Application of hyperbaric oxygen in liver transplantation

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Abstract

In recent years, hyperbaric oxygen (HBO) has been used in the treatment of a lot of diseases such as decompression sickness, arterial gas embolism, carbon dioxide poisoning, soft tissue infection, refractory osteomyelitis, and problematic wound, but little is known about its application in liver transplantation. Although several studies have been conducted to investigate the protective effects of HBO on liver transplantation and liver preservation, there are still some controversies on this issue, especially its immunomodulatory effect. In this short review, we briefly summarize the findings supporting the application of HBO during liver transplantation (including donors and recipients).

Key words: hyperbaric oxygen; liver transplantation; liver ischemia/reperfusion; oxidative stress; pre-conditioning; immunomodulation; liver regeneration; organ preservation

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Introduction

Hyperbaric oxygen (HBO) therapy is defined as the inhalation of 100% oxygen under elevated atmospheric pressure, that is, at a pressure higher than the pressure found on the surface of the earth at sea level, which is defined to be 100 kPa (Camporesi and Bosco, 2014). In 1937, Dr. Albert Behnke serving in the U.S. Navy first suggested the use of oxygen at elevated pressures during recompression therapy for the bends (now known as decompression sickness, DCS). With the improvement of understanding of HBO, it has been widely used as an adjunctive treatment for various pathological states, predominantly related to hypoxic and/or ischemic conditions, including arterial gas embolism, carbon dioxide poisoning, soft tissue infection, refractory osteomyelitis, and problematic wound, and the indications to HBO treatment are still increasing (Wang et al., 2014; Fife et al., 2016). For example, it is also applied in the treatment of cluster headache, post-traumatic stress disorder and autism spectrum disorder (Petersen et al., 2014; Eve et al., 2016; Xiong et al., 2016). As compared to pharmacotherapy, HBO seems to be safe for patients because its side effects are rare and oxygen toxicity appears primarily when it is used at very high doses and for a longer duration than recommended (Camporesi, 2014).

Liver transplantation is widely accepted as the definitive treatment in end-stage liver disease, selected liver malignancies and acute liver failure (Zarrinpar and Busuttil, 2013). The advances in patient selection criteria, organ preservation, operative techniques, perioperative care and efficacy of immunosuppressive agents significantly improve the outcome of liver transplantation. However, ischemia, preservation and reperfusion injury (IPRI) and immune rejection are two major problems causing transplantation failure (Zarrinpar and Busuttil, 2013). Studies have shown that HBO is protective against organ ischemia/reperfusion (I/R) injury (Zhai et al., 2016) and has the immunomodulatory effects (Feldmeier et al., 2003). Thus, some investigators have attempted to investigate the application of HBO in liver transplantation. In this paper, we briefly summarized

the findings on the application of HBO in liver transplantation from *in vitro* and *in vivo* studies.

Rationale for the Clinical Application of Hbo in Liver Transplantation

Protective effects of HBO on liver I/R

During the liver transplantation, the donor liver undergoes ischemia before collection, then is preserved and thereafter undergoes reperfusion, which may significantly cause damage to the liver. Liver I/R has been a major challenge in the liver transplantation (Yamanaka et al., 2014). Increasing studies indicate that liver I/R is closely related to the initiation and severity of acute rejection after liver transplantation (Xiao et al., 2010). Some studies have confirmed that HBO is protective on liver I/R injury (Baldim et al., 2013; Silveira et al., 2014). However, Chaves et al. (Chaves, 2009, 2016) found the effects of HBO on liver I/R injury were dependent on the time of HBO administration: A favorable effect was obtained when HBO was administered early during ischemia, but HBO given in later periods of reperfusion was associated with a more severe sum index percentage of liver damage.

