Helium-Oxygen Mixture to Facilitate Ventilation in Patients With Bronchiolitis Obliterans Syndrome After Lung Transplantation

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A combination of helium and oxygen (heliox) can facilitate gas exchange and limit peak inspiratory pressures through reduced resistance to gas flow and decreased turbulent flow. The combination of these gases has been used for a variety of upper and lower airway conditions, including patients who were spontaneously breathing, receiving noninvasive ventilation, as well as during mechanical ventilation. To date, there are no reports regarding the use of heliox in patients with bronchiolitis obliterans syndrome following lung transplantation. We report the use of such a combination of gases in 2 patients with bronchiolitis obliterans syndrome following lung transplantation as a supportive measure to facilitate ventilation during the initial treatment course for acute respiratory failure in the ICU. A heliox mixture was administered with noninvasive ventilation and with mechanical ventilation through the ventilator in a heart-lung transplant recipient and a lung transplant recipient, respectively. *Key words: acute respiratory failure; helium; oxygen; heliox; heart and lung transplantation; bronchiolitis obliterans syndrome.* [Respir Care 2013;58(4):e42–e46. © 2013 Daedalus Enterprises]

Introduction

Helium is an inert gas with the lowest density of any gas other than hydrogen, which is flammable and therefore of limited clinical use. Helium was first isolated from atmospheric air in 1895 by Sir William Ramsey, with the first reports of its clinical application by Alvan L Barach in the 1930s, for treatment of upper-airway obstruction.[1,2] Subsequently, helium has been combined with oxygen (heliox), to improve gas exchange in patients with upper-airway obstruction of various etiologies, including viral and post-extubation subglottic edema, laryngeal edema, and laryngeal tumors.[3-6] Additional reports have demonstrated its efficacy in more distal airway obstruction, including asthma in spontaneously and mechanically ventilated patients.[6-11] Helium has no direct harmful or toxic effects upon human tissues, and has been used previously in both adults and children without sequelae.

Lung transplantation is being used increasingly, in both the adult and pediatric populations, to treat end-stage lung disease of various etiologies. Both acute as well as acute on chronic issues may cause respiratory failure following lung transplantation. As many patients may have some component of respiratory insufficiency at baseline, even minor changes in respiratory function may result in respiratory failure. In some cases these conditions are reversible with effective therapy for infectious causes or acute allograft rejection, while progressive or worsening function may require consideration of a second transplant. As a bridge during the initial treatment of such patients, alternative modes of respiratory support may be needed.

We have recently cared for 2 patients with severe bronchiolitis obliterans syndrome (BOS), one after lung transplantation and the other after heart-lung transplant transplantation. In both patients, ventilatory support with heliox provided temporary improvement in their respiratory sta-

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tus. To date there are no reports of the use of heliox in patients following lung transplantation. The potential application of such therapy in this unique population is discussed. Review of these cases and presentation in this format was approved by the institutional review board of Nationwide Children's Hospital.

Case Report 1

A 33-year-old woman, who underwent heart and bilateral lung transplantation 2 years previously for complex congenital heart disease, was transferred to our institution for acute respiratory failure. She had a history of pulmonary atresia, with intact ventricular septum and right ventricle hypoplasia, whose surgical history prior to transplant included a Waterston shunt, main pulmonary artery ligation, and Maze procedure. Her post-transplant course was complicated by chronic rejection with severe BOS and vasculopathy of the cardiac allograft, as well as superior vena cava stenosis requiring stent placement, esophageal stenosis that also required stent placement, and the development of a mediastinal hematoma. Previous pulmonary function testing was consistent with mixed obstructive and restrictive defects, with the most recent spirometry demonstrating an FVC of 0.83 L (22% of predicted) and an FEV_1 of 0.67 L (21% of predicted).

At the outside hospital, noninvasive ventilation was started with bi-level positive airway pressure (BPAP) at 16/8 cm H_2O with an F_{IO_2} of 0.5. Due to increased vascular markings on chest radiograph, intravenous furosemide was administered. After initial stabilization she was transferred by helicopter to our facility for further care. Upon arrival she continued to have labored breathing; however, the remainder of the examination was unchanged from baseline, other than a liver margin 3 cm below the right costal margin. A chest radiograph demonstrated new findings of bibasilar air space disease and small pleural effusions, suggestive of acute heart failure, with otherwise stable widened mediastinum due to a mediastinal hematoma (Fig. 1). An initial arterial blood gas (ABG) revealed a pH of 7.19, P_{aCO_2} of 99 mm Hg, and P_{aO_2} of 151 mm Hg. A 12-lead electrocardiogram demonstrated a new right bundle branch block, and transthoracic echocardiogram showed worsening diastolic function. Although cardiac enzymes were negative, a B-type natriuretic peptide was elevated at 1,379 pg/mL (normal 0–100 pg/mL).

