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Safety of hyperbaric oxygen therapy for management of central airway stenosis after lung transplant

Kamran Mahmood[1], **Bryan D. Kraft**[1], **Kristen Glisinski**[2], **Matthew G. Hartwig**[3], **Nicole P. Harlan**[1,4], **Claude A. Piantadosi**[1,4], and **Scott L. Shofer**[1]

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Duke University Medical Center, Durham, NC, USA

[2]Department of Medicine, Duke University Medical Center, Durham, NC, USA

[3]Division of Cardiovascular and Thoracic Surgery, Department of Surgery, Duke University Medical Center, Durham, NC, USA

[4]Center for Hyperbaric Medicine and Environmental Physiology, Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA

Abstract

Background—Central airway stenosis (CAS) is common after lung transplantation and causes significant post-transplant morbidity. It is often preceded by extensive airway necrosis, related to airway ischemia. Hyperbaric oxygen therapy (HBOT) is useful for ischemic grafts and may reduce the development of CAS.

Methods—The purpose of this study was to determine whether HBOT could be safely administered to lung transplant patients with extensive necrotic airway plaques. Secondarily, we assessed any effects of HBOT on the incidence and severity of CAS. Patients with extensive necrotic airway plaques within 1–2 months after lung transplantation were treated with HBOT along with standard care. These patients were compared with a contemporaneous reference group with similar plaques who did not receive HBOT.

Results—Ten patients received HBOT for 18.5 (interquartile range, IQR 11–20) sessions, starting at 40.5 (IQR 34–54) days after transplantation. HBOT was well tolerated. Incidence of CAS was similar between HBOT-treated patients and reference patients (70% vs 87%, respectively; P=.34), but fewer stents were required in HBOT patients (10% vs 56%, respectively; P=.03).

Correspondence: Kamran Mahmood, MD, MPH, Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, Duke University Medical Center, DUMC 102356, Durham, NC, USA. k.mahmood@duke.edu.

AUTHORS' CONTRIBUTIONS

Kamran Mahmood, Bryan D. Kraft, Claude A. Piantadosi, Matthew G. Hartwig and Scott L. Shofer: Designed and implemented the study; Kamran Mahmood, Kristen Glisinski, Nicole P. Harlan and Scott L. Shofer: Collected the data; Kamran Mahmood and Scott L. Shofer: Responsible for data analysis; All authors contributed to the writing of the manuscript; Kamran Mahmood: The guarantor of work and takes responsibility for the integrity of work, from inception to published article.

CONFLICT OF INTEREST

All the authors have no conflict of interest relevant to the study.

Conclusions—This pilot study is the first to demonstrate HBOT safety in patients who develop necrotic airway plaques after lung transplantation. HBOT may reduce the need for airway stent placement in patients with CAS.

Keywords

airway obstruction; hyperbaric oxygen; lung transplantation

1 INTRODUCTION

Lung transplantation improves the survival and quality of life in patients with end-stage lung disease, but may result in large airway complications, [1,2] most commonly central airway stenosis (CAS). This is seen in about 15% of patients, [3–8] and can be associated with degraded allograft function, need for repetitive invasive procedures, and increased mortality in some studies.[3,9]

The etiology of CAS is unknown, but likely involves large airway ischemia at the time of transplant due to loss of the bronchial circulation and poor retrograde perfusion.[3,10–13] The evidence for bronchial ischemia includes exudative, necrotic airway epithelial plaques arising in the early post-transplant period and commonly preceding the development of CAS.[14,15] It has been shown that allograft airways have reduction in local tissue oxygen saturation up to 1 year following transplant.[11] Moreover, we found an association with increased expression of genes under regulation by hypoxia-inducible factor-1α in allograft bronchial epithelium and CAS, further supporting a role for airway ischemia in the development of large airway complications. [13] On this basis, we hypothesized that patients who develop extensive necrotic airway plaques post-transplantation may benefit from modalities that improve oxygen delivery and wound healing, such as hyperbaric oxygen therapy (HBOT).

HBOT provides 100% oxygen at pressure above 1 atmosphere absolute (ATA) and improves oxygen delivery to ischemic tissue by raising the partial pressure of dissolved oxygen, promoting angiogenesis, neovascularization, and attenuation of inflammation. [16,17] HBOT is approved for treatment of acute and chronic ischemic conditions such as diabetic foot ulcers, skin graft failure, and delayed complications of radiation therapy.[18–23] It has also been reported to improve healing of surgical airway anastomoses following both tracheal reconstruction and lobar resection for lung cancer.[24,25] We postulated that if HBOT could be used safely, it may promote airway healing in patients with necrotic bronchial epithelial plaques following lung transplantation. We performed a pilot evaluation of HBOT safety in lung transplantation patients with extensive necrotic plaques and compared them with a contemporaneous group of patients who did not receive HBOT.

