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Review article

The effectiveness of hyperbaric oxygen modalities against vascular component of traumatic brain injury

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ABSTRACT

Intracranial bleeding occurs in a substantial percentage of patients with neurotrauma and may gravely impact clinical outcomes. Hyperbaric oxygen has been tested for traumatic brain injury (TBI), however its effect on the hemorrhagic component of TBI remains poorly understood. The characteristics of intracranial bleeding vary in different animal models of TBI. HBO appears to combat vascular injury and to reduce hemorrhagic complications. While the number of studies is limited, a decrease in intracranial bleeding and protection from BBB destruction may determine the effectiveness of HBO in TBI.

Based on the results of experimental and clinical studies, this review advocates that intracranial bleeding in the course of TBI is the indispensable aspect of outcome assessment and postulate the search for new markers of traumatic vascular injury responsive to oxygen treatment.

1. Introduction

Brain trauma that is the third frequent cause of neurological impairment and is also a major cause of neurologic dysfunction in young individuals.[1] TBI in humans can be classed into closed head injury, penetrating. injury, and explosive blast injury or more broadly into focal or diffuse type.[2] Upon diffuse injuries the only focal injury can be bleeding into the subarachnoid space (subarachnoid hemorrhage – SAH), which is the most common type of vascular injury in brain trauma. It is however usually minor. Contusions are also kinds of traumatic vascular injury, particularly to small blood vessels.[2] Contusions produced by focal impact models in rats and mice gradually increase over time, resulting in a dramatic atrophy that may persist for up to 1 year following injury.[3]

2. The involvement of hemorrhage in traumatic brain injury

Interestingly, traumatic brain injury of all types may include components triggered by hemorrhagic events, such as inflammatory response or tissue hypoxia.[4] Concordantly, hypoxia inducible factor 1α (HIF-1α) is upregulated in cerebral tissues after TBI due to tissue hypoxia (44% of severe cases) and neurotransmitter excitotoxic release.[5] TBI invariably involves the damage to blood vessels and can be associated with microvascular injury that results in release of brain cell products into the peripheral circulation.[6,7] In addition, vessel disruption exposes neural tissue to a variety of blood components.[8] Petechial hemorrhages that occur in diffuse vascular injury, may promptly lead to a deadly outcome. Intracranial bleeding complicates 40–50% of brain traumas and largely contributes to an unfavorable course of disease.[9] Intracranial hemorrhage in patients with traumatic brain injury, especially when hematoma volume exceeds 50 mL, results in poor neurologic outcomes and high mortality.[10] In turn, traumatic cerebral microbleeds have been proposed as markers of long-term clinical and intellectual outcomes.[11,12] As in primary hemorrhagic stroke, the bleeding after trauma may show a tendency towards expansion.[10,13] Delayed post-traumatic hematomas can also occur.[2] The traumatic cerebral *vascular injury* (TCVI) underlies a significant fraction of TBI-related disability.[14] In experimental studies, the volume of hemorrhage correlated with functional outcomes at 30 days ($p < 0.05$) after TBI in rabbits.[15] Although subdural hematoma is a common consequence of TBI, it is relatively understudied.[3] The same applies to cerebral microbleeds and microvascular injury, especially in older TBI victims.[16–18] TBI acutely and deeply disturbs vascular complexity, thus leading to hemodynamic and behavioral alterations.[19] Brain edema, intracranial pressure (ICP), cerebral blood flow, cognitive performance, lesion volume, and neuronal loss have been commonly taken into account for the assessment of mild, moderate, and severe TBI, and effects of investigational therapies, while the impact of hemorrhage/iron load has been less acknowledged.[14,20]

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3. The use of hyperbaric oxygen for traumatic hemorrhagic brain injury

