The history of hyperbaric oxygen therapy and kidney transplant surgery

AHMED JAN MALAZAI M.D.1, DAWIT G. WORKU M.D., M.S.1, JENNIFER MCGEE M.D.1,
KEITH VAN METER M.D.2, DOUGLAS P. SLAKEY M.D., MPH, FACS1

1 The Tulane University School of Medicine, New Orleans, Louisiana, USA
2 Louisiana State University School of Medicine, New Orleans, Louisiana, USA

CORRESPONDING AUTHOR: Dr. Douglas P. Slakey –dslake@tulane.edu

INTRODUCTION
Because of the increasing reliance on renal transplantation as the treatment of choice for most patients with end-stage renal disease and the resultant shortage of donor organs, improved methods of organ procurement and organ preservation are more important than ever. Improving organ preservation would increase the number of viable organs available for transplantation and, in theory, improve post-transplant organ function.

Patients spend an average of three to five years on the waiting list for a kidney transplant. According to the U.S. Government Accountability Office Report of 2007, Medicare’s cost of maintaining a kidney transplant recipient is approximately $8,550 per year, a fraction of the cost of dialysis, which is $50,938 annually [1]. Both the pre-transplant waiting time and expense would be reduced if there were more organs available. One strategy to achieve this is to improve methods of organ storage.

Organs recovered from deceased donors for transplantation are inevitably damaged by the ischemia after cessation of cardiac and respiratory function. Before – and after – declaration of brain death, an organ donor may experience a variable period of hemodynamic instability, hypotension and tissue hypoxia. Following organ procurement, organs immediately begin to suffer from hypoxia, with resultant cell swelling, decreased cellular ATP and mitochondrial energy stores, along with degradation of cell membranes and increased expression of immunologically active cell membrane proteins (i.e., MHC, adhesion molecules, P-Selectin, cytokines).

To complicate matters further, there is the issue of ischemic reperfusion injury (IRI) once an organ is transplanted and blood supply restored. The two periods of ischemia, cold storage and warm ischemia reperfusion, are distinct in the type of cellular and ischemic damage the organ is subjected to. Methods used to improve organ storage and viability before and during transplantation must take the different mechanisms of ischemic stress into account. The history of hyperbaric oxygen therapy has mostly involved its application during cold storage, but as more is learned about the effects of hyperbaric oxygen at the cellular and molecular level, application during cold and warm ischemia may be both feasible and beneficial.

Hyperbaric oxygen therapy (HBO2T) involves the breathing/administration of pure oxygen while in a sealed chamber that has been pressurized at one and one-half to three times the normal atmospheric pressure. In the early 1900s, Orville Cunningham observed that individuals with some forms of heart diseases fared better overall if they lived closer to sea level than at high altitudes. He successfully treated a colleague with influenza who was near death due to lung restriction, and later developed a hyperbaric chamber. After his attempts to use HBO2T to treat a host of other conditions failed, the method was abandoned and his chamber scrapped.

Hyperbaric chambers were later developed by the military in the 1940s to treat deep-sea divers who suffered from decompression sickness. In the 1950s, HBO2T was first used during heart and lung surgery. In the 1960s, HBO2T was used for carbon monoxide poisoning, and it has since been studied and used for a number of health-related applications.

In the United States, the Undersea and Hyperbaric Medical Society, known as UHMS, lists 13 indications for reimbursement) uses of hyperbaric oxygen therapy:

- air or gas embolism;
- carbon monoxide poisoning;
- carbon monoxide poisoning complicated by cyanide poisoning;
- clostridial myositis and myonecrosis (gas gangrene);
- crush injury, compartment syndrome, and other acute traumatic ischémias;
- decompression sickness;
- arterial insufficiencies;
- central retinal artery occlusion;
- enhancement of healing in selected problem wounds;
- severe anemia;

Copyright © 2011 Undersea & Hyperbaric Medical Society, Inc.
• intracranial abscess;
• necrotizing soft tissue infections (necrotizing fasciitis);
• osteomyelitis (refractory);
• delayed radiation injury (soft tissue and bony necrosis);
• skin grafts and flaps (compromised);
• acute thermal burn injury.