2 METHODS

2.1 Patient selection and hyperbaric oxygen

We reviewed patients who underwent single or bilateral orthotopic lung transplantation at Duke University Medical Center[26] and developed persistent, extensive necrotic airway

plaques between March 2013 and January 2015. Patients with extensive necrotic airway plaques were identified by the primary lung transplantation providers during routine, surveillance bronchoscopy at 1–2 months post-transplantation and referred to the interventional pulmonary group for consideration of HBOT. Based on local experience, those patients with extensive plaques extending (at a minimum) from the surgical anastomosis to the segmental airways of the lower lobes, as shown in Fig. 1, are at increased risk for the development of CAS and were offered HBOT, which was administered at the Duke Center for Hyperbaric Medicine and Environmental Physiology (Durham, NC). The planned treatment regimen was twenty, 2-hour sessions of 100% oxygen at 2 ATA administered by head tent in a multiplace hyperbaric chamber once a day. The technique was similar to other uses of HBOT. Treatment was initiated within approximately 1 month of diagnosis of extensive, persistent necrotic plaques. Tolerance to HBOT was assessed daily at the end of the treatment sessions by pressure-related symptoms such as ear pain, and by the appearance of new respiratory symptoms including cough, mid-sternal chest pain, shortness of breath or any other complaints.

We identified a reference group of patients who developed severe post-transplant necrotic airway plaques but were not referred to the interventional pulmonary group for consideration of HBOT. These patients were identified by review of all 1-month post-lung transplant bronchoscopy reports between March 2013 and January 2015 for the presence of severe airway plaques with documentation of the extent of the plaques. These patients received standard post-lung transplantation care. The study was approved by the Duke University Institutional Review Board (Pro#00021763).

2.2 Surgical technique of lung transplantation

The standard procurement and surgical technique of lung transplantation at our institution have been published.[25] Bilateral transverse sternothoracotomy (Clamshell incision) is used for bilateral sequential lung transplant and posterolateral thoracotomy for single-lung transplant. The donor bronchus is transected 1–2 rings proximal from the lobar take off. Bronchial anastomosis is performed in an end-to-end fashion using a 4-0 absorbable monofilament suture in a running fashion. Unnecessary manipulation of peribronchial tissue is avoided, but no revascularization of bronchial arteries is performed. All the patients receive standard induction and maintenance immunosuppression.

2.3 Diagnosis and treatment of CAS

Surveillance bronchoscopy was performed at 1, 3, 6, 9, 12 months and yearly thereafter, or as clinically indicated. CAS was defined as the inability to introduce a 6.3-mm-outer diameter flexible bronchoscope through central airways that are normally traversable (Fig. 2).[3] Local standard care for CAS is serial balloon bronchoplasty for a total of three treatments, followed by airway stent placement for refractory stenosis in symptomatic patients.[3,27] The same protocol was closely followed for both the groups to prevent unnecessary airway stenting.

2.4 Statistical analysis

Descriptive statistics are presented as mean (standard deviation) when normally distributed or median (interquartile range, IQR) when not normally distributed. Continuous variables were compared using a two-tailed, Student's *t*-test, and categorical variables were compared using Fisher's exact test or chi-square test, as statistically appropriate. *P* value of <.05 was considered statistically significant Logistic regression analysis was performed to assess the relationship between stent placement and HBOT. SAS 9.4 (Cary, NC, USA) and Microsoft Excel 2010 were used for statistical analysis.

3 RESULTS

Our institution performed 233 lung transplantations between March 2013 and January 2015, and 26 (11.1%) patients developed persistent, extensive necrotic airway plaques at 1–2 months after transplantation. Ten patients were administered HBOT, along with standard care for CAS, which included serial bronchoplasty followed by stent placement. These patients were referred for HBOT due to the presence of extensive airway plaques at the discretion of the primary provider (Table 1). The reference group comprised of 16 patients with similarly extensive necrotic plaques who were not referred for HBOT, and treated with standard care only. The patients in reference group were probably more stable clinically based on evaluation of treating transplant physicians, as reflected by better FEV1 and FVC (Table 2). Patients were followed for a median of 565 (IQR, 415–754) days. HBOT was started at a median of 40.5 (IQR 34–54) days after lung transplantation, with an average of 18.5 (IQR 11–20) sessions completed. HBOT was well tolerated among the patients, with only one patient reporting transient blurriness of vision and anxiety.