In the liver I/R, a large amount of inflammatory mediators and chemokines are produced by inflammatory cells and other cells, which then activate leukocytes, platelets and endothelial cells. The subsequent expression of adhesion molecules on vascular endothelial cells may promote the adhesion of leukocytes to endothelial cells, leading to the aggregation and infiltration of leukocyte into cells. HBO may reduce the migration and adhesion of leukocytes *via* decreasing the expression of adhesion molecules CD11 and CD18, two ligands of intercellular cell adhesion molecule-1 (ICAM-1) (Jones et al., 2010). *In vitro* experiment indicates that single HBO treatment not only reduces the expression and polarization of CD18 and CD11, but also decreases ICAM-1 expression on endothelial cells (Khiabani et al., 2008), which may attenuate the adhesion of leukocytes to endothelial cells. The inhibition of endothelial-neutrophil interaction has been ascribed as a mechanism underlying the protective effects of HBO on I/R injury (Buras and Reenstra, 2007).

Nitric oxide (NO) has dual roles in the liver I/R injury. Endothelial NO synthase (eNOS) is mainly expressed in endothelial cells and may dilate the microcirculation in case of hypoxia. On the contrary, inducible NO synthase (iNOS) may be activated by interleukin-1 (IL-1), tumor necrosis factor α (TNF-α) and lipopolysaccharides (LPS) in neutrophils and macrophages, leading to the elevated production of NO, which may increase the vascular permeability and cause damage to tissues. The toxic effects of iNOS derived NO is largely ascribed to the reaction between NO and superoxide, but not to the NO *per se*. *In vitro* and *in vivo* studies have shown that HBO is able to selectively induce the activation of eNOS and inhibit the iNOS activation, exerting protective effects (Sakoda et al., 2004; Giannone et al., 2012).

In the liver I/R injury, a large amount of reactive oxygen species (ROS) are produced in cells, especially in inflammatory cells, causing damage to the cell membrane and organelles *via* lipid peroxidation, protein nitration and DNA modification. There is evidence that HBO is able to inhibit I/R induced oxidative stress (Koca et al., 2010). In addition, HBO is also able to inhibit the hepatocyte apoptosis to exert hepatoprotective effects (Chaves et al., 2009). HBO may improve liver I/R injury *via* inhibiting hepatocyte apoptosis in ischemia phase, but HBO in reperfusion phase fails to suppress the hepatocyte apoptosis (Chaves et al., 2009). This may be explained as that HBO administered in ischemia phase improves the oxygen supply in tissues, which attenuates the production of ROS in reperfusion phase. Thus, it is recommended that early administration of HBO in patients receiving liver transplantation may improve their prognosis. A recent study also indicates the hepatoprotective effects of HBO are time-dependent (Losada et al., 2013).

Immunomodulatory effects of HBO

In animal studies, HBO is shown to possess immunomodulatory effects on the organ (Song et al., 2010) and cell (Aljitawi et al., 2014) transplantation, which is mainly characterized by the inhibition of humoral immunity and cellular immunity. The clinical indicators of overall immune suppression after HBO exposure include a decreased response to antigens, a weakening of autoimmune responses and a slower rejection of allografts (Brenner et al., 1999). Kaufman et al. (2004) found HBO was able to depress cell-mediated immunity in mice, which could be reversed by intravenous administration of autologous macrophages. T lymphocytes play a crucial role in the immunity, and HBO may also regulate the functions of T lymphocytes. MacKenzie et al. (2000) found pretreatment of allogeneic stimulator cells with HBO culture (HOC [95% O_2, 5% CO_2, 172 kPa]) abrogated cytotoxic T lymphocyte (CTL) activity, proliferative responses, and interferon (IFN) gamma production in a 7-day mixed lymphocyte reaction (MLR). There is evidence showing that the effects of HBO on lymphocytes are related to the pressure of HBO. Our previous study showed HBO had dual roles in the regulation of T lymphocyte function: HBO at 100 kPa for 60–90 minutes was able to improve the activity of cytotoxic T lymphocytes (CTL), but HBO at 150 kPa for 30–60 minutes inhibited this activity (Liu et al., 2009). In addition, HBO may inhibit