Methods of increasing the effectiveness of treatment for brain trauma and traumatic hemorrhage are still being searched for, especially since mechanical traumas as those caused by accidents will be never completely eliminated. One of the treatments for traumatic brain injury is hyperbaric oxygen therapy when patients breathe 100% oxygen above 1.0 atmosphere absolute (ATA).[21] When there is a significant mass effect from hematoma or a contusion with a significant volume of blood, the surgical intervention is warranted.[22] In these cases HBO can be considered as supportive therapy in combination with surgery. HBO can be also investigated in combination with pharmacological agents capable of reducing intracranial hemorrhage progression after TBI.[23] In milder cases and for the chronic sequelae of TBI, HBO alone may prove beneficial. The rationale behind HBOT includes combating cerebral hypo-perfusion in tissues adjoining traumatic lesion and hematoma. Hyperbaric therapy, which decreases ICP due to the relief of brain edema and/or a reduced cerebral blood volume, alleviates the collapse of microcirculation.[24] It may also acutely reduce bleeding by constricting cerebral arterioles. On a molecular note, HBO has been shown to reduce HIF-1α in the post traumatic brain (lateral fluid-percussion injury rat model; LFP) as well as to reduce the TBI-induced hippocampal apoptosis and to prevent blood–brain barrier (BBB) destruction.[25] The involvement of HIF-1α and its downstream targets in the BBB disruption has been well documented.[26] Down-regulation of HIF-1α after TBI (LFP) reduced proapoptotic protein BNIP3 and conferred neuroprotection in the mouse brain.[27]

4. Hemorrhagic events in animal models of traumatic brain injury

Numerous animal models were developed for research aiming at replication of particular type of traumatic brain injury.[28] They enable studies of mechanisms of injury and investigational therapies, with increasing application of stem cells.[29] TBI models are generally better standardized when compared to the models of cerebrovascular diseases. Especially fluid percussion injury (FPI) and cortical controlled impact (CCI) models are highly reproducible. Stereotactically applying traumatizing stimulus with a controlled force to a head appears to be more consistent than the e.g. complex procedures used in cerebral vessel occlusion for brain ischemia that may produce a greater variability of the brain insult severity. In addition, due to biomechanics of injury that is similar to that in humans, animal models of traumatic brain injury leave little doubt as to whether they replicate clinical situation. Thus the use of TBI animal model may provide a high consistency of results, what may strengthen their translational potential.

Remarkably, however, the bleeding may occur in all commonly used models.

Fluid percussion injury (FPI) model is suitable for investigations of blunt-force trauma.[30] FPI resulting from fluid pressure pulse can replicate intracranial hemorrhage and brain swelling.[7] Besides, this model is used for the studies of repetitive HBO on remyelination and sensorimotor function recovery.[31] TBI in this model induced cerebral hematomas and iron deposition in rats brain and several authors postulated studies of the role of iron released from the cerebral hematoma in TBI.[32]

The controlled cortical impact (CCI) produces traumatic brain injuries with neuropathological changes seen in human TBI.[33] In this model, a rod hits the surgically exposed cortical dural surface, what can cause blood vessel breakage and acute subdural hematoma.[34] The bleeding is robust and leads to acute subdural hematoma and BBB dysfunction.[35] There is more hemorrhage than observed in FPI. Time, velocity and depth of impact can be controlled. Moderate and severe cortical impact model (CCI) produces an impairment of long-term spatial learning-memory ability. It also produces hippocampus damage and white matter injury.[36]

Weight drop models (WD) of TBI replicate focal cerebral contusions and produce injury after craniotomy or the closed head injury. Some variants of WD have been developed to model sports concussions followed by functional disturbances without structural injury that could be detected by conventional imaging techniques.[37] Weight-drop impact acceleration injury following craniotomy, where guided weight is used, produces hemorrhages followed by cavity formation in white matter, directly under the contused cortex, however with a relatively high variability in injury severity. Marmarou's weight drop model replicates closed head injury, as impact force is applied to the cranium. It produces diffuse axonal injury, petechial hemorrhages and widespread damage to microvasculature.[38] Severely injured animals also showed traumatic subarachnoid hemorrhage and hemorrhagic contusions.[39] These models can replicate diffuse axonal injury (DAI) that often occurs as a result of motor vehicle accidents.[37] Clinically, brain MRI investigations with diffusion tensor imaging (DTI) techniques has been used to effectively evaluate the microstructure of white matter and nerve fibers morphology.[40] The DAI analysis established in laboratory settings is based on amyloid precursor protein (APP) that may be immunodetected as early as 2–4 h after trauma. The routine histological stains show swollen axons as eosinophilic spheroidal structures. In severe diffuse axonal injury cases, there are widespread acute white matter hemorrhages.[41]

