

REVIEW ARTICLE

Hyperbaric oxygen therapy and liver transplantation

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Liver transplantation is the treatment of choice for end stage liver disease and is often used for primary liver malignancies. The main limitation of its wider application is the availability of suitable donor organs. The use of marginal donor organs, split-liver transplantation and living-related liver transplantation techniques contribute to increase the donor pool. However, the use of these techniques is associated with a higher risk of post transplantation organ dysfunction, predominantly due to ischaemia, preservation and reperfusion injury (IPRI). A number of studies have demonstrated that hyperbaric oxygen (HBO) therapy influences IPRI and consequential acute cellular rejection. This article reviews the rationale of HBO therapy in the field of transplantation with particular emphasis on liver transplantation.

Key Words: *acute rejection, ischaemia reperfusion injury, hyperbaric oxygen, liver failure, liver support*

Introduction

Liver transplantation is an established therapeutic modality for acute and chronic liver diseases. The improvement in outcome of liver transplantation is related to advances in patient selection criteria, organ preservation, operative techniques, perioperative care and efficacy of immunosuppressive agents. The resultant increase in demand for donor organs, widely estimated to be between 15 and 80 per million population, has led to the development of many strategies [1]. These include the use of split-liver transplantation [2,3], living-related transplantation [4,5], domino transplantation [6], non-heart beating donor transplantation and the use of marginal donor organs. These techniques result in the procurement of an organ that potentially has suboptimal function compared with normal organs, either due to the reduction in mass or the functional quality of the tissue [7]. Such organs are more susceptible to ischaemia, preservation and reperfusion injury (IPRI), which accounts for the majority of graft loss.

A further cause for donor organ damage is acute cellular rejection (ACR), which affects approximately 30–40% of patients after transplantation. Although ACR is effectively treated with modern immunosuppressive agents, this adds significantly to

the postoperative morbidity and overall cost of transplantation. Recent evidence suggests a correlation between the severity of IPRI and ACR. Limiting the severity of IPRI may reduce the incidence of primary non-function (PNF) as well as ACR after liver transplantation. Hyperbaric oxygen (HBO) therapy has been shown to reduce the severity of IPRI as well as modulate both humoral and cellular immune response. This paper provides an overview of the relationship between IPRI and ACR and the potential therapeutic implications of HBO therapy in liver transplantation.

Pathophysiology of the interaction of IPRI and ACR

The cumulative effect of warm ischaemia and cold preservation is an energy deficiency within the Kupfer and endothelial cells leading to intracellular oedema [8]. The early stages of reperfusion are characterized by a depletion of L-arginine, a precursor of the potent vasodilator nitric oxide (NO) and an elevation of endothelin-1 (ET-1). The latter stimulates hepatic stellate cell contraction, leading to sinusoidal narrowing, congestion and impaired flow. The low velocity within the sinusoids progressively promotes leucostasis, further hindering sinusoidal blood flow

and exacerbating the hypoxic injury to the donor organ [9]. Activation of Kupffer cells follows with the release of potent inflammatory cytokines such as tumour necrosis factor (TNF)- α and interleukin-1 (IL-1) as well as the production of reactive oxygen species (ROS) [10]. The proinflammatory activity of these cytokines manifests through many pathways, including the increased expression of adhesion molecules. These further increase the leukocyte–endothelial cell interactions and the induction of IL-8 synthesis [11–14].

An additional effect of IPRI is its potential to stimulate host response in the form of acute cellular rejection. Many antigens that are not normally present on vascular endothelium and biliary epithelium are expressed in response to IPRI. This exposure results in an innate immune response that involves humoral components such as cytokines, complement and coagulation proteases as well as cellular components made up of macrophages and neutrophils. This initial response is followed by an adaptive immune response which leads to the activation of T and B cells acting specifically against exposed allo-antigens. Apart from antigen exposure, IPRI-induced tissue injury also results in the increased expression of adhesion molecules. These include P and E selectins as well as vascular cell adhesion molecule (VCAM). Chemokines such as macrophage chemoattractant protein 1 (MCP-1) and IL-8 lead to the mobilization of macrophages and neutrophils towards the injured tissue. Integrins are then expressed allowing leukocytes to adhere and transmigrate to the target tissues. IPRI also leads to the activation of the complement system by both the classical and alternate pathways. Activation of the latter pathway leads to the release of further IL-8 and platelet activating factors (PAFs), which aggravates the inflammatory response at the site of injury.