the development of both sheep erythrocyte-specific B cells and helper T cells after the immunization. Spontaneous immunoglobulin production of NZB and MRL/lpr spleen cells was also significantly suppressed by HBO. Furthermore, autoimmune symptoms such as proteinuria, facial erythema and lymphadenopathy in MRL/lpr mice were significantly inhibited after long term HBO exposure (Saito et al., 1991). Xu et al. (1997) also found different types of immune cells had distinct sensitivities to HBO, and $CD4^+CD8^+$ double positive cells in the thymus and $B220^+$ B cells in the spleen were more sensitive than $CD4^+$ or $CD8^+$ single positive T cells in the thymus, and Thy-1^+ T cells in the spleen, respectively. Ueno et al. (1999) investigated the immune function of 12 non-cirrhotic patients who underwent elective hepatectomy for liver cancer after 2 courses of HBO treatment (200 kPa, 100% O_2, 60 minutes) at 3 hours and 24 hours after hepatectomy. Their results showed the peak levels of polymorphonuclear leukocyte elastase (PMNE) and thrombomodulin (TM) were diminished and delayed, and the elevated expression of CD18 (a protein related to leukocyte adhesion) was clearly suppressed after HBO exposure. In the rats with acute pancreatitis, Bai et al. (2014) found HBO could induce the apoptosis of peripheral blood lymphocytes to attenuate the disease.

Of course, there are conflicting results about the effects of HBO on immune function. Feldmeier et al. (1987) found no effects on a broad range of immune parameters in healthy human volunteers exposed to a typical clinical course of HBO. The results from a study of Gassas et al. (2011) showed HBO therapy, as a sole agent, did not delay skin graft rejection in a highly immunogenic mouse model. Xu et al. (1997) proposed that lymphocyte subpopulations from normal and autoimmune mice displayed differential sensitivities to HBO. Thus, some investigators propose that the effects of HBO are closely related to the pressure, duration and sessions of HBO administered, the host status and the tissue oxygenation.

Anti-infection capability is another characteristic of HBO. Studies have shown that the functions (especially the anti-bacterial activity) of neutrophils are closely related to the oxygen tension (McGovern et al., 2011). When the partial oxygen pressure (PO_2) is higher than 30 mmHg (1 mmHg = 0.133 kPa), the killing activity of neutrophils is normal; the PO_2 lower than 30 mmHg significantly compromises the respiratory burst (a phenomenon representing the killing activity of immune cells) in these cells, which might be ascribed to the impairment of mitochondrial respiratory chain (Wiese et al., 2012). Under this condition, HBO may improve the anti-bacterial activity of immune cells (Pakman, 1971; Bornside et al., 1975), and enhance the bactericidal effect of antibiotics (Kolpen et al., 2016). This may be helpful for the prevention of post-operative infection.

Effects of HBO on liver regeneration

It is well known that the liver has a potent regenerative capability. After liver injury, the liver will manifest active regeneration to repair the injury. Study has shown that liver regeneration is associated with oxygenation. Yoshioka et al. (1998) found the liver regeneration was proportional to the oxygen consumption, and after liver injury, the metabolism requires an increased amount of oxygen for mitochondrial oxidative phosphorylation to restore hepatic energy charge. Shimizu et al. (2000) also found the increase in portal blood flow and oxygen supply produced by arterialization of the portal vein had beneficial effects on hepatic energy metabolism and liver regeneration. In the accelerated liver regeneration, oxygen for normal regeneration will be insufficient. Theoretically, HBO may increase the oxygen for the mitochondrial oxidative phosphorylation, leading to the elevated production of adenosine triphosphate (ATP). Tolentino et al. (2006) found HBO increased dry weight of the remaining liver, regeneration rate, and DNA content at 24 and 48 hours after 70% hepatectomy, and the hepatocyte proliferation rate was significantly higher among animals treated with HBO at 48 hours after surgery. In an *in vitro* experiment, HBO was found to stimulate the proliferation of primary rat hepatocytes (Mizuguchi et al., 2005). The accelerated liver regeneration was also confirmed in patients after hepatectomy (Suehiro et al., 2008). Ijichi et al. (2006) postulated that these effects were ascribed to the elevated expression of vascular endothelial growth factor after HBO. In the study of Tran et al. (2012), therapy with HBO resulted in a rapid increase in hepatocyte proliferation, and this increase occurred as early as 12 hours and continued to 24 hours and 48 hours after treatment. There is evidence showing that angiogenesis after liver injury is beneficial for the liver regeneration (Li et al., 2015). Studies have shown that HBO is able to improve angiogenesis in injured tissues (Montecorboli et al., 2015). Thus, there is the possibility that HBO after hepatectomy may improve liver regeneration *via* inducing liver angiogenesis.

