EFFECT OF HYPERBARIC OXYGEN THERAPY ON THE DEVELOPMENT OF AIRWAY STENOSIS IN PATIENTS WITH SEVERE AIRWAY EXUDATIVE PLAQUES EARLY AFTER LUNG TRANSPLANTATION

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BACKGROUND:

Central airway stenosis (CAS) is seen in 8-15% patients after lung transplantation.[1,2] Development of airway stenosis can cause decline in pulmonary function, increased respiratory symptoms, increased infections, and occasionally death[3]. The lungs are unique in containing dual circulatory supply from the pulmonary circulation which is reanastomosed during lung transplantation, and the bronchial circulation which is not. Perfusion of the large airways is thought to occur via retrograde flow from vascular plexus' between the bronchial and pulmonary arterial circulation until new collateral circulation to the bronchial arterial system can develop in the weeks following transplantation[3]. Assessment of large airways perfusion has been surprisingly poorly studied, but development of airways ischemia post-transplantation is thought to be involved with development of CAS and other airway complications, opportunistic infections, particularly fungal infections, and possibly with chronic allograft rejection.[1,4]

CAS is managed with balloon dilation followed by airway stent placement for recurrent stenosis.[4-7] A limited number of retrospective studies have shown that the treated airway complications do not affect survival.[1,8] However, these airway complications prolong mechanical ventilation, hospital and ICU length of stay, increase cost, and adversely affect quality of life[3].

Patients undergo frequent bronchoscopy in the weeks and months following lung transplantation. Many, if not most patients develop some element of necrotic desquamation of the epithelium locally referred to as "exudative plaques" or "pseudomembranes"in the large central airways two to four weeks after lung transplantation. There is a spectrum of involvement, but prior work would suggest that up to 50% of patients who develop the most severe manifestations of these plaques go on to develop some form of large airway complication, most commonly CAS[9]. Our local experience supports this observation. There is no established intervention available for these patients, however, because airway ischemia is thought to play an important role in this process, our group has treated a small group of patients with hyperbaric oxygen therapy (HBOT) with anecdotal improvement in the appearance of the airways as well as a perceived reduction in frequency and severity of anticipated airway complications in some patients.

HBOT is defined as compression of the body with at least 1.4 atmospheres absolute pressure (ATA) of pure oxygen. It is believed to decrease inflammation, control infection, enhance perfusion and promote wound healing.[10] It is used for treatment of chronic refractory wounds, including diabetic, small arterial and radiation-related wounds, as an adjunct to surgical reconstruction wounds, flaps or grafts, and chronic osteomyelitis.[11-13] It has been shown to improve wound healing and decrease the need for limb amputations in diabetic patients. HBOT is not necessary or recommended for normal or uncompromised grafts or flaps, but where the graft or flap is compromised by hypoxia, ischemia or congestion, HBO_2 has been shown to be extremely useful in graft salvage (14). Our preliminary experience with HBOT in lung transplant patients with severe pseudomembranes has been encouraging. We perceive that use of this technique has hastened resolution of the pseudomembranes, improved infectious complications and decreased the incidence of CAS. Based on this preliminary experience we feel systematic examination of this approach is warranted.

OBJECTIVES:

The objective of this study is to evaluate the effect of HBOT on subsequent airway complications in lung transplant recipients with evidence of ischemic changes in the large airway epithelium. Study subjects with extensive desquamation (exudative plaques) of the large airway epithelium in the early post-transplant period will be randomized to HBOT or usual care and followed clinically for 12 months following randomization. We hypothesize that HBOT will decrease the number of airway complications in the treated subjects.

SUBJECT ENROLLMENT

Standard post-lung transplantation care includes a bronchoscopy with transbronchial lung biopsy at 1 month after surgery. We believe that it is in this early period, when the neovascularization of the large airways is thought to occur, that subjects are most likely to benefit from HBOT. Patients who are noted to have extensive exudative plaques (grade 3 or 4) at their 1 month bronchoscopy will be referred for a standard follow-up bronchoscopy 2 to 3 weeks later. Should the patient show no sign of improvement in their airways, or worsening of the plaques they will be considered eligible for enrollment in the study.