Accumulating evidence indicates an association between IPRI and the onset and severity of acute rejection. The significance of the innate immune response and its relationship to the adaptive immune response has become clearer. The initial signal activation for the innate response is mainly provided through dendritic cells. A number of stress proteins that are expressed as danger signals, namely the heat shock protein family (HSP), act as endogenous ligands to Toll-like receptors (TLRs) [15]. Extracellular release of HSPs resulting from cell injury is thus able to act through TLRs to induce activation and maturation of antigen-presenting cells (APCs), particularly dendritic cells [16,17]. Other studies have not only confirmed the role of ROS in inducing the endogenous ligands of TLRs but also the central role played by TLR4 to establish the full impact of hepatic IPRI [18].

Tissue injury that follows due to IPRI leads to activation of donor APCs within the graft and recipient APCs that enter the graft. Activated APCs

then migrate to secondary lymphoid tissue where they interact with T cells and induce the allo response. Activation of APCs by TLRs also overcomes the suppression of T helper cells by CD4⁺ CD25⁺ T cells, allowing progression of the adaptive response [19]. It may be hypothesized that reducing IPRI and minimizing the activation of TLRs may leave the APCs in an inactivated state, leading to antigen-specific tolerance [20]. Absence of previous evidence supporting the relationship between IPRI and the severity of allo rejection have been attributed to the use of potent immunosuppressive agents [21]. More recent clinical studies have shown a closer association of IPRI and ACR [22] and the important role played by the innate response [23,24].

The pathophysiology underlying acute cellular rejection is complex, multi-factorial and not fully understood. The host response to donor allo-antigens is centred on the major histocompatibility complex (MHC) antigens, while donor dendritic cells within the organ are thought to exert the most potent stimulus for the onset of acute rejection [25–27]. Antigen recognition may occur by direct or indirect allo-recognition. Antigen specificity is maintained by T-cell receptor (TCR) complex while CD4 and CD8 act as co-receptors, binding to class II and class I MHC antigens, respectively. Once the TCR is engaged to an allo-antigen a series of intracellular events leads to the production of IL-2 [28–30]. Maximal IL-2 production by activated T cells is dependent on co-stimulation through a number of molecules, the most important of which seems to be CD28. The majority of CD4⁺ T cells and approximately 50% of CD8⁺ T cells express CD28 on their surface, the absence of which fails to induce an immune response from such T cells [31].

Activation of IL-2 and IL-2 receptors is followed by IL-3, IL-4, IL-5, IL-6 and interferon- γ . These activities lead to the transformation of the T cells to take on differentiated functions, such as immunoregulation and cytotoxicity. The exact roles of various cytokines remain unclear, although there is cross-regulation between the two types of CD4⁺ cells and some cytokines have been shown to have both immunostimulatory and immunomodulatory effects. Activated CD8⁺ T cells achieve destruction of target cells by the secretion of perforins and granzymes. Perforins create large pores in the target cell membrane leading to cytolysis, while granzymes activate apoptosis in the target population [32].

Mechanisms of the immunomodulatory effects of hyperbaric oxygen

The focus of HBO therapy has been directed towards its effect on IPRI. Researchers have also identified a significant immunomodulatory effect in animal studies by treating grafts in culture [33] as well as the recipients [34,35]. These studies have demonstrated a

suppressive effect on both humoral [36] and cell-mediated immunity [35]. As the mechanisms of allograft rejection became better understood, the potential mechanisms of action of HBO were further investigated. Most of these studies were aimed at understanding the effects of HBO on the release of cytokines and modulation of leukocyte function and have been conducted via *in vitro* or *in vivo* studies in normal human volunteers.

The effect of both HBO and its components (normobaric hyperoxia and hyperbaric normoxaemia) on the release of TNF- α has been studied in detail [37]. *In vitro* studies have shown that the release of TNF- α from unstimulated macrophages requires both the hyperbaric and hyperoxaemic components. In contrast, macrophages exposed to bacterial lipopolysaccharide (LPS) only require the hyperbaric component. Some investigators demonstrated an initial increase in TNF- α and IL-1 secretion in patients with Crohn's disease [38] and normal volunteers [39] during HBO therapy but a subsequent reduction with prolonged HBO therapy. Whether prolonged exposure to HBO inhibits production or if it was due to initial depletion of these cytokines is uncertain [38]. The study of IFN- γ in human volunteers also further supports the immunomodulatory effect of HBO therapy. Production of IFN- γ by peripheral blood lymphocytes was significantly inhibited for 24 h following exposure to HBO therapy. Further studies have demonstrated this effect to be attributed predominantly to the hyperbaric effect rather than to hyperoxaemia [40]. Animal studies have further supported the depressive effect on IFN- γ by hyperbaric therapy in the absence of hyperoxaemia [41]. This has led to the conclusion that the hyperbaric effect acts on the cellular cytoskeleton, leading to a reduction in IFN- γ rather than the increase in oxygen tension.