The cryogenic model of TBI is termed cold-injury-induced-brain-trauma (CIBT). A deeply cooled metal rod is applied by craniotomy in order to produce a cryogenic lesion.[42] The model of cryogenic injury bears a resemblance to a cerebral hemorrhagic contusion and is also used to model vasogenic brain edema.[43,44]

The penetrating ballistic-like brain injury (PBBI) replicates the rapid temporary brain cavitation caused by a projectile entering the brain.[45] The bleeding is extensive in this model owing to the penetrating nature of the injury. These models may use experimental guns that emulate the shooting of commonly used firearms, thereby inflicting head wounds, as those seen in humans.[46,47]

Blast injury models replicate rapid transmission of acoustic wave through the brain tissue and blast winds, and is a major cause of TBI in the modern war theatre.[41] In addition, the hemorrhagic shock and hypovolemia may complicate blast injury, as observed in the victims of terrorist attacks.[48] Although blast injury is usually mild, severe cases are known as well. Typically, blast-exposed mice showed no macroscopic tissue damage or haemorrhage several weeks after exposure.[49] These models use compressed air to induce blast wave. More often than contusion, DAI and petechiae can be found. There may be a vasospasm, similarly as in clinical cases.[17] Non impact blast injury is also characterized by extreme hyperaemia.[50] Clinically, blast injury quite often can result in posttraumatic stress disorder characterized by neuropsychiatric symptoms indicative of frontal lobe dysfunction.[51] In turn, postconcussion syndrome is a set of physical, cognitive and behavioral symptoms that stem from persisted brain injury after mild TBI-induced concussion.[52]

Repeated mild TBI models generate concussion as well as subconcussion that occur in a wide variety of sports characterized by repeated head impacts. Acutely, microhemorrhages are common, followed by a presence of hemosiderin and hematoidin-laden macrophages, whereas the resolution of hemorrhagic lesions can be prolonged for months.[41] A recent study of TBI in juvenile rats found the strongest correlation between cell death and the presence of extravascular blood, which could serve the purpose of stratification of injury severity. Concordantly, the mildest TBI

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had the least amount of blood visible on susceptibility weighted imaging (SWI)-identified intracerebral hemorrhage method.[53,54]

The surgical brain injury model replicates mechanical damage to the brain and cerebral vascular tissues, introduced during brain surgery.[55] Even though the bleeding is controlled with intraoperative packing and saline irrigation in this model, the impact of extravasated blood may correspond to intra-operative bleeding as seen during neurosurgical operations.[56]

In summary, all these models to some extent also replicate traumatic cerebral microvascular injury (TCVI) characterized by the damage to small blood vessels in the brain. It may occur as a consequence of neurotrauma e.g. in the athletes[6] and can result in blood flow occlusion (stasis), blood–brain barrier disruption, reactive neuroinflammation, and the hemorrhage, most often microbleeds.

5. The assessment of hyperbaric oxygen effect on vascular injury upon brain trauma

However, rare are the studies that examine the effect of investigational HBO therapy on cerebral vascular injury and hemorrhagic changes upon traumatic brain injury.[14] It seems that the ability of HBO to reduce hemorrhagic component of neurotrauma might provide an important outcome criterion. Intracranial blood deposits resulting from trauma can be assessed both histologically e.g. by using Perls' iron stain as well as with MRI scan, especially employing susceptibility weighted imaging (SWI) sequence, sensitive to the iron content of extravascular blood that appear as dark regions on MRI.[12,53] Furthermore, post-traumatic lesions, often being a contused tissue i.e. damaged tissue mixed with blood, can be also examined by using MRI presentation using the SWI method. Blood deposits after TBI can be determined by histogram analysis of lesion T2 values as well.[57]

In addition, testing the alterations in brain water content, indicating dynamics of brain edema to a large degree reflects the severity of injury in the microvascular compartment and provides a good approximation of response to treatment.[13,58]