The initial treatment efforts were focused on avoiding the need for endotracheal intubation and mechanical ventilation, so the decision was made to attempt the administration of heliox through noninvasive ventilation (BPAP). Concurrently, aggressive intravenous diuresis with furosemide was started, along with increasing her baseline dose of carvedilol. Heliox administration was achieved via the ventilator (Respironics V60, Phillips Healthcare, Andover, Massachusetts) and an oronasal mask. (This ventilator is not FDA approved specifically for the administration of heliox.) The desired dose of 60% helium and 40% oxygen was achieved by utilizing an external blender connected directly to the inlet of the ventilator. The dose was confirmed by the use of an oxygen analyzer. The patient was closely monitored to ensure maintenance of desired S_{pO_2}, P_{aCO_2}, and minute volume. Additionally, there were only minimal changes in the inspiratory and expiratory pressures with conversion to heliox.

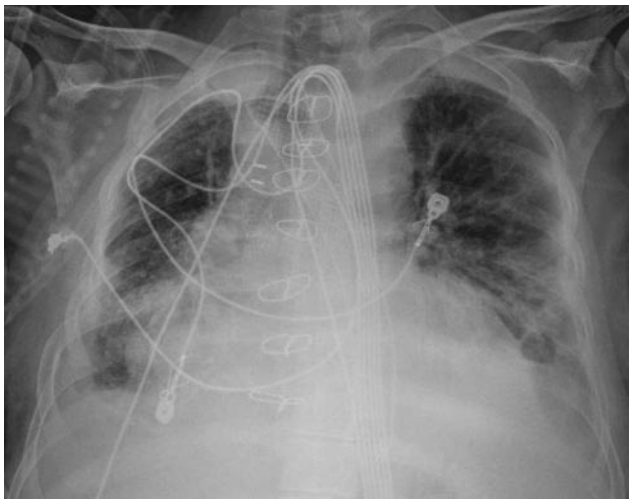

Fig. 1. Chest radiograph demonstrating cardiomegaly with bibasilar air space disease and small pleural effusions, with stable sternotomy wires, esophageal stent, and vascular stent present with stable widened mediastinum due to a mediastinal hematoma.

Upon administration of the heliox, the subsequent ABG improved, with an increase in the pH and a decrease of the P_{aCO_2}. Over the next 3–6 hours the pH ranged from 7.26 to 7.28, the P_{aCO_2} from 53 to 72 mm Hg, and the P_{aO_2} from 85 to 99 mm Hg while the patient was clinically improving. Despite the improvements in her respiratory status, her renal function continued to decline, with development of oliguria and an increase in the serum creatinine from 1.2 to 2.4 mg/dL (normal 0.5–1.2 mg/dL), due to worsening diastolic heart failure with repeat brain natriuretic peptide of 1,611 ng/L, and abdominal ascites, with elevated intra-abdominal pressure. Her hypervolemia and compromised renal failure affected her breathing pattern and resulted in the need for endotracheal intubation 36 hours after admission. After endotracheal intubation, ventilation was accomplished easily, so the heliox was discontinued. Her oliguria resolved after placement of a peritoneal drain, with resulting excellent response to the intravenous diuresis. She was ultimately extubated 2 days later, with renal recovery occurring over the next 4 days, with normalization of the serum creatinine. Due to advanced BOS, she and the family did not want any further heroic therapy, so