Exclusion Criteria

Exclusion criteria include: use of mechanical ventilation with FiO_2 greater than 40%, use of extracorporeal membrane oxygenation, use of inhaled nitric oxide, presence of pneumothorax, pregnancy, or inability to provide informed consent. In addition, subjects who are deemed to be

too clinically unstable to be transported safely to the hyperbaric facility by their treating physicians will be excluded from enrollment.

Randomization

Once subjects are deemed eligible for enrollment, they will be questioned as to their interest in participating in the study by the treating physician. Those interested will be approached by the study coordinator for informed consent. Once informed consent is obtained, subjects will be randomized to usual care or HBOT by selection of a pre-prepared envelope containing the randomization assignment. We will target a total enrollment of 40 subjects with 1:1 enrollment to either HBOT or usual care.

Subject Compensation

Subjects will not be compensated for participation in the study. However, they will not be charged for hyperbaric treatment or the research biopsies. The airway and rejection surveillance bronchoscopies are part of current standard care in the Duke lung transplant program and are continued accordingly in the study. All participants will be recruited at DUHS.

STUDY PROCEDURES

Hyperbaric Therapy

The HBOT will be performed with the standard HBOT protocol used at Duke for the treatment of compromised grafts and flaps. This is 2 hours of breathing >99% medical grade oxygen inside an air-pressurized chamber at 2 ATA once a day for 20 sessions. These sessions will be scheduled 3-5 times per week, depending on the availability of the patient and the hyperbaric medicine physician. The HBOT procedure used for this study will be identical to that used for clinical practice in the Duke University Health System Center for Hyperbaric Medicine and Environmental Physiology, including the oxygen that is used in the chamber. Patients will receive treatment through the regular clinical hyperbaric service. These are routine, not special, treatment sessions and they will receive them alongside other Duke University Medical Center patients being treated for other reasons. The medical grade oxygen used is a part of the Duke University Health System Center for Hyperbaric Medicine and Environmental Physiology hyperbaric chamber system.

The patients sign the standard Duke informed consent for the administration of HBOT inside the chamber. The primary risks, which each occur in less than 10% of patients, are middle ear barotrauma from the changes in barometric pressure (resolves in a few days) and temporary near-sightedness that may occur after 20 to 30 sessions, and resolves in 2-3 months, but which can rarely leave some persistent myopia that requires a change in eyeglass prescription. The other

risks are very rare (<1%) and include oxygen-induced convulsions, and pneumothorax, and there is a very remote chance of mechanical or electrical failure in the chamber resulting in a fire.

Airway Surveillance

While the patients randomized to receive usual care will not undergo HBOT, both study groups will receive standard serial bronchoscopies for airway clearance and for the collection of bronchoalveolar lavage fluid for culture data, due to the high rate of infection in lung transplant patients. All subjects will undergo the standard surveillance bronchoscopies every 3 to 4 weeks (x3) for clearance of the exudate from the airway, as well as monitoring progression of the airway abnormalities. Additional bronchoscopies will be performed as clinically indicated. Following the completion of the airway surveillance, subjects will revert to the standard rejection surveillance schedule of bronchoscopy every 3 months for the first year post-transplant.

At each surveillance bronchoscopy, subjects will have the standard bronchoalveolar lavage performed for detection of infectious agents. Due to the high evidence of airway infections in patients with severe exudative plaques, a lavage is performed during each bronchoscopy as a part of standard practice to collect microbiologic data. As participants in this study, an, endobronchial biopsy of the airway epithelium will be performed at the main carina to collect a sample of recipient epithelium as well as at the first subcarina for each donor lung. Three samples will be collected from each of the biopsy sites. These samples are small (1 to 2 mm) and are thought to have a minimal clinical risk of minor bleeding associated with the procedure. Biopsy will add roughly 3 minutes total to each procedure. These samples will be used for mRNA extraction to detect expression of genes associated with response to tissue hypoxia.

