBOT group both after the 15th treatment and at 45 days ( $P < 0.001$ ). The HBOT group had less wrist edema compared to the control group both after the final treatment and at 45 days ( $P < 0.001$ ). The authors concluded that HBOT was effective in decreasing pain and swelling, and increasing wrist ROM in patients with CRPS;<sup>38</sup> however, it is not clear that these results are generalizable to other populations. The sample size was relatively small and consisted of young, presumably otherwise healthy, members of the military. Additionally, all patients received HBOT within 1.5 months of the original injury. Further studies must be undertaken to demonstrate the effectiveness of HBOT in treating CRPS in patients with more chronic injuries and other comorbidities.

### Trigeminal Neuralgia

A small RCT suggests that HBOT may also be useful in treating idiopathic trigeminal neuralgia (TN).<sup>18</sup> Forty-

two patients (8 men, 34 women; mean age  $56.5 \pm 7.6$  years) with idiopathic TN who were being treated with carbamazepine for their neuropathic pain were randomly assigned to 70 minutes of HBOT at 1.8 ATA for 10 consecutive days ( $n = 20$ ), or sham treatment with room air in a hyperbaric oxygen chamber ( $n = 22$ ). Effectiveness of the treatment was quantified by the change in dose of carbamazepine required to keep pain minimal and by changes in VAS scores.

Patients had suffered from TN for 2 to 20 years, with a mean  $\pm$  SD duration of  $14.6 \pm 5.1$  years. All had been treated with carbamazepine for over 3 months. The treatment group had a significant decrease in average carbamazepine dose compared to pretreatment dose after 10 days of HBOT that lasted for 60 to 90 days post-HBO treatment. The average dose of carbamazepine was also significantly lower in the HBOT treatment group compared to the sham treatment group for up to 60 days post-HBOT. VAS scores for the HBOT treatment group were also significantly decreased from baseline and compared to the sham treatment group after 10 sessions of HBOT and up to 6 months following treatment.<sup>18</sup> Interestingly, carbamazepine doses and VAS scores were also decreased in the sham group, although not to the same degree as the treatment group, indicating the existence of a placebo effect.

### DIRECTIONS FOR FUTURE RESEARCH

There is a growing body of evidence that HBOT has a positive effect in various pain conditions. Future research should be directed at identifying chronic pain patients who can benefit from HBOT and defining the optimal time for the intervention and relevant dose-response curves specific for each condition. However, conducting randomized controlled trials can be challenging due to many factors. First, the optimal dose and duration of HBOT is not well established even for recognized chronic HBOT indications. The treatment regime usually consists of 20 to 40 ninety-minute HBOT sessions (4 vs. 8 weeks of treatment) with 100% oxygen administered under 2.0 to 2.4 ATA. Second, patient blinding may be a potential problem as a true placebo condition cannot be achieved: to blind the patients in the sham group, a short time of exposure to elevated pressure may be required at the beginning of the sham session to replicate the sensation of HBOT. This may lead to short times of increased plasma oxygen partial pressure. Third, recruitment of chronic pain patients for a study with a sham group that may undergo at least 15

to 20 ninety-minute sessions in the hyperbaric chamber may be challenging both practically and ethically.

### CONCLUSIONS

HBOT has been shown to have antinociceptive and analgesic effects in animal models of nociception, as well as modulatory effects in animal models of inflammatory and neuropathic pain. Early clinical research demonstrates promise for the use of HBOT in the treatment of several human pain syndromes. However, adequately powered and methodologically sound studies are required to determine whether HBOT is a safe and efficacious treatment modality for patients suffering with chronic pain conditions.

### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

### AUTHOR CONTRIBUTIONS

HC is supported by a Merit Award from the Department of Anaesthesia at the University of Toronto and by the *STAGE Training Program in Genetic Epidemiology from the Canadian Institutes of Health Research*. AS and RK collected the data, analyzed the results, and wrote the article. HC and JK participated in analyzing the data and writing the article. All authors discussed the results and commented in the article. JK is supported by a Canadian Institutes of Health Research Tier 1 Canada Research Chair in Health Psychology at York University.