Early studies reporting an immunosuppressive effect from HBO therapy implicated a defect in the macrophage-monocyte system [34,42]. Recent studies investigating leukocyte function in response to HBO therapy have focused mainly on *in vitro* functions of neutrophils (PMNs) and lymphocytes. PMN function, particularly bactericidal ability, is related to the oxygen tension of its environment [43]. HBO therapy was shown to not impede the ability of PMNs to phagocytose or develop the oxidative burst by Gadd et al., demonstrating that PMN phagocytosis was possibly independent of the oxygen tension [44]. PMNs have the ability to inhibit T-lymphocyte function in their vicinity due to the release of myeloperoxidase and H₂O₂ [45–47]. This appears to be one of the mechanisms by which immunomodulation of T cells seem to occur after HBO therapy, as demonstrated by Gadd et al. where inhibition of T-lymphocyte proliferation was noted in response to HBO therapy. Despite this finding, there appear to be

subpopulations of T lymphocytes that are resistant to the inhibitory effects of PMN-induced H₂O₂ [46].

An *in vitro* study by MacKenzie et al. demonstrated the failure of peripheral blood monocytes treated with HBO therapy to activate lymphocytes when exposed to allogenic stimuli [48]. In this study the investigators elegantly demonstrated the inhibition of cytotoxic T lymphocyte activation by HBO therapy. The main focus was shown to be due to its effect on CD4⁺ cells. The addition of the T helper 1 cytokine IFN- γ to the culture reversed this effect. The administration of anti-IL-4 and anti-IL-10 blocking antibodies which are T helper 2-related cytokines also restored normalcy to the T lymphocytes. However, when the CD4⁺ cells were removed prior to re-stimulation, the CTL activity was restored. Interestingly, the addition of IL-2 to cells treated by HBO did not stimulate CTL activity, suggesting that the mechanism of HBO immunomodulation was other than the creation of anergy. It is more likely, based on the above results, that HBO therapy acts by modulating the CD4⁺ cells which cross-regulate each other. An increase in the activity of T helper 2 cells and suppression of T helper 1 cells is likely to be one mechanism of its action. HBO therapy may also act through the modulation of the relative concentration of high affinity and low affinity IL-2 receptors on T lymphocytes. Binding to the high affinity receptors promotes proliferation while the reverse is true of the low affinity ones. HBO may lead to a change in the proportion of the two receptors leading to reduced T-cell proliferation [49,50].

HBO therapy has also been shown to alter cell surface MHC class I antigen expression. The binding of MHC class I specific antibodies showed reduced affinity after thyroid and human fetal pancreas allografts were cultured with exposure to HBO therapy [51–54]. The expression of CD4 was slightly decreased when treated by HBO in culture, while that of CD28, CD80 and CD8 remained unchanged. Altered peptide ligands interacting with the TCR/CD3 complex may partially activate T cells leading to different signal transduction pathways [55]. Such altered peptide ligands have the capacity to turn a potentially harmful T helper 1 response into a protective T helper 2 cell response [56,57]. Recognition of this phenomenon and the understanding that such T cells may then undergo phenotypical changes has led to further insights into the potential action of HBO therapy. In addition to the potential direct immunomodulatory effects, HBO therapy may also significantly affect ACR by modulating the severity of IPRI. The effects of HBO therapy on IPRI have been studied in detail in many clinical and experimental situations.

Mechanisms of action of HBO on IPRI

HBO has been used with beneficial therapeutic effect in a wide variety of models of IPRI including

myocardium, skeletal muscle, small intestine and the liver [58]. Despite the theoretical adverse effects of generating ROS during reperfusion, the majority of *in vivo* studies have shown a reduction in the tissue injury when reperfusion is performed in the presence of HBO. HBO interacts with the effects of IPRI at numerous interfaces, which include the endothelium, neutrophils, mediators of inflammation, microvascular blood flow [59], lipid peroxidation and cellular energy levels.