6. Experimental studies of hyperbaric oxygen for traumatic vascular brain injury

6.1. Studies of hyperbaric oxygen administered after experimental traumatic brain injury

However, the effectiveness of HBO against traumatic vascular injury may vary in different brain trauma injury models that replicate various clinical scenarios. It can also depend of different treatment regimens. Several studies showed improved outcomes of traumatic brain injury when the hyperbaric oxygen was used after the brain insult.[59] In the lateral fluid percussion injury study in rats, 2ATA HBOT started 3 h after surgery, and was given 1 h/daily for three consecutive days. The authors reported that this model reproduced petechial intraparenchymal and subarachnoid hemorrhages. At 4 days after HBO treatment they found over 3-fold increase in the number of BrdU positive, newly forming endothelial cells as compared to NBA control, indicative of angiogenesis. Thus HBO could stimulate the repair process in milieu of vascular injury. They also found that the cortical lesion volume was reduced by 84.6%.[60] This is by far the most impressive impact of HBO on the extent of brain injury reduction across experimental studies. In another study by Yang et al. using this model, daily HBO treatments (1.5 ATA, 90 min each) administered for 15 days reduced excess brain water content by 41.6%, as determined 15 days after TBI. This beneficial effect was observed when the first treatment started at 6 h after TBI, while more delayed treatment was ineffective.[25] Three HBO sessions, 90 min. each, were administered at 2.5 ATA at 1 h, 24 h and 48 h after brain trauma induced by cold injury in the rabbit. In the control group the lesion exhibited peripheral hemorrhages adjacent to the edematic zones. HBO significantly reduced edematic areas in the brain by 44.4% on day 4, while the area of trauma-induced necrosis was reduced by 18.6%.[43]

As revealed by Chen et al., neuroprotection of HBO (1 h at 2ATA) against CCI-induced brain injury can be mediated by interleukin-10 (IL-10).[61,62] IL-10 is known to inhibit brain injury around hematoma.[63] Moreover, HBO upregulated the vascular expression of tight junction proteins, including zonula occludens-1 (ZO-1) and claudin-5, thus improved the blood–brain barrier after TBI.[62]

6.2. Hyperbaric oxygen preconditioning for vascular injury in brain trauma

Beside post-injury treatment studies, HBO was also experimentally applied as part of the preconditioning paradigm. Surgical brain injury (SBI) is particularly amenable to preconditioning treatment, as many surgeries are planned; thus HBO-PC could be applied as the preventive measures in anticipation of injury. SBI model is used to replicate the injury of cerebral tissue during neurosurgical procedures, however it can be also considered in approximating the conditions upon certain traumas sustained during combat operations (frontal lobe lesions). It replicates not only tissue loss, pulling and tearing in general mechanical damage but also the bleeding that occurs during neurosurgical procedures.[64]

Indeed, HBO-PC (5 sessions at 2.5 ATA) reduced neurological deficits at 24 and 72 h after SBI in mice. Upon preconditioning there was a reduction of brain edema by 39.4% and 55.9% at 24 and 72 h, respectively, in the right frontal lobe.[65] HBO-PC also reduced blood deposits and the volume of lesioned tissue.[64] Clearly, the effect of HBO-PC was not diminishing over time after the insult, despite no additional HBO treatments were applied after conditioning. Interestingly, NS398, the inhibitor of cyclooxygenase-2 (COX-2), abolished the lowering effect of HBO-PC on brain edema. This approach verified the requirement of COX-2 participation in the mechanism of preconditioning with hyperbaric oxygen prior to surgical brain trauma. HBO-PC effect appeared to be delayed, as no benefit was noted when HBO (2.5ATM, 1 h) was applied 2 h prior to surgical injury.[66]

In the weight drop rat model of TBI at high altitude, 5HBO-PC (2.5ATA) significantly reduced the percentage of brain water content after TBI and neuropathological alterations including hemorrhages. Noticeably, preconditioning reduced the number of MMP-9-positive cells after TBI, which suggests that the mechanism of HBO preconditioning-induced neuroprotection may be related to its inhibitory effect on MMP-9 expression.[67] From the aforementioned TBI studies comes an indication that HBO preconditioning regimen that is either too short or too extensive may not provide neuroprotection.