The HBOT and reference groups were well matched for age, underlying lung disease, type of transplantation, and severity of airway plaques (Table 1). Necrotic airway plaques were first identified in HBOT and reference patients approximately 1 month post-transplant (29 vs 30 days, respectively; *P*=NS), and resolved by approximately 4–5 months post-transplant (111 vs 150 days, respectively; *P*=NS). Rates of CAS were similar between groups (70% vs 87.5% in HBOT and reference groups, respectively; *P*=.34). However, patients treated with HBOT displayed a shorter time to the development of CAS and time to first balloon bronchoplasty compared with reference patients (48 vs 96 days, respectively; *P*=.01). Additionally, despite the high rates of CAS seen in both groups, only one patient (10%) in the HBOT group required airway stent placement compared with nine patients (56%) in the reference group (*P*=.03) (Table 2), with an odds ratio of stent placement with HBOT of 0.09 (95% CI 0.01–0.85). There was no difference between the groups in the incidence of pulmonary infection or acute rejection. Mortality was similar in both groups (30% vs 31%, *P*=NS).

4 DISCUSSION

This pilot study is the first report on the safety and feasibility of HBOT for the management of patients at risk for the development of CAS following lung transplantation We found that HBOT could be administered safely in this setting without significant complications involving the lungs, such as pneumothorax. Although the study was not designed for

efficacy, we noted that the incidence of CAS was the same in patients treated with HBOT and a contemporaneous reference group; however, there was a beneficial effect of HBOT on reduction in airway stent placement in treated patients.

CAS is a consequence, at least in part, of bronchial ischemia after lung transplantation. Hence, the rationale for use of HBOT is similar to that for other ischemic flaps and grafts where the circulation may have been compromised during the procedure.[21] At the time of lung transplantation, bronchial circulation is not commonly revascularized leaving the bronchial mucosa dependent on retrograde pulmonary venous blood flow from the alveolar —bronchial capillary plexi.[28,29] In murine models of transplant-associated bronchiolitis obliterans syndrome, there is evidence that persistent small airway ischemia leads to allograft rejection, fibrosis, and small airway stenosis.[11,12] We recently demonstrated that donor upper and lower bronchi have reduced tissue oxygen saturation compared to native airways, as measured during bronchoscopy up to 30 days after lung transplantation. We also found significant upregulation of hypoxia-inducible genes in donor airways, with expression of VEGFA, KDR, and HMOX1 being associated with prolonged respiratory failure, prolonged hospitalization, extensive airway necrosis, and CAS.[13]

In large airway ischemia models in mice, HBOT has been shown to promote anastomotic healing,[30–32] and is known to improve oxygen delivery and wound healing by inducing angiogenesis and neovascularization, recruiting endothelial stem cells, and reducing inflammation. [33–36] Recent reports have also indicated that HBOT can be safely administered to patients with postoperative airway compromise. One report has described minimal complications and good outcomes in five patients given HBOT for necrotic tracheal anastomoses after tracheal resection. [24] Another report has described no complications and good outcome in a patient given HBOT for presumed ischemia at the anastomotic site following lobar resection and extensive carinal reconstruction.[25] Ours is the first report of the use of HBOT in patients who have developed necrosis of allograft airways after lung transplantation, and indicates HBOT can be administered safely in this setting.

The development of necrotic airway plaques after lung transplantation is common and is a known risk factor for CAS.[14,15] The patients in our study with post-transplant necrotic airway plaques also showed a high incidence of CAS, and treatment with HBOT did not reduce rates of CAS. We observed that patients in HBOT group developed CAS earlier compared to the control group. This may reflect closer monitoring with more frequent bronchoscopies in this group. However, patients who received HBOT showed a decreased trend for airway stenting, despite a similar incidence and distribution of airway stenosis. We speculate that HBOT may accelerate airway revascularization allowing for the development of fibrotic wound healing, resulting in earlier stenosis which then resolves with continued neovascularization.

Limitations of our pilot study include small sample size, case–control design, lack of randomization of patients selected for HBOT, and lack of provider blinding. The study was not designed to demonstrate efficacy of HBOT for CAS and stent placement prevention. Our patients received HBOT only for persistent plaques that lasted for at least 1–2 months post-transplant with HBOT initiated a median of 40 days post-transplantation. Earlier initiation of

HBOT might be more effective in reducing CAS incidence. Finally, HBOT side effects related to barotrauma were captured by clinical interview and examination. A checklist could be employed in future studies to systematically identify side effects of HBOT.