The earliest demonstrable effect of HBO is on adhesion of neutrophils within the microcirculation. A significant reduction in rolling and adhesion on neutrophils is noted [59]. Recently, Kihara et al. demonstrated a significant reduction in the accumulation of neutrophils and severity of IPRI in a rat model when HBO was delivered within 3 h. This resulted in a significant reduction in neutrophil accumulation, suppression of malondialdehyde (MDA) within the affected tissue and reduced congestion within sinusoids [60]. Furthermore, HBO therapy resulted in the specific reduction in the expression of CD11/18 adhesion molecule which acts as a ligand to ICAM-1, thus leading to the above effect [61]. Neutrophil adhesion also occurs through the up-regulation of selectins (P and E selectins) and the immunoglobulin superfamily (ICAM-1), all of which are expressed on endothelial surfaces. P-selectin is present in its pre-made form within cells and therefore up-regulates and binds very rapidly to its ligand CD15 on the neutrophils. E-selectin up-regulation requires new synthesis and is thus slower and binds to the sialyl-Lewis molecule on neutrophils. As previously mentioned, ICAM-1 molecules bind to CD18 on neutrophils and are induced by IL-1, TNF- α and bacterial LPS. *In vitro* experiments have shown that single doses of HBO have a significant effect on IPRI-injured endothelial cells and neutrophil adhesion, by reducing not only CD18 and CD11 expression but also endothelial ICAM-1 expression [62,63]. The latter effect is thought to act through the induction of endothelial nitric oxide synthase (eNOS) [64]. This contradicts other studies which demonstrated increased expression of ICAM-1 with prolonged HBO therapy. However, the latter studies were conducted on normal tissue not exposed to the deleterious effects of IPRI, which may explain the different outcomes.

NO is a free radical which plays a major role in various aspects of IPRI. It is produced by three types of NOS. eNOS is constitutively expressed in endothelial cells and plays a role in vasodilatation of the microcirculation in response to hypoxia. Inducible NOS (iNOS) is produced by neutrophils and macrophages in response to a number of stimuli including IL-1, TNF- α and bacterial LPS. The NO produced by iNOS activation results in increased vascular leak and tissue injury, unlike the beneficial effects of eNOS. This toxicity is likely to be due to the greater production of superoxide radicals rather than toxicity

from NO itself. Normobaric oxygen therapy has been shown to induce eNOS production while HBO therapy reduces serum nitrite/nitrate concentration in a rat shock model, where the likely source of nitrate is from iNOS. A number of *in vitro* and *in vivo* studies have subsequently confirmed the ability of HBO to selectively induce eNOS while inhibiting iNOS production [65].

Lipid peroxidation occurs in the presence of IPRI, due to the release of ROS leading to cell membrane and organelle injury. Exposure to normobaric 100% oxygen increases the degree of such injury during reperfusion. Although HBO has been noted to increase ROS, a number of studies on IPRI have confirmed the reduction of lipid peroxidation when exposed to HBO [66,67]. The underlying mechanism of this effect remains ill understood. Similarly the interaction between HBO therapy and cytokine release remains contradictory. Spontaneous TNF- α production from normal tissue increases with HBO therapy in animal studies [68]. However, initial HBO exposure inhibits TNF- α production following subsequent exposure to bacterial LPS. Other studies have shown that stimulus-induced synthesis of TNF- α and IL-1 is inhibited transiently. In an intestinal IPRI model HBO was shown to inhibit the production of TNF- α [69]. Prolonged exposure to HBO reverses this effect leading to an increased production of IL-1 [70]. In other animal studies, once shock had been induced HBO tended to reduce the production of TNF- α , suggesting a possible role in the treatment of IPRI. Yet another mode of its effect may be through the inhibition of apoptosis. Specific inhibition of the apoptosis executor caspases 3 and 7 has been shown to reduce graft injury from IPRI [71]. Studies on cerebral ischaemia have further confirmed the ability of HBO to inhibit apoptosis leading to a reduction in IPRI [72]. Furthermore, a number of *in vitro* and *in vivo* studies have confirmed the ability of HBO therapy to stimulate hepatocyte regeneration [66,67,73].