6.3. Neuroimaging of bleeding in traumatic brain injury

Interestingly, both pre- and post-treatment with HBO reduced the susceptibility weighted imaging (SWI)-identified intracerebral hemorrhage following repetitive mild traumatic brain injury (rmTBI). In animals receiving HBO for cortical controlled impact injury 3 days apart, a 3-fold reduction in hemorrhage volumes was observed, when compared to shams.[68] Moreover, in juvenile rmTBI model (30 days old rats, equivalent to human age of 12 years), HBO at 2 ATA, started at 1 day after the initial injury and continued for 3 days, reduced MRI-identified hemorrhagic volume, approximately 3-fold, at 24 h post 2nd impact, and improved tissue histopathology at 14 days.[69]

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The broader use of MRI in experimental studies would allow to more meticulously examine the hemorrhagic component of TBI. Also using other techniques such as Pearls' iron stain, iron content assays and molecular biology methods, researchers can examine the role of blood degradation products and iron metabolism pathways in hemorrhagic and traumatic injuries. The involvement of iron in the pathogenesis of TBI and its role as a priming factor for further neurodegenerative diseases has been postulated.[70] Recent resurgence of research in this regard can be observed in case of SAH.[71,72]

6.4. Mechanisms of hyperbaric oxygen for neurotrauma

It can be postulated that the impact of HBO on neurotrauma may in part depend upon the modulation of HIF-1 downstream targets, similar as for molecular hydrogen based therapeutics or anti-inflammatory drugs.[73–75] Other mechanisms may include apoptosis reduction, vascular repair and expedited hematoma resolution.[76] Interestingly, HBO has a potential to increase the beneficial effect of stem cell transplantation for CNS injuries, as seen when mesenchymal stem cells were administered for the repair of spinal cord injury or pressurized fluid brain trauma.[77,78] Another issue that deserves study is to what degree HBO treatment is capable of enhancing neurovascular unit repair after CNS injury based on the activation of endogenous vasculogenic stem cells.[79–81]

6.5. The validity of different hyperbaric oxygen modalities

In general, although the data are limited, the comparison between HBO pretreatment and post-treatment for TBI condition indicates grater benefit for post-injury therapy. In addition, preconditioning with HBO due to hyperbaric component may to some extent provide a subinjurious oxidative stress on the preconditioned cells, which than may or may not be followed by a post-traumatic injury. Hence the risks for healthy controls subjected to HBO or high oxygen and hyperbaria should be carefully examined. On the other hand, it is well known that HBO can reduce oxidative stress when administered after traumatic injuries, either through decreased free radical formation or enhancement of endogenous antioxidant defenses.[82]

6.6. Hyperbaric oxygen for traumatic brain injury in the clinical setting

The effectiveness of HBO in the aspect of traumatic brain injury was tested in the clinical setting, where several clinical trials using 1.5–2 ATA HBO against TBI, brought mixed results. Studies by Rockwold (severe TBI) and Boussi-Gross (mild TBI) presented encouraging results,[83,84] whereas studies by Cifu (post-concussive syndrome) yield negative results.[85] Wolf et al. (mTBI/PCS) reported only subgroups with favorable therapeutic responses.[86] Intriguingly, HBO may appear as more effective in severe TBI where the hemorrhagic component is more common. Although the "Hyperbaric Oxygen Therapy in Chronic Stable Brain Injury" (HYBOBI) study reported the safety of HBOT (60 daily HBO sessions at 1.5 ATA 100% oxygen) for stroke, anoxia or trauma, the neurological results were inconclusive, despite clinical improvement observed in many participants. The investigators advocated further carefully designed clinical trials as worth to be conducted.[87] Thus the HYBOBI2 trial (A Double-blind Randomized Trial of Hyperbaric Oxygen Versus Sham for Persistent Symptoms After Brain Injury) led by dr. Weaver is still a recruiting, randomized, double-blind study that uses two sets of 40 hyperbaric oxygen sessions (100% oxygen at 1.5 atmospheres absolute, 60 min) with repeated assessment, and is scheduled to end in 2021. Other trials are underway, recruiting patients with traumatic brain injury that have abnormal findings, including hemorrhagic cortical contusions or petechial hemorrhages or foci of altered signal that represents white matter damage.[88,89] In contrast, quite a few small clinical studies with a limited number of patients show promise of HBO use for TBI. MRI findings suggest that HBOT can induce cerebral angiogenesis, nerve fibers regeneration and improved cognitive scores in post-concussion syndrome patients ($n = 15$) treated with HBOT (60 sessions at 2 ATA) 6 months to 27 years (10.3 ± 3.2 years) from injury.[90] Based on the results from 32 patients who completed the HBO trial at 1.5 ATA, Mozayeni et al. detected neurocognitive improvement in the majority of measures.[91] HBO was found to be worthy of clinical applications in patients with TBI. The repeated treatment seems to be necessary to achieve therapeutic goals in patients with TBI.