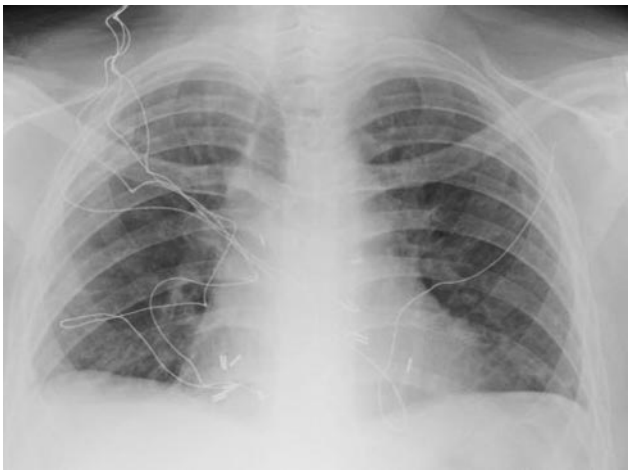

Fig. 2. Chest radiograph demonstrating low lung volumes with subtle nodular opacities throughout the lungs, without focal disease, pneumothorax, or pleural effusion.

she was discharged home with hospice 1 week after extubation and died upon arrival home.

Case Report 2

A 28-year-old woman, who underwent bilateral lung transplantation 3 years previously for sarcoidosis and pulmonary hypertension, was admitted through the emergency department for acute respiratory failure. Her post-transplant course was complicated by severe BOS and gastroesophageal reflux with delayed gastric motility, requiring placement of a gastrojejunostomy tube. Previous pulmonary function testing was consistent with mixed obstructive and restrictive defects, with the most recent spirometry demonstrating an FVC of 0.92 L (31% of predicted) and an FEV_1 of 0.46 L (18% of predicted). The patient presented to the emergency department with an altered mental status and increased inspiratory crackles, with no other remarkable changes noted on examination. Chest x-ray demonstrated subtle nodular opacities, without focal disease (Fig. 2). The initial ABG revealed pH of 6.90, P_{aCO_2} of 169 mm Hg, and P_{aO_2} of 66 mm Hg, so her trachea was intubated, and she was placed on mechanical ventilation. Ventilation continued to be difficult with conventional ventilation and high frequency oscillatory ventilation. Despite multiple different modalities of ventilation and alterations in the settings, severe hypercarbia persisted, with a $P_{aCO_2} > 150$ mm Hg despite a peak inflating pressure (P_{Imax}) up to 62 cm H_2O.

A trial of heliox at a dose of 60% helium and 40% oxygen was subsequently initiated by connecting an 80/20 helium-oxygen gas source directly to the inlet of the ventilator (Avea, CareFusion, San Diego, California), using a 50 psi connector. (The Avea is FDA approved specifically for heliox administration, and internally sets the heliox concentration based on the F_{IO_2} setting.) An extended systems test was performed to ensure proper circuit leak and compliance.

Following the administration of heliox, an immediate improvement was seen in ventilatory effort, and improvements on ABG measurements were noteworthy. Over the next 24 hours the pH ranged from 7.24 to 7.31 and the P_{aCO_2} from 65 to 77 mm Hg. During this time, oxygenation remained adequate (P_{aO_2} ranging from 78 to 122 mm Hg). Over the next 4 days the P_{Imax} was able to be weaned to 36–38 cm H_2O, with acceptable levels of oxygenation and ventilation. Due to the severity of the patient's underlying lung disease, the heliox did not have much of an impact on the final outcome for this patient, with quick development of multi-system organ failure. As she was not a re-transplant candidate, the family requested that renal replacement therapy not be instituted, and the patient died on hospital day 6, as the decision was made not to escalate care.

Discussion

Short-term administration of heliox leads to a definite clinical improvement in patients with lower airway disorders. Helium enhances the diffusion effect on the elimination of carbon dioxide, which diffuses 4- to 5-fold faster through heliox than through nitrogen-oxygen mixture; therefore, for the same partial pressure of CO_2, a greater amount of CO_2 would be eliminated per unit of time.[12,13] Additionally, heliox has lower density than either 100% oxygen or any concentration of oxygen in room air with nitrogen. During turbulent gas flow, resistance is directly proportional to the density of the gas and inversely proportional to the radius to the 4th power, as described by the Poiseuille law, where resistance equals $8\eta L/\pi r^4$, where η is the gas density, L is the tube length, and r is the tube radius. As the density of the inspired gas is increased, flow decreases for a given pressure.

In the setting of worsening lower airway obstruction, the primary goal of therapy is to relieve the bronchospasm and increase the radius of the lower airways. However, the usual therapies administered for bronchodilation and respiratory support can take hours to take effect. Lowering the density of inspired gas with the use of heliox can decrease the resistance to gas flow within minutes, resulting in improved gas exchange, thereby immediately allowing a decrease in P_{Imax} and limiting the risk of barotrauma, as noted in our second patient.