Effects of HBO on organ preservation

The prevention of preservation induced liver injury is pivotal for the early recovery of cell metabolism and graft dysfunction after transplantation. Traditionally, the liver after resection is stored at 0–4°C, which allows the preservation of liver function for 12 hours, but the time is shorter for marginal liver donors due to their susceptibility to I/R injury (Tekin et al., 2004). Under this condition,

the cell metabolism is reduced by 90–95% (van der Plaats et al., 2004). However, under hypothermic condition, the metabolism in the liver still requires oxygen, and once the oxygen can not be supplied to the graft, hepatocyte injury or even death will be present.

In as early as 1960s, some researchers investigated the effects of concomitant HBO on liver preservation. In 1967, 24 hours liver preservation was achieved with continuous pulsatile perfusion and HBO (Slapak et al., 1967). In 1970, Uchida et al. (1970) investigated the liver preservation under hypothermia (4°C) and HBO by *in vitro* perfusion study and by transplantation to another animal by an auxiliary procedure. *In vitro* experiments showed rising perfusion pressure, decreasing flow rate and weight gain. In the 6-hour preserved liver oxygen consumption, bi1e excretion and sulphobromphthalein (BSP) elimination showed little changes from the controls. In enzyme assay, increasing values were obtained, and this was related to prolongation of storage. *In vivo* experiments showed the 6-hour preserved liver displayed good concentration of Tc^{99m} and excretion of bile, but these functions were poor in 12-hour preserved liver. In 1972, Spilg et al. (1972) investigated the pig liver preservation of hypothermia with and without HBO in a potassium-rich solution, and their results showed 10- and 12-hour storage was unsuccessful using simple hypothermia alone (2–5°C), but 12-hour preservation was successfully achieved with the addition of HBO at 300 kPa. Tran et al. (2012) found HBO could attenuate the ischemia, preservation and reperfusion injury in a rat model of liver transplantation (reductions in apoptosis, necrosis and serum alanine transaminase). In 2012, Giannone et al. (2012) found the addition of HBO in the novel hyperbaric hypothermic machine perfusion (HHMP; Celsior solution, 2 atmosphere absolute (ATA); 1 ATA = 100 kPa) produced an extra benefit on liver preservation. Sgarbi et al. (2011) recommended the perfusion of the graft with hyperoxic solution for human transplantation because it fully preserved mitochondrial morphology and function of explanted livers.

Clinical Application of Hbo in Liver Transplantation

In 12 non-cirrhotic patients who underwent elective hepatectomy for liver cancer, 2 courses of HBO at 200 kPa were administered for 60 minutes at 3 and 24 hours after hepatectomy, and none had post-operative hyperbilirubinemia or hepatic failure after HBO, but 3 had post-operative hyperbilirubinemia and 1 had intraperitoneal infection (Ueno et al., 1999). Post-operative HBO in donors could reduce the incidence of wound numbness, aspertate aminotransferase (AST), total bilirubin and total bile acid and increase albumin and liver regeneration (Suehiro et al., 2008).

