Effect of Heliox on Respiratory Outcomes during Rigid Bronchoscopy in Term Lambs

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Abstract

Objective. To (1) compare physiologic changes during rigid bronchoscopy during spontaneous and mechanical ventilation and (2) evaluate the efficacy of a helium-oxygen (heliox) gas mixture as compared with room air during rigid bronchoscopy.

Study Design. Crossover animal study evaluating physiologic parameters during rigid bronchoscopy. Outcomes were compared with predicted computational fluid analysis.

Setting. Simulated ventilation via computational fluid dynamics analysis and term lambs undergoing rigid bronchoscopy.

Methods. Respiratory and physiologic outcomes were analyzed in a lamb model simulating bronchoscopy during foreign body aspiration to compare heliox with room air. The main outcome measures were blood oxygen saturation, heart rate, blood pressure, partial pressure of oxygen, and partial pressure of carbon dioxide. Computational fluid dynamics analysis was performed with SOLIDWORKS within a rigid pediatric bronchoscope during simulated ventilation comparing heliox with room air.

Results. For room air, lambs desaturated within 3 minutes during mechanical ventilation versus normal oxygen saturation during spontaneous ventilation (P = .01). No improvement in respiratory outcomes was seen between heliox and room air during mechanical ventilation. Computational fluid dynamics analysis demonstrates increased turbulence within size 3.5 bronchoscopes when comparing heliox and room air. Meaningful comparisons could not be made due to the intolerance of the lambs to heliox in vivo.

Conclusion. During mechanical ventilation on room air, lambs desaturate more quickly during rigid bronchoscopy on settings that should be adequate. Heliox does not improve ventilation during rigid bronchoscopy.

Keywords
bronchoscopy, model, foreign body, pediatric, heliox, lamb

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Ingestion or aspiration of foreign bodies is a significant source of mortality and morbidity in the United States and is responsible for approximately 17,000 emergency department visits for children each year, with 80% of incidences occurring among those <3 years old.1 Asphyxiation due to foreign body aspiration is responsible for >3500 deaths per year and is the third-leading cause of accidental death of children <4 years old.2 Because radiographic imaging has poor sensitivity, rigid bronchoscopy is often required for confirmation and removal.3 Delayed diagnosis of a retained airway foreign body can result in pneumonitis, pneumonia, pulmonary abscesses, and bronchiectasis.4,5

The development of the rigid bronchoscope has saved countless lives over the years. Prior to its invention, the mortality following foreign body aspiration was approximately 23%.6 With the introduction of the Hopkins rod lens in 1963 and more recent advances in anesthetic techniques, the current estimated mortality associated with bronchoscopy during foreign body removal is between 0.5% and 1.1%.3,7 Even so, concerns about ventilation during bronchoscopy are raised by a still unacceptably high complication rate, particularly during retrieval of tracheobronchial foreign bodies. Hypoxemia and hypercarbia occur in about 1 in 4 patients.3,7 Major complications associated with ventilation include pneumothorax, pneumomediastinum, cardiac arrest, and hypoxic brain injury.3

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Conversion to tracheostomy or thoracotomy during endoscopic foreign body removal happens in nearly 1% of cases.7

We recently analyzed the macro- and microscopic flow dynamics of pediatric bronchoscopes as compared with endotracheal tubes, using computer-aided design (CAD) software in pressure- and volume-controlled mechanical ventilation (MV) systems. We found that nearly all sizes of bronchoscopes in this study demonstrated reduced volume flow, higher resistance, and increased turbulence than similar outer-diameter endotracheal tubes.8 Clinically, this correlates with greater difficulty to adequately ventilate and oxygenate with a rigid bronchoscope, leading us to question the suitability of the device for positive pressure ventilation. Corroborating in vivo studies regarding the use of the ventilating rigid bronchoscope as an airway device are lacking.

The objectives of this study are to validate the findings of our CAD model by determining the specific respiratory physiologic effects on lambs ventilated through a rigid bronchoscope through various