In vivo studies of HBO therapy in transplantation

Despite extensive studies on the *in vitro* effects of HBO therapy on allografts, few studies have been conducted on its effects *in vivo*, most of which concentrate on the effect on ischaemia reperfusion and amelioration of tissue hypoxia. Several studies on bone and thyroid allografts have demonstrated accelerated union and immunomodulatory effect of HBO therapy [74]. The main finding was a reduction in the expression of MHC class I antigen on the allografts [51,53]. HBO therapy has a number of different roles in pancreatic islet cell transplantation, as it also improves the initial allograft hypoxia that is associated with graft failure. A more detailed study of islet allograft transplantation was preformed by

Juang et al., who demonstrated a significant advantage in using HBO therapy [75]. Better outcome was noted with pre-transplantation HBO therapy to the donor as well as twice-daily HBO therapy in the post transplantation period. The use of syngenic animals as donor and recipient indicates that the graft survival advantage in this study is related to non-immunological mechanisms [75]. Rat fetal spinal transplantation into adult Wistar rats also demonstrated similar, non-immunogenic advantages from HBO therapy. These were due to a combination of reduction in tissue hypoxia and tissue oedema and an increase in microvascular proliferation at the graft interface leading to better graft survival [76].

A rat model of liver transplantation was used by Chen et al. to demonstrate the effect of a single episode of pre-transplantation HBO therapy [77]. Post sinusoidal blood flow rate was increased and leukocyte adherence reduced. Tissue levels of MDA were reduced while tissue ATP levels were increased [77]. However, no *in vivo* studies on liver transplantation have specifically investigated the immunomodulatory effect of HBO therapy.

Another potential role for HBO therapy is its use in acute liver failure. Liver failure induced by carbon tetrachloride (CCL₄) poisoning in rats was shown to improve survival from 31% to 96% when applied immediately after ingestion of the substance. When applied 24 h later, the survival only improved from 36% to 50% [78]. This effect seems to be specific against the actions of CCL₄ and more study is required in its application for other causes of acute liver failure. HBO therapy seems to be protective against hepatotoxic agents that undergo reductive biotransformation through the cytochrome P450 system and aggravates the injury caused by those that undergo oxidative transformation [79].

Clinical experience of HBO therapy in liver transplantation

A handful of clinical studies have been published on the use of HBO therapy in relation to liver transplantation. All such studies relate to either its use in the post transplantation period for the management of hepatic artery thrombosis (HAT) [80,81] or its use in acute liver failure prior to transplantation [82,83]. A single case report of a 3-year-old with fulminant hepatic failure did not show any advantage to HBO therapy. The clinical improvement was related to episodes of plasma exchange. However, HBO therapy was instituted only on day 18 and as such may have missed the window of effectiveness [82]. Blum et al. reported four children with hepatic coma treated by exchange transfusion of whom three underwent HBO therapy [84]. Exchange transfusion was noted to be clinically effective while HBO therapy did not contribute to an improvement in their neurological status [84]. HBO therapy was used to treat early post

transplantation HAT in children by Mazariegos et al. [81]. This study investigated 375 patients who underwent liver transplantation between 1989 and 1998, of whom 31 developed HAT (7.5%) at a mean time of 8.2 days. Fourteen patients (between 1989 and 1994) were treated conventionally and served as the historical control group. Seventeen patients underwent HBO therapy within 24 h of HAT between 1994 and 1998. Eight patients in each group underwent re-transplantation, at a mean time of 12.7 days for the control group and 157 days for the HBO group. None of the re-transplantations in the HBO group was due to hepatic necrosis. There was one death in the HBO group and five in the control group, although the latter had a much longer follow-up. Hepatic arterial collaterals were noted on Doppler ultrasound at a mean time of 14 days in the HBO group while the control group demonstrated such development at a mean time of 31 days. This may in part explain the lack of hepatic necrosis in the HBO group [81].