In addition to decreasing resistance, a gas mixture with a lower density and higher viscosity may improve gas flow, as a result of conversion from turbulent to laminar flow. In the setting of acute narrowing of the lower airways, areas of lung that normally have laminar flow may suddenly develop turbulent flow, thereby increasing resistance, decreasing gas flow, and increasing the work of

breathing. The tendency for flow to be laminar or turbulent within a given region can be quantified by a dimensionless ratio of inertial to viscous forces, termed the Reynolds number: $2rv\eta/y$, where r is the tube radius, v is the average gas flow, η is the gas density, and y is the gas viscosity. With the substitution of helium for nitrogen, the Reynolds number may decrease, resulting in more laminar flow and further decreasing resistance to gas flow. These effects may be particularly prominent in the distal airways, where gas flow is generally more laminar in the normal state.

For decades, heliox has been used as a therapeutic option for a variety of upper and lower airway conditions. Substituting helium, which is a low density gas under atmospheric conditions, for nitrogen in a gas mixture changes the physical properties of the inhaled gas. By decreasing the gas mixture density, airway resistance is decreased without changing the anatomy, resulting in improved gas flow, as predicted by the fluid dynamic paradigm. We speculate that the laminar flow from the heliox optimized gas exchange by improving gas flow and decreasing lower airway resistance in both of these patients with severe BOS after lung transplantation. The improved gas exchange simply provided time for the patients to be treated and given time to respond to the other therapies implemented at admission, thus leading to temporary clinical improvement. Therefore, the importance of this novel use of heliox in the early treatment period for both of these lung transplant recipients with severe chronic allograft rejection and acute respiratory failure was its effective, although temporary, supportive effects in facilitating improved ventilation.

Delivery of heliox requires special equipment, systems, and trained respiratory therapists to facilitate safe and effective administration. Heliox can be a successful therapeutic intervention administered through a BPAP device or traditional mechanical ventilator, given alone via a traditional face mask, or used in conjunction with nebulizer machines. However, there are several important pitfalls requiring the awareness of clinicians and respiratory therapists alike. For example, not all ventilators are compatible or FDA approved for heliox use. Heliox utilization through non-compatible devices or by inexperienced therapists may in fact cause harm by altering oxygen concentration or ventilator parameters. Therefore, close monitoring and frequent follow-up assessment following the initiation of heliox is warranted. It is also important to recognize that heliox may have effects on nebulized drug delivery, by changing the mass of the inhaled medication and the aerosolized particle size itself.[14]

At our institution, respiratory therapists receive training in heliox equipment and administration techniques. Using a Respironics V60 ventilator, a tank of heliox is consumed in 2 hours with the price being $120 per tank, so a day of therapy would be approximately $1,440. The cost of labor by respiratory therapy would also have to be included to determine global expense for heliox administration. There is no limitation in length of therapy with heliox.

We noted an immediate and dramatic effect in both of our patients, with an immediate decrease in the P_{aCO_2}, shortly after the initiation of heliox therapy. In our first patient there was a subjective decrease in work of breathing, while a progressive decrease in the P_{Imax} was possible in our second patient. Unfortunately, given the baseline chronic respiratory insufficiency in both of our patients, and confounding factors, including issues of non-adherence and anatomical considerations, neither of the patients was a candidate for re-transplantation. Endotracheal intubation was necessary in our first patient, related more to her intravascular volume status than her primary lung dysfunction, while our second patient eventually died from multi-system organ failure. Despite the outcome in our second patient, heliox was continued throughout her hospitalization, and even during her final day we were able to achieve effective ventilation and oxygenation with a P_{Imax} of 36–38 cm H_2O and an F_{IO_2} of 0.3–0.4 with heliox.

In conclusion, we report that heliox was well tolerated and improved ventilation during respiratory compromise in patients with chronic allograft rejection or BOS after lung transplantation. To our knowledge, there are no previous reports of the use of heliox therapy in lung and heart-lung transplant recipients. Although neither one of these patients survived, in large part due to the severity of chronic allograft rejection, heliox did improve ventilation for a short period of time; therefore, we feel a trial of a heliox should be considered in lung and heart-lung transplant patients with BOS at times when ventilation is difficult.

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