Measurements and Data Collection

Primary outcomes: Need for airway stent placement and rate of acute rejection in the 12 months of observation as determined by transbronchial lung biopsy.

Secondary outcomes: Include development of airway stenosis, need for balloon bronchoplasty, development of clinically significant pulmonary infection as defined by initiation of antimicrobials to treat the suspected organism, development of airway dehiscence following enrollment in the study, development of bronchiolitis obliterans syndrome, and bronchial epithelial gene expression.

Additional clinical data to be collected will include spirometric data, frequency of hospitalization, hospital days, ICU days, mechanical ventilation days, need for tracheostomy, and survival.

TREATMENT ARM CROSSOVER

Should patients enrolled in the usual care arm develop airway complications such as airway stenosis, dehiscence, or airway malacia, or if the patient fails to improve their exudative plaque score over the period of observation, they may be offered hyperbaric therapy with continued collection of clinical data. Subjects will be eligible for crossover therapy between 8 and 12 weeks after the initial study bronchoscopy.

There are two criteria for a patient to qualify for HBOT crossover treatment. The first criterion is the development of an airway complication, most likely airway stenosis requiring intervention. This is clinically defined by our group as an airway that is no longer traversable with a therapeutic (6.4mm OD) bronchoscope. Other complications are airway dehiscence or malacia (excessive loss of structural integrity). The second criterion is failure of the airway exudate to improve in score severity during the 8 week observation period. This is measured using the scoring system outlined in Table 1.

RISK/BENEFIT ASSESSMENT

It is currently unknown if treatment of patients with severe exudative plaques in the early post-lung tranplant period with HBOT will prevent development of large airway complications. Our limited anecdotal experience suggests it may improve outcomes. The risks of the procedure are small and detailed above. The potential benefits are significant since airway stenosis can lead to worse allograft function, increased infections, and occasionally death. Subjects randomized to usual care will be at usual risk of airway complications. Given the clinical equipoise regarding HBOT treatment in lung transplant, we feel this is an ethical treatment decision for this patient population.

COST TO THE SUBJECT

There will be no additional costs to the subject over usual care. The hyperbaric treatment will be provided at no charge to the subjects.

DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Data analysis will be performed by the primary investigators. Categorical data will be analyzed using Fisher's exact test given the small sample size, while continuous data will be assessed for statistical significance with Student's t-test. Our prior work with airway stenosis in lung transplant recipients documented a 15% rate of stenosis in all transplant patients. Our clinical experience suggests a rate 2 to 4-fold higher in patients with severe ischemic desquamation of

the large airways. Experience with HBOT in this population is limited, but rates of significant airway stenosis may be as low as 10% after therapy. Sample size calculations using a 60% stenosis rate in the usual care group, a 10% stenosis rate in the HBOT group with a p-value of 0.05 suggest that a sample of 14 subjects/group will have an 80% power to detect statistical significance. We will target a total of 40 subjects to allow for subject withdrawal and loss due to the development of critical illness in this tenuous population. Intention to treat analysis will be used for all patients based on initial randomization, with subgroup analysis for the crossover patients for airway stent placement. All biologic samples will be collected by week 6, prior to any patient crossover events.

DATA and SAFETY MONITORING

Data will be stored on a secured Access database located on the PIN station "U" drive in an secured folder. All subject entries will be de-identified using a study assigned identification number. The key to the study identifiers will be kept in a locked file cabinet in the study coordinators office. Database use will be limited to the primary investigators, co-investigators, and the study coordinator.

Primary risks are related to bronchoscopy with minimal risk of bleeding related to the endobronchial lung biopsy, and some discomfort from the bronchoscopy itself which is part of usual post-transplant care. Additional risks of hyperbaric treatment are detailed above and very rare. Any adverse events that occur during the study will be immediately reported to the IRB.

Table 1. Pseudomembrane Scoring System

Stage	Definition
Stage 0	No exudate
Stage 1	Limited to anastomosis
Stage 2	Anastomosis to upper lobe orifice, including medial bronchus intermedius
Stage 3	Involvement of the lower lobe orifice
Stage 4	Covers all visible airways

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