6.7. Putative biomarkers for hyperbaric oxygen treatment in traumatic vascular injury

Nevertheless important are the markers of excessive treatment that need to be implemented in humans, although they have been long determined in the animals studies that frequently include comet assay, LPO assay and protein oxidation assays, often directly on cerebral tissues. As for biomarkers of oxidative stress in humans, they need to fulfill an easy to obtain sample criterion, hence e.g. blood tests would be preferred.[92,93]

The STAIR recommendations and RIGOR guidelines refer to good laboratory practice, that needs to be maintained for preclinical studies in order to advance to clinical trials, are particularly important for the studies of TBI complicated by hemorrhage, where outcome measures are subject to dynamic changes and can be elusive. As for HBO treatment, it would be worthwhile to switch from viewing hemorrhage as plaguing the purity of animal models of TBI to viewing it as a vital subject to therapeutic assessment. The reviewed herein impact of HBO on the extent of bleeding and percent water content reveals the particularly high effectiveness reached in rmTBI model when HBO is administered at 2 ATA, both including pre- and post-treatment. The use of MRI, where available, may increase quantitation confidence by allowing a total lesion assessment in the treatment group, compared to the standardized lesion in untreated controls.[68] As postulated for hematoma enlargement and BBB disruption after TBI, the circulating miRNA levels should be also investigated in search for biomarkers of vascular injury upon brain trauma.[94,95]

Another viable proposal may suggest to look at the iron metabolism proteins e.g. hepcidin that are involved in iron dependent mechanisms of cell death, including ferroptosis.[72] Novel strategies of TBI management may require combined HBO treatment and other interventions, e.g. new classes of histone deacetylase inhibitors.[96]

7. Conclusions and future directions

While only scarce clinical studies show the benefits from HBOT for brain ischemia, there is preliminary evidence that HBO may be effective for patients with TBI. The design of future clinical trials needs to address the selection of appropriate targets in evaluation, gender and age recognition, time window to commence the therapy, and determination of responsive population, which would help to avoid loss of translational potential.[97] In addition, humans have gyrencephalic brains, what calls for a caution when interpreting the results of research performed on lissencephalic rodents.[39] There is relatively little white matter in rodents, greater tolerance to acceleration forces, distinct bony structures of the skull and rigidity of tentorium cerebelli.[98]

In order to evaluate HBO-based modalities, future studies should calculate not only the reductions in edema but a reduction

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in intracranial bleeding, as both appear to be viable indicators of brain damage, suitable for traumatic injury assessment. These indicators of brain injury reduction with HBOT should be calculated in order to estimate the efficacy of different HBO treatment regimens across studies. There are no targeted therapeutic interventions for bleeding or edema development in TBI.[53] However, hyperbaric oxygen has a profound impact on the extent of the hemorrhagic complications after TBI. Since the diminution of hemorrhagic burden varies amongst different models of TBI, it requires study whether the most significant reduction of bleeding complications may correspond with the greatest therapeutic potential of HBO. The ability of HBO to reduce hemorrhagic sequelae of TBI might stand for its overall beneficial effects for this condition.

The assessment of hemorrhagic burden lies within the search for biomarkers of TBI responsive to HBO treatment. The elaboration of molecular markers that could be specific for hemorrhagic aspect of TBI is warranted.

Conflict of interest

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