During the last 50 years, promising research work has demonstrated benefits from using hyperbaric oxygen (HBO₂) in organ storage in terms of increasing potential storage time, improved early function of organs, reducing ischemia reperfusion injury and modulation of early immune response. This paper reviews the data regarding the use of HBO₂ for kidney transplantation, and discusses the potential for future studies.

METHODS
A Medline literature search (via PubMed) was conducted from the year 1950 to November 2010. Key words for the Medline search included hyperbaric oxygen, hyperbaric oxygen treatment, kidney storage, kidney preservation, kidney transplant, organ preservation. Only papers published in English in peer-reviewed journals were included. A total of 115 articles were identified as potentially relevant based on these Medline searches. All of these were obtained in full length and examined.

Upon review of these articles, approximately five additional references were discovered by perling (i.e., checking the reference sections for articles otherwise missed). These were references located in publications not typically found through Medline. Old publications (not available online) were obtained through Rudolph Matas library at Tulane University School of Medicine. Review papers containing information already considered were ignored. All new articles published up to the point of the final draft of this manuscript (December 2010) were reviewed.

Kidney storage by hypothermia alone
In the earliest transplant period, the 1950s and 1960s, hypothermia alone was the principle method of organ storage. In 1959, Levy demonstrated that hypothermia causes a decrease in oxygen consumption by kidneys stored prior to transplantation [4]. In 1963, Calne et al., at Westminster Hospital, London, United Kingdom, conducted a series of experiments exploring renal preservation by ice cooling. They succeeded in demonstrating viable canine kidney storage for up to 12 hours [5]. Between 12 and 17 hours, the damage was sometimes partially reversible, and after 17 hours the kidneys were irreversibly damaged.

Atarr, at the University of Maryland, Bigelow, at the University of Toronto, and Spurr, at the University of Iowa, each demonstrated a significant decrease in oxygen consumption and carbon dioxide production in organs subjected to hypothermia [6-8]. Using canine models, the researchers succeeded in storing kidneys with hypothermia for up to 28 hours with hypothermia alone [9,10].

The use of HBO₂ in transplant surgery (1960s and 1970s)
Transplant surgeons continued to experiment with novel methods to prolong the storage time of organs. In 1963, Richards performed a series of experiments on the effect of hyperbaric oxygen in increasing oxygen content of tissue once blood supply was occluded [11]. He reported a study in a canine model where 100 dogs were submitted to total circulatory, respiratory, or respiratory and circulatory arrest at 3 atmospheres absolute (ATA) and a 98% oxygen and 2% carbon dioxide (CO₂) mixture, and a temperature of 29°C. The reversible survival time was up to 60 minutes, demonstrating normal ECG and EKG following resumption of cardiac and respiratory function.

The calculated tissue oxygen stores at normothermic, normobaric conditions was 12-13cc/kg, and the oxygen consumption 3-4cc/kg/minute, providing a three- to four-minute survival time to the subjects in complete circulatory and respiratory arrest. Once the subjects were placed in hypothermia at 29°C, oxygen consumption decreased to 1-1.5cc/kg/minute; and at 3 ATA, with a gas mixture of 98% oxygen and 2% CO₂, the oxygen tissue stores were 45-50cc/kg, which correlated with the increased survival from 45-60 minutes in total respiratory and circulatory arrest.

Other researchers had published similar results, demonstrating that HBO₂, even without hypothermia, could provide adequate organ oxygen stores to allow for recovery after circulatory arrest [12,13].