It seems that HBO has not been used in the patients receiving liver transplantation. Currently, the application of HBO in liver transplantation is confined to case reports about the hepatic artery thrombosis (HAT) after liver transplantation (Franchello et al., 2010), and there are no prospective randomized, controlled studies published. However, these reports also provide important information on the protective effects on liver transplantation. The largest case series were reported by Mazariegos et al. (1999). They investigated 375 patients receiving liver transplantation between 1989 and 1998, of whom 31 (7.5%) developed HAT within a median of 8.2 days (Mazariegos et al., 1999). Patients receiving liver transplantation between 1989 and 1994 served as historical controls, and those undergoing liver transplantation between 1994 and 1998 received HBO treatment within 24 hours after HAT. Eight patients in each group received a second liver transplantation, but the median time to re-transplantation was 12.7 days in control group and 157 days in HBO group. None in HBO group received re-transplantation due to liver necrosis. Moreover, one patient died in HBO group, but 5 died in control group. Color Doppler ultrasound showed the collateral circulation of hepatic artery was present at a median of 14 days in HBO group and 31 days in control, which might, at least partially, explain no liver necrosis in HBO group.

Pan et al. (2006) reported 4 cases of hepatic arterial complications after liver transplantation and HBO at 2.0 ATA was administered at 1–2 times/day. Their results showed HBO was effective to improve the general conditions of these patients, bilirubin returned to normal, ultrasound failed to identify new necrotic foci, and the original liquefaction necrotic foci reduced or even disappeared. Yang et al. (2006) also reported 4 patients with HAT after liver transplantation were treated with HBO (2 ATA; 1–2 times/day), and results showed HBO was able to improve liver function and inhibit liver necrosis. Bayrakci (2008) investigated the application of HBO in liver preservation of 2 cases, both patients recovered favorably. Thus, the authors recommended HBO could serve as a promising candidate as a bridge to transplantation, keeping the donated organs viable.

Central pontine myelinolysis (CPM) is the most serious neurological complication of orthotopic liver transplantation (OLT), and may increase the early mortality (Uchida et al., 2014). Although the pathogenesis of CPM after OLT is still poorly understood, electrolyte imbalances, the rapidcorrection of the serum sodium concentrationand the administration of immunosuppressive agents are found to be associated with the development of CPM following organ transplantation (Lee et al., 2009; Fukazawa et al., 2011). Zhang et al. (2009) applied HBO therapy in a male patient with CPM following living donor liver transplantation after

the presence of moderate coma, and the patient presented with good light reflex in both pupils, mild coma, increased autonomic activities, improved tension of limb muscles, and elevated Glasgow-Pittsburgh score.

Discussion

HBO has been accepted for the treatment of a variety of diseases, but its application in liver transplantation is limited. The fact that HBO is able to increase the oxygen supply to the target tissue is unquestioned regardless the HBO induced the vascular contraction. This is more so in the liver because it has dual blood supply. In addition, the protective effect of HBO on liver I/R injury has been investigated to a great depth, and some mechanisms have been proposed (anti-oxidative, anti-inflammatory and anti-apoptotic effects). Thus, it can be not only used in donors, but in recipients. In addition, HBO is also applicable in liver preservation according to available findings, which might preserve the liver function, prolong the time of liver preservation and improve the outcome of liver transplantation. These are major factors supporting the application of HBO in liver transplantation. However, there is still controversy on its immunomodulation although a majority of studies show HBO has immunosuppressive effect in case of diseases.

In recent years, increasing investigators focus on the organ protection of HBO pre-conditioning (Liu et al., 2012; Losada et al., 2014). This strategy is also applicable in donors before liver collection and in recipients before liver transplantation. Whether HBO preconditioning is better than HBO treatment in patients with liver transplantation or whether HBO preconditioning combined with HBO treatment may further improve the organ protection are needed to be further investigated in future studies. If this is confirmed, it will be of great clinical importance because HBO is easily administered, has few side effects and reduces medical cost.

Author contributions

HL, literature collecting and analysis; CHH, drafting the article; XJS, designing this article; WWL, structuring, revising and confirming the article.

Conflicts of interest

The authors declare that there is no conflict of interest in this paper.

Plagiarism check

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