In conclusion, HBOT can be administered safely in patients with large airway complications after lung transplantation. HBOT is well tolerated and not associated with significant complications. The preliminary findings suggest that HBOT may reduce the need for placement of airway stents. These prospects require validation in a prospective, randomized controlled trial currently under way at our institution (clinicaltrials.gov: NCT02363959).

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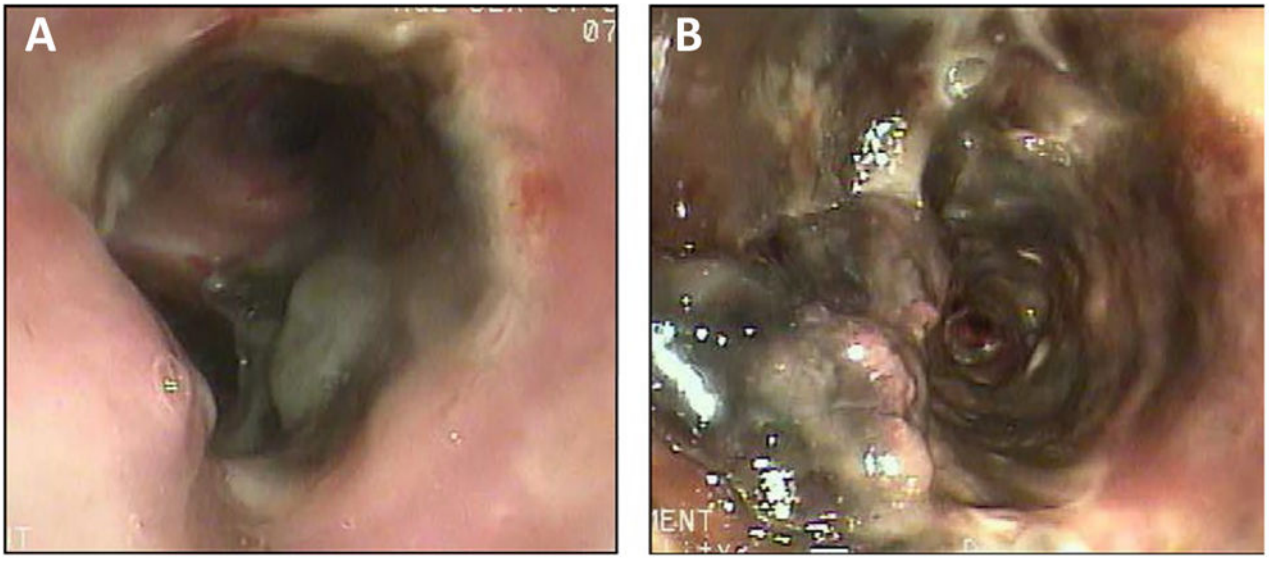

FIGURE 1.

Anastomoses of the left (A) and right (B) mainstem bronchi with necrotic plaques before hyperbaric oxygen therapy

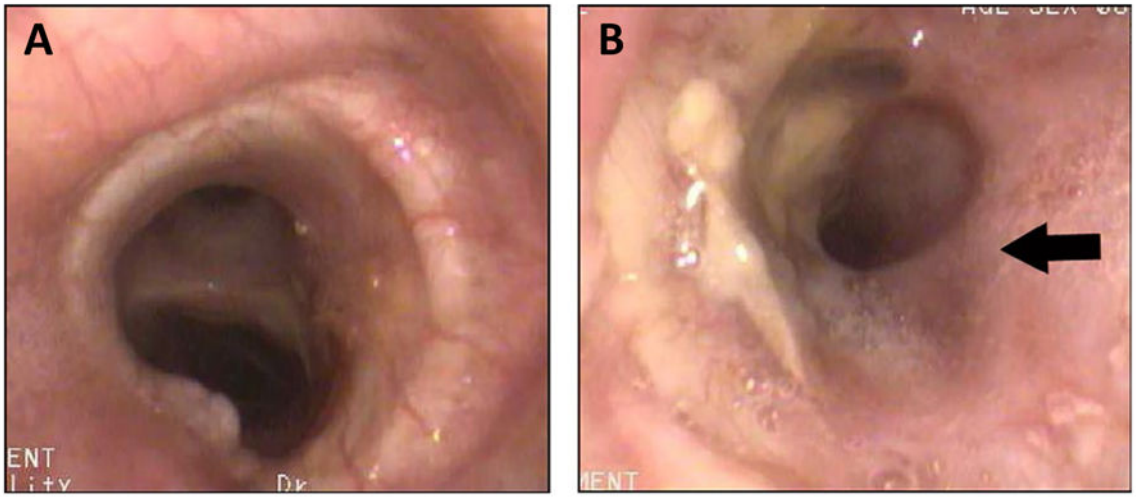

FIGURE 2.