These experiments have obvious implications for transplantation, both for the pre-treatment of donors prior to organ procurement and also for the storage of organs after procurement. The combination of decreasing organ oxygen demand and increasing tissue oxygen stores should allow for increased organ storage times and may preserve organ energy and integrity. If this were the case, then organ function after transplantation should be improved.
The aforementioned studies caught the attention of the transplant community, which realized the potential beneficial effect of supplementing hypothermia with hyperbaric oxygen to improve organ storage and enhance organ viability. This led to the studies of Manax and Lillehei, at the University of Minnesota Medical School. They first published their data in 1964 on kidney, heart and intestinal preservation by combined hypothermia with hyperbaric oxygen [14]. In their experimental model, a right nephrectomy was performed in 50 dogs, and the excised kidney was perfused with preservation solution and stored for 24 hours at 2°-4°C and 3 ATA of oxygen. The kidney was auto-transplanted to the neck of the dog from which it was removed. These kidneys were able to sustain the life of the dog in a healthy state indefinitely, even after a contralateral (left) nephrectomy to remove the normal remaining kidney. Normal blood urea nitrogen (BUN) levels, urine osmolarity and serial biopsies were obtained. Control group kidneys preserved with either hypothermia (2°-4°C) alone or hyperbaric oxygen (3 atmospheres absolute) alone for 24 hours invariably showed severe ischemic damage and were unable to sustain the life of the animal after contralateral nephrectomy. In addition to kidney preservation, the researchers succeeded in demonstrating successful heart and intestine preservation for up to 48 hours with a combination of hypothermia and hyperbaric oxygen therapy.

However, the authors tempered their enthusiasm by noting the potential for oxygen toxicity. “Much of the confusion over the use, action, limitation and physiology of hyperbaric oxygen relate[s] directly to the present uncertainty of oxygen toxicity as it relates to whole animals and to individual organs . . . We must realize that oxygen under pressure is toxic, although evidence suggests that hypothermia reduces this toxicity. These are important but difficult considerations when so little is known about the biochemical effects of oxygen poisoning. Oxygen toxicity is selective and does not affect all tissues and organs equally.” [13,14]

The transplant team at the University of Minnesota School of Medicine continue their HBO2-transplant research and in 1965 reported successful preservation of mongrel dog kidneys for 24 hours at 2°C and 3 atm (4 ATA) and for 48 hours at 2°C and 7.9 atm (8.9 ATA) HBO2 [15]. The criterion for success in their study was the ability of the single auto-transplanted cervical kidney to sustain the life of the animal in a healthy state after the contralateral nephrectomy two to four weeks following transplantation. They reported survival of the auto-transplanted animals for greater than one year [15]. They also published their results on individual organ susceptibility to HBO2 [16], including lungs, hearts, kidneys and ilea stored under various conditions: 4°C, for 24 to 72 hours at 3 ATA, 8 ATA, 10 ATA and 15 ATA. They found that kidneys stored at 4°C and 3 ATA were viable after 24 hours but appeared dark and non-functional after 48 hours (Table 1, above), whereas those stored at 4°C and 10 ATA or 15 ATA were viable and functional at 48 hours and 72 hours respectively. The same results were found with hearts. On the other hand, ilea showed no difference in viability or nutrient absorption when stored for 24 hours at 3, 8, 10 or 15 ATA pressures. These findings led Lillehei to conclude: “These findings indicate that the critical oxygen tension required for successful whole organ preservation is related not only to the temporal limits of storage but also to the core depth of the tissues being stored.” [16]

From this point on, both review articles and book chapters began including HBO2 as an adjunct to hypothermia in organ preservation. In a review article published in 1966, Lillehei and his group advocated that the future of organ transplantation was sure to include hyperbaric oxygenation [17]. In another review article, Idriss put his hopes of organ preservation and longer storage on the combination of hypothermia and HBO2:

<table>
<thead>
<tr>
<th>Kidneys stored with HBO2 at:</th>
<th>24 hours</th>
<th>48 hours</th>
<th>72 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>4°C and 3 ATA</td>
<td>Viable</td>
<td>Dark and nonfunctional</td>
<td>Dark and nonfunctional</td>
</tr>
<tr>
<td>4°C and 10 ATA</td>
<td>Viable</td>
<td>Viable</td>
<td>Non-viable</td>
</tr>
<tr>
<td>4°C and 15 ATA</td>
<td>Viable</td>
<td>Viable</td>
<td>Viable</td>
</tr>
</tbody>
</table>