HBO therapy in liver transplantation – discussion

Since its inception in 1662 and practical application in 1930, application of HBO therapy has continued to elicit controversy [85]. Its use is well established in the treatment of decompression sickness and generally accepted for the treatment of carbon monoxide poisoning, gas embolism and radio-necrosis [86]. Its remains controversial in the management of chronic wounds, refractory osteomyelitis, burns, ischaemic flaps and multiple sclerosis. The fact that HBO therapy increases the oxygen supply to the target tissue is unquestioned. This is more so in the liver with its dual blood supply. In addition, the effect of HBO therapy in ameliorating IPRI has been investigated to a great depth [87]. However, its potential role in immunomodulation remains uncertain [37,88]. Liver transplantation and HBO therapy have some common limitations. Both require extensive financial, medical and supportive infrastructure to function adequately. This simple commonality may allow both specialties to be situated within the same facility or within easy supportive range, thus providing an advantage in their clinical application. As the demand for liver transplantation grows and innovation forces the clinician to accept grafts of smaller volumes (split-liver, living-related OLTx) and those with less viable hepatocytes (marginal donor liver, steatotic livers) it becomes imperative to develop methods of minimizing donor organ injury and loss due to the IPRI and the process of rejection. In particular, the use of marginal donor organs is associated with an increased risk of PNF and primary poor function (PPF) of the graft, leading to longer stays in intensive care units, morbidity and mortality. PNF is a relative emergency often requiring urgent re-transplantation. Based on the available scientific evidence, HBO seems to have

the capacity to influence the outcomes of liver transplantation at multiple levels.

The effect of HBO therapy on IPRI is the one that has been most investigated, defined and applied in clinical practice, although not in the field of liver transplantation. HBO therapy seems to reduce the effect of IPRI by various mechanisms depending on where it is applied, including exposure to the donor organ prior to re-implantation as well as the recipient both before and after transplantation [89,90]. It has the potential to reduce IPRI and improve graft function in the post transplantation period. It may be of particular relevance when marginal or reduced size donor organs are used. HBO therapy also has a role to play in the management of post transplantation complications. Clinical evidence suggests that HBO therapy may delay or even eliminate hepatic necrosis following HAT [81]. It has also been used in acute fulminant hepatic failure [82,84]. In both situations it may provide badly needed time for an urgent donor organ to be made available. In the latter situation it may act as a hepatic assist device in conjunction with haemofiltration and plasma exchange procedures [83].

Another important role for which there is much animal and *in vitro* evidence but no clinical studies is its role in immunomodulation. If the laboratory studies were proven in the clinical situation, it may provide the opportunity to minimize drug-based immunosuppression, particularly in the first week following transplantation. The effect of minimizing IPRI is also known to reduce immune activation as it prevents the up-regulation of MHC class II molecules in the donor organ [23,91]. The effect of HBO therapy in ultimately inhibiting the transcription of immunomodulatory cytokines, especially IL-2 along with its ability to reduce the expression of MHC class I antigens, has potential implications for a further, low dose regime of immunosuppression. Finally, the proven effect on pancreatic islet cell uptake and graft survival may allow a similar improvement in the newly developing technique of hepatocyte transplantation.

Most strategies aimed at minimizing IPRI act through very specific pathways. This includes the use of preservation solutions, hepatic microcirculatory expansion [92], continuous *ex vivo* hepatic perfusion, inactivation of Kupffer cells [93] and inhibition of complement activation [94,95]. Similarly the mainstay of controlling ACR remains with immunosuppressive therapies targeting specific channels such as inhibition of calcineurin [96], use of antimetabolites [97] or more recently the use of interleukin receptor blockade [98]. One of the major and unique potential advantages of HBO therapy is that it affects the processes of IPRI and ACR through numerous cellular and molecular mechanisms. In addition it may play potential roles as a liver support adjunct for fulminant hepatic failure, post transplantation graft dysfunction and acute hepatic artery thrombosis. The

difficulty of moving critically ill patients in and out of the chambers and the high infrastructure requirements have been major obstacles to the delivery of HBO therapy in the clinical setting. However, the technology relating to the delivery of HBO therapy has advanced significantly in the past decades and overcome most of such impediments. The older generation of single chamber units were small with limited space and cumbersome access which increased the difficulty of managing complex patients. Modern multi-chamber units, especially the rectangular hyperbaric systems, are large by comparison, with adequate internal space for multiple patients, active medical intervention and easy drive-in access for bed-bound critically ill patients and supporting equipment. Almost all liver transplantation activity occurs at major referral centres which have the capacity, staff and infrastructure required for the functioning of an HBO chamber and the safe delivery of HBO therapy to critically ill patients. Thus, HBO therapy, often described as 'a treatment looking for a disease' has the potential to intervene and influence the outcomes of liver transplantation through multiple avenues. However, more research is required on the influence of HBO therapy in liver transplantation, specifically in its effect on immune response and liver support prior to clinical applicability.

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