Anastomoses of the left (A) and right (B) mainstem bronchi with resolution of necrotic plaques after hyperbaric oxygen therapy. Stenosis of the bronchus intermedius is now present (arrow)

TABLE 1

Patient characteristics

	HBOT (n=10)	Control (n=16)	*P* value
Age, mean (SD), y	54 (18)	58.6 (16.7)	.51
Male gender	6 (60%)	10 (62.5%)	1.0
Race			
Caucasian	9 (90%)	15 (93.7%)	1.0
African American	1 (10%)	1 (6.2%)	
Lung transplant type			
BOLT	8 (80%)	14 (87.5%)	.62
SOLT	2 (20%)	2 (14%)	
Transplant indication			
IPF	5 (50%)	8 (50%)	.63
Sarcoidosis	1 (10%)	1 (6.2%)	
CF	2 (20%)	2 (12.5%)	
GPA	2 (20%)	0	
COPD	0	1 (6.2%)	
RA—pulmonary fibrosis	0	1 (6.2%)	
LAM	0	1 (6.2%)	
Pulm HTN	0	1 (6.25%)	

BOLT, bilateral orthotopic lung transplantation; SOLT, single orthotopic lung transplantation; IPF, idiopathic pulmonary fibrosis; CF, cystic fibrosis; GPA, granulomatosis with polyangiitis; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; LAM, lymphangioleiomyomatosis; Pulm HTN, pulmonary hypertension; HBOT, hyperbaric oxygen therapy.

TABLE 2

Patient outcomes after lung transplantation

	HBOT (n=10)	Control (n=16)	*P* value
Days from transplant to diagnosis of necrotic airway plaques, median (IQR)	29 (24–33)	30 (24–31)	.58
Days from transplant to necrotic airway plaque resolution, median (IQR)	111 (83–176)	150 (112–165)	.96
CAS	7 (70%)	14 (87.5%)	.34
Site of CAS			
Anastomotic+non-anastomotic	3 (30%)	3 (18.7%)	.34
Non-anastomotic only	4 (40%)	11 (68.7%)	
Days from transplant to CAS, median (IQR)	48 (39–69)	96 (65–137)	.01
Site of CAS			
Right mainstem	0	2 (12.5%)	.77
Bronchus intermedius	4 (40%)	6 (37.5%)	
Right upper lobe	2 (20%)	5 (31.2%)	
Right middle lobe	3 (30%)	6 (37.5%)	
Right lower lobe	2 (20%)	1 (6.2%)	
Left mainstem	2 (20%)	2 (12.5%)	
Left upper lobe	5 (50%)	10 (62.5%)	
Left lower lobe	3 (30%)	2 (12.5%)	
Patients requiring airway stent placement	1 (10%)	9 (56.2%)	.03
Types of airway stent			
Silicone	1 (10%)	5 (31.2%)	.06
Hybrid	0	5 (31.2%)	
Metal	3 (30%)	1 (6.2%)	
Site of airway stent			
Right mainstem	0	3 (18.7%)	.14
Bronchus intermedius	1 (10%)	6 (37.5%)	
Left mainstem	1 (10%)	1 (6.2%)	
Left upper lobe	1 (10%)	0	
Baseline post-transplant FEV1, mean (SD), L[a]	1.30 (0.4)	1.64 (0.6)	.17
Baseline post-transplant FVC, mean (SD), L[a]	1.64 (0.6)	2.13 (0.8)	.16
Change in FEV1, mean (SD), L[b]	0.34 (0.44)	−0.01 (0.56)	.13
Change in FVC, mean (SD), L[b]	0.32 (0.49)	0.32 (0.37)	.97
Acute rejection within 3 mo of transplantation	4 (40%)	10 (62.5%)	.42

	HBOT (n=10)	Control (n=16)	*P* value
Pulmonary infection within 3 mo of transplantation [c]			
Gram-negative bacilli	7 (70%)	9 (56%)	.92
Gram-positive cocci	2 (20%)	4 (25%)	
Fungi	5 (50%)	10 (62%)	
Mycobacteria	4 (40%)	8 (50%)	
Mortality	3 (30%)	5 (31.2%)	1.0

CAS, central airway stenosis; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HBOT, hyperbaric oxygen therapy; IQR, interquartile range.

[a] FEV1 and FVC values at baseline after the lung transplantation

[b] Change between baseline spirometry after lung transplant and follow-up values in 3 months.

[c] Pathogenic organism growth based on cultures of bronchoalveolar lavage and endobronchial biopsy of plaques.