TABLE 1 – Kidney viability under various conditions from Lillehei et al.
“With regard to long-term preservation, we have found that moderate decrease of the metabolic rate by moderate hypothermia (24°C) in conjunction with hyperbaric oxygenation at three atmospheres (absolute) to provide the oxygen requirement and continuous perfusion to provide nutrition to the cells offers reasonable hope of success in long-term preservation of whole organs” [18].

In 1966 Ladaga et al., reported a series of experiments on the effect of HBO2 and hypothermia on the preservation of the canine kidney [19]. In this model, mongrel dogs were subjected to a nephrectomy, with preservation of the kidney for 24 hours under hypothermia (Group I), hyperbaric oxygen (Group II) or hypothermia and hyperbaric oxygenation (Group III) for 24, 48 and 72 hours, with reimplantation (auto-transplant) and contralateral nephrectomy two to three weeks later. Groups I and II had no survivors, all dying in seven to 10 days of uremia. In contrast, Group III animals survived the two-week study period, and 75% survived 10 days of uremia. In contrast, Group III animals survived the two-week study period, and 75% survived 10 days of uremia. The study also showed a correlation between the degree of HBO2 and post-transplant organ function, as animals with organs stored under higher hyperbaric pressures (3 ATA) had significantly improved survival when compared to 2 ATA. The pathologic examination of the kidneys from Groups 1 and 2 showed a hemorrhagic and necrotic renal parenchyma with leukocyte infiltration and complete loss of nuclear staining. This was contrasted with those of Group III that showed a normal histological architecture, with sporadic slight tubular swelling. Organ preservation beyond 24 hours proved unsuccessful, with 100% mortality.

The metabolic-reducing capacity of hypothermia was well recognized at that time. However, kidneys stored beyond six to eight hours with hypothermia alone were rarely capable of supporting the life of the animal following contralateral nephrectomy [20-22]. In view of his study results, Ladaga hypothesized that adding hyperbaric oxygen therapy to hypothermic organs during storage provided a greater concentration of oxygen to tissues that are metabolically dormant. This contrasts slightly with other authors of the period who believed that the contribution of hyperbaric oxygen therapy to organ preservation was based on both a higher oxygen support but to the inhibition of certain key metabolic enzymes, which at the time were not defined [23-25].

**Effect of HBO2 on kidney preservation**

Despite promising studies demonstrating the beneficial effects of HBO2 on kidney preservation for transplantation, the exact mechanism/mode of this effect was still unknown, and remains largely uncertain in 2011. Several authors questioned the effectiveness of HBO2 in improving organ storage for transplantation. For example, in 1966, Matloof et al. monitored canine renal parenchyma PO2 using a Clark oxygen electrode during hyperbaric storage. His results raised doubt as to whether oxygen actually diffused across the renal capsule under hyperbaric conditions [26].

In 1967, Rassat and associates performed a series of experiments designed to verify the beneficial effect of HBO2 during kidney storage (27). In these canine experiments, both kidneys were removed and weighed. A cannula was inserted in the artery and in the vein and the organ was perfused via the artery with 200 ml of electrolyte solution at 2°C. The organs were maintained at 2°C under a pressure of 1, 4, or 8 ATA of either oxygen or nitrogen for 24 hours. At the end of the preservation period the solution was analyzed for potassium, lactic acid, chloride, sodium and glucose concentrations. The authors concluded: “The beneficial effect of hyperbaric oxygen for preservation of isolated kidneys is demonstrated by a diminished potassium release and a reduced lactic acid production. The latter may result from an improved oxygen diffusion. . .”