### REFERENCES

- Jain KK. *Textbook of Hyperbaric Medicine*, 3rd ed.. Seattle, WA: Hogrefe and Huber Publishers; 1999.
- Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. *Plast Reconstr Surg*. 2011;127(Suppl 1):131S–141S.
- Emmanouil DE, Dickens AS, Heckert RW, et al. Nitrous oxide-antinociception is mediated by opioid receptors and nitric oxide in the periaqueductal gray region of the midbrain. *Eur Neuropsychopharmacol*. 2008;18:194–199.
- Zelinski LM, Ohgami Y, Chung E, Shirachi DY, Quock RM. A prolonged nitric oxide-dependent, opioid-mediated antinociceptive effect of hyperbaric oxygen in mice. *J Pain*. 2009;10:167–172.
- Thom SR, Bhopale V, Fisher D, Manevich Y, Huang PL, Buerk DG. Stimulation of nitric oxide synthase in cerebral cortex due to elevated partial pressures of oxygen: an oxidative stress response. *J Neurobiol*. 2002;51:85–100.
- Ohgami Y, Zylstra CC, Quock LP, Chung E, Shirachi DY, Quock RM. Nitric oxide in hyperbaric oxygen-induced acute antinociception in mice. *NeuroReport*. 2009;20:1325–1329.
- Heeman JH, Zhang Y, Shirachi DY, Quock RM. Involvement of spinal cord opioid mechanisms in the acute antinociceptive effect of hyperbaric oxygen in mice. *Brain Res*. 2013;1540:42–47.
- Chung E, Zelinski LM, Ohgami Y, Shirachi DY, Quock RM. Hyperbaric oxygen treatment induces a 2-phase antinociceptive response of unusually long duration in mice. *J Pain*. 2010;11:847–853.
- Gibbons CR, Liu S, Zhang Y, et al. Involvement of brain opioid receptors in the anti-allodynic effect of hyperbaric oxygen in rats with sciatic nerve crush-induced neuropathic pain. *Brain Res*. 2013;1537:111–116.
- Zhang Y, Stolz PA, Shirachi DY, Quock RM. Reduced antinociceptive responsiveness to hyperbaric oxygen in opioid-tolerant mice. *Eur J Pain*. 2014;18:1032–1039.
- Sumen G, Cimsit M, Eroglu L. Hyperbaric oxygen treatment reduces carrageenan-induced acute inflammation in rats. *Eur J Pharmacol*. 2001;431:265–268.
- Wilson HD, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment decreases inflammation and mechanical hypersensitivity in an animal model of inflammatory pain. *Brain Res*. 2006;1098:126–128.
- Wilson HD, Toepfer VE, Senapati AK, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment is comparable to acetylsalicylic acid treatment in an animal model of arthritis. *J Pain*. 2007;8:924–930.
- Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain*. 1988;33:87–107.
- Mychaskiw G 2nd, Pan J, Shah S, et al. Effects of hyperbaric oxygen on skin blood flow and tissue morphology following sciatic nerve constriction. *Pain Phys*. 2005;8:157–161.
- Thompson CD, Uhelski ML, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment decreases pain in two nerve injury models. *Neurosci Res*. 2010;66:279–283.
- Li F, Fang L, Huang S, et al. Hyperbaric oxygenation therapy alleviates chronic constrictive injury-induced neuropathic pain and reduces tumor necrosis factor- $\alpha$  production. *Anesth Analg*. 2011;113:626–633.
- Gu N, Niu JY, Liu WT, et al. Hyperbaric oxygen therapy attenuates neuropathic hyperalgesia in rats and idiopathic trigeminal neuralgia in patients. *Eur J Pain*. 2012;16:1094–1105.
- Han G, Li L, Meng LX. Effects of hyperbaric oxygen on pain-related behaviors and nitric oxide synthase in a rat model of neuropathic pain. *Pain Res Manag*. 2013;18:137–141.
- Yamaguchi H, Naito H. Antinociceptive synergistic interaction between morphine and n omega-nitro 1-arginine methyl ester on thermal nociceptive tests in the rats. *Can J Anaesth*. 1996;43:975–981.



21. Quock LP, Zhang Y, Chung E, Ohgami Y, Shirachi DY, Quock RM. The acute antinociceptive effect of HBO(2) is mediated by a NO-cyclic GMP-PKG-KATP channel pathway in mice. *Brain Res.* 2011;1368:102–107.
22. Zhao BS, Meng LX, Ding YY, Cao YY. Hyperbaric oxygen treatment produces an antinociceptive response phase and inhibits astrocyte activation and inflammatory response in a rat model of neuropathic pain. *J Mol Neurosci.* 2014;53:251–261.
23. Eftedal OS, Lydersen S, Helde G, White L, Brubakk AO, Stovner LJ. A randomized, double blind study of the prophylactic effect of hyperbaric oxygen therapy on migraine. *Cephalalgia.* 2004;24:639–644.
24. Fife CEM JS, Berry JM, Sutton TE. Hyperbaric oxygen and acute migraine pain: preliminary results of a randomised blinded trial. *Undersea Biomed Res.* 1992;19:106–107.
25. Hill RK. A blinded, crossover controlled study of the use of hyperbaric oxygen in the treatment of migraine headache. *Undersea Biomed Res.* 1992;19:106.
26. Myers DE, Myers RA. A preliminary report on hyperbaric oxygen in the relief of migraine headache. *Headache.* 1995;35:197–199.
27. Wilson JR, Foresman BH, Gamber RG, Wright T. Hyperbaric oxygen in the treatment of migraine with aura. *Headache.* 1998;38:112–115.
28. Bennett MH, French C, Schnabel A, Wasiak J, Kranke P. Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. *Cochrane Database Syst Rev.* 2008;3:CD005219.
29. Di Sabato F, Fusco BM, Pelaia P, Giacobozzo M. Hyperbaric oxygen therapy in cluster headache. *Pain.* 1993;52:243–245.
30. Di Sabato F, Giacobozzo M, Cristalli G, Rocco M, Fusco BM. Effect of hyperbaric oxygen on the immunoreactivity to substance P in the nasal mucosa of cluster headache patients. *Headache.* 1996;36:221–223.
31. Hardebo JE. The involvement of trigeminal substance P neurons in cluster headache. An hypothesis. *Headache.* 1984;24:294–304.
32. Di Sabato F, Rocco M, Martelletti P, Giacobozzo M. Hyperbaric oxygen in chronic cluster headaches: influence on serotonergic pathways. *Undersea Hyperb Med.* 1997;24:117–122.
33. Bellato E, Marini E, Castoldi F, et al. Fibromyalgia syndrome: etiology, pathogenesis, diagnosis, and treatment. *Pain Res Treat.* 2012;2012:426130.
34. Fassbender HG, Wegner K. Morphology and pathogenesis of soft-tissue rheumatism. *Z Rheumaforsch.* 1973;32:355–374.
35. Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen pressure in primary fibromyalgia. *Scand J Rheumatol.* 1986;15:165–173.
36. Yildiz S, Kiralp MZ, Akin A, et al. A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy. *J Int Med Res.* 2004;32:263–267.
37. Wolfe F, Smythe HA, Yunus MB, et al. The American college of rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum.* 1990;33:160–172.
38. Kiralp MZ, Yildiz S, Vural D, Keskin I, Ay H, Dursun H. Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome. *J Int Med Res.* 2004;32:258–262.

Copyright of Pain Practice is the property of Wiley-Blackwell and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.