A variety of theories has been proposed to explain the data demonstrating a beneficial effect of HBO2 during organ storage. Some researchers like Lyons and Dietzman [28] proposed that HBO2 decreased cellular metabolism, while others demonstrated that HBO2 did not stop metabolism but, on the contrary, suggested that metabolism could go on up to 22 days [29,30]. Rudolf and Mandel hypothesized that oxygen per se may not be as important as the pressure of the gas itself [31]. They supported their claim by referring to organ storage experiments done by others using gases (other than oxygen) under hyperbaria [32].

**Experimentation with use of hyperbaric gases other than oxygen**

Combined hyperbaric and hypothermic kidney preservation with gaseous media other than oxygen – including nitrogen (N2), helium (He), xenon (Xe) and a mixture of gases – has been examined. Rickart et al. studied how different gaseous media were able to reduce the catabolism of high-energy phosphates and to what extent
such effects depend on the pressure of the gaseous media applied [33]. They noted that after HBO2, the preservation of adenosine triphosphate (ATP) content in rabbit kidney tissues remained low and did not change considerably, even with the increased pressure of oxygen. In contrast, with hyperbaric nitric preservation, initially low ATP content in the tissue increased significantly with increasing pressure of N2 [33]. When xenon gas was applied in pressure ranges between 4 and 5 ATA, tissue ATP content was even greater, exceeding that recorded with any other gas [33]. In their experiments, the best preservation of cellular viability and structure was demonstrated with hyperbaric xenon. Although the mechanisms involved were not clear, the authors suggested the higher lipid solubility of xenon might play a role.

Extreme pressure and kidney preservation
Investigators began to study the effects of using hyperbaria (pressure) greater than those considered “standard” (2-4 ATA). In 1970, Hans Løkkegard, at the Medical Department of Rigshospitalet, Denmark, studied the preservation of kidneys for 24 hours by means of hypothermia (5°C) and HBO2 at extreme pressures (15, 25, 50 ATA) in experiments using a pig model (34). At none of these pressures was survival of pigs achieved when contralateral nephrectomy was performed simultaneously with auto-transplantation. The use of 25 and 50 ATA caused greater damage to tissues than 15 ATA [34]. When contralateral nephrectomy was postponed for three weeks after the transplantation, the function of kidneys cold-preserved at 15 ATA oxygen was reduced compared to a control group of auto-transplanted, not long-term-preserved kidneys [34]. Ladaga et al. reported that in experiments with oxygen pressures of 2, 5, 10, 20 and 30 ATA, the least pronounced histological changes and the highest renal clearance following delayed contralateral nephrectomy were seen with 5 and 10 ATA of HBO2 [35].

Clinical studies
No large scale clinical data are available that systematically examines the use of HBO2 therapy in kidney transplantation. A few case reports have been published describing protocols and outcomes of HBO2 use in clinical transplantation. Lillehei et al. described three cases of human kidney transplantation using grafts preserved by hypothermia and HBO2 at 4 ATA [14]. The donor in the first case was a 38-year-old female who died acutely from hemorrhage. Both kidneys were procured, and the first kidney was immediately transplanted to a 9-year-old girl. The second kidney was immersed and maintained in a balanced salt solution (“Tis-U-Sol”) in a hyperbaric chamber at 2°C at 4 ATA while the first kidney transplant was completed. The second kidney was then transplanted into a 50-year-old recipient 11 hours after the death of the donor. Within a few days, both transplanted kidneys were functioning. The young girl was reported to have survived up to the time of publication (four months). The kidney preserved in HBO2 continued functioning until the 50-year-old recipient died on the 16th post-operative day due to a cerebral vascular accident. Postmortem examination and biopsy of the transplanted kidney showed no evidence of rejection, and only a moderate degree of damage ascribable to the 11-hour period of ischemia [14].

The third case involved a 48-year-old man in end-stage renal failure being maintained on chronic dialysis. In this case, the donor was a 20-year-old man who died of an unspecified chronic disease. The kidneys were procured and placed in hyperbaric chamber at 2C under 8.9 ATA of oxygen, the left kidney for three hours and the right for eight hours. Both kidneys were transplanted into the same recipient, who underwent bilateral native nephrectomy and splenectomy. Following surgery, both kidneys resumed function by the third postoperative day but the patient died on the eighth postoperative day of overwhelming Klebsiella. At autopsy, both transplanted kidneys were viable and showed no irreversible changes associated with the period of in vitro preservation.

Hitchcock and colleagues described their use of hyperbaria for human kidney transplantation with long ischemia times. In a series of eight reported cases, all of the transplanted kidneys functioned immediately, and only one of the eight was said to have shown any significant degree of acute tubular necrosis manifesting as significant oliguria (delayed graft function). They also reported that the kidneys have had very good function for several months [36].

Treatment of deceased donors with hyperbaric oxygen prior to organ procurement
Patients who meet criteria for brain death inevitably develop a progressive deterioration in organ function due to cardiac instability and other ill-defined factors. Tissue hypoperfusion is characteristic. Several authors have hypothesized that hyperbaric oxygen treatment of donors may result in less cellular injury from ischemia, reperfusion and no-reflow phenomenon, thus yielding organs that will be in an optimized state for transplantation.
Bayrakci published two case reports in which HBO₂ therapy was used in brain-dead organ donors before harvesting kidneys and transplanting [37]. In the first case, a 7-year-old boy was found unresponsive due to carbon monoxide poisoning. Hyperbaric oxygen at 2.5 ATA was administered for two hours within six hours of the accident, followed by another session the next day. ALT, AST, BUN, creatinine, uric acid, CK-MB and troponin levels were all elevated on admission (249 U/L, 347 U/L, 0.8 mg/dL, 10.5 mg/dL, 57.2 ng/mL, 1.5 ng/mL, respectively) and declined subsequently (93 U/L, 66 U/L, 7.9 mg/dL, 0.6 mg/dL, 3.1 mg/dL, 2.8 ng/mL, 0.3 ng/mL, respectively). The child did not recover, and after the declaration of brain death and parental consent, cardiac valves, kidneys and liver were procured from the patient. Both kidneys functioned within eight hours after transplantation, and none of the recipients required hemodialysis. The liver was successfully transplanted as well.

The second case was the 9-year-old sister of Case 1. She was also treated with HBO₂ therapy but progressed to brain death. Kidneys and liver were harvested and successfully transplanted.

Mechanism of the protective effect of HBO₂ following ischemia and reperfusion injury

Until recently the mechanisms by which HBO₂ exerts its protective effect in kidney/cell preservation was unknown. It is well documented that ischemia-induced cellular events play a critical role in the mechanism of kidney damage during storage. Recent investigations into the mechanisms of renal damage following ischemia in animal models suggest an early contribution of endothelial dysfunction and a local inflammatory response as major components of the evolving ischemic injury to the kidney [38-40]. A major event in the induction of tissue injury is the generation of oxygen-free radicals [39,40,43]. Accumulation of anaerobic metabolism products – e.g., lactate – leads to further cell damage. Once the blood supply is restored, leukocytes adhere to ischemic tissues, due to increased expression of adhesion molecules (e.g., P-Selectin) on endothelium-releasing proteases and free radicals, which leads to pathological vasoconstriction and tissue destruction [41]. As a consequence of these events, the recovery of blood supply to the ischemic kidney may be significantly delayed and reduced once the kidney is transplanted and blood supply restored. Figure 1 (facing page) illustrates the proposed inflammatory cascade in ischemic reperfusion injury (IRI). Each point in the cascade is a potential target for HBO₂ therapy.

For example, in ischemic rat tissues, HBO₂ has been shown to inhibit neutrophil adherence to vessel walls and to decrease post-ischemic vasoconstriction in skin grafts [43]. The decrease in neutrophil adhesion in HBO₂-treated ischemic reperfusion models is due to an interference of the neutrophil-specific adhesion molecule, CD-18 [44], and the cellular adhesion molecule ICAM-1 [45]. HBO₂ also reduces the expression of E-Selectin [46]. In several experimental conditions, HBO₂ has been shown to exert its beneficial effect in part by increasing the activity of Cu/Zn superoxide dismutase (Cu/Zn-SOD) and other antioxidant cellular defense mechanisms, thereby altering the balance between generation and removal of oxygen-free radicals [47-49], and decreasing IRI. Finally, because HBO₂ limits post-ischemic reductions in ATP production, lactate accumulation in ischemic tissue is reduced [50].

Guerer A. was successful in demonstrating that HBO₂ treatment prior to renal ischemia reduced peroxidation of lipid membranes in a rat model [51]. In 2007, Solamazgul published results of a study to determine the effect of HBO₂ on kidneys subjected to IRI in rats. Rats with a single kidney were subjected to warm ischemia by clamping the renal artery for 30 minutes, followed by 24 hours of reperfusion. One group received HBO₂ therapy for 60 minutes at 2.5 ATA starting at the 15th minute of reperfusion. HBO₂ significantly reduced blood urea nitrogen (BUN) and creatinine levels measured after reperfusion (p<0.05). Histology from the I/R group revealed severe tubular damage and neutrophil infiltration, whereas the kidneys from animals treated with HBO₂ showed significantly less tubular damage and neutrophil infiltration in comparison (p<0.05) [52].

Future directions

Since the first kidney transplant, there have been many advances in the science of organ storage, such as modified preservation solutions (i.e., Euro-Collins and ViaSpan®). Pulsatile perfusion has also been used with varying success. While these advances have, over time, improved kidney function after cold storage, there are still limits, and most transplant surgeons prefer to have less than 24 hours of cold storage time for kidney transplants, and even shorter times for other solid organs.

After the introduction of newer preservation solutions in the 1980s, there was little interest in HBO₂ T
as witnessed by very little research being published on the topic. The reasons for this are not entirely clear but probably relate to both the lack of research funding and interest in HBO2T as well as the difficulty in arranging the use of HBO2T equipment in concert with the complexities of arranging deceased donor transplants. Today, with increasing understanding of the cellular and molecular effects of HBO2T and the improved availability of smaller and lighter hyperbaric chambers, studying the effect of HBO2T with various preservation fluids and with perfusion would add considerably to the understanding of the effects of HBO2T on organ storage ischemic injury.

It is well recognized that there are three distinct periods of ischemia that occur during the process of organ procurement, storage and transplantation. First, within the donor, warm ischemia may occur from hypoperfusion, especially if the brain-dead donor is unstable, and also at the time of the procurement operation. Treating the donor prior to the organ procurement operation might improve organ viability and reduce immunogenicity, but data is lacking. Second, cold ischemia during storage has a significant impact on organ function, and is during this ischemic period that HBO2T has been most evaluated. Given the beneficial impact of newer preservation solutions and perfusion, the cold ischemic period continues to offer the potential for a positive impact of HBO2T. Third, there is warm ischemia that occurs during the transplant operation. It is possible that pretreating the recipient prior to transplant surgery may have a beneficial effect. Similarly, treating the recipient after transplantation with HBO2T might ameliorate some detrimental effects or ischemia reperfusion.

CONCLUSION
Since the earliest days of transplantation, HBO2T has been considered as having a role in organ storage to both prolong storage time and to improve organ viability. Clinical application has been limited by two main factors. First, hyperbaric equipment is not always available at transplant centers. To date most research into HBO2T and transplant organ storage has been limited to centers having both HBO2 and transplantation. In addition, given the frequent need to move organs from the donor hospital to transplant centers, this makes HBO2T during storage (at least initially) impractical. Second, until quite recently, there was little convincing scientific evidence explaining the underlying mechanisms. Given the publication of recent studies that demonstrate HBO2 having a beneficial effect toward reducing IRI and also reducing aspects of the early initiators of the immune response to the transplanted organ, we hope there will be a renewed interest in the potential for HBO2T to positively impact organ function when transplanted after cold storage.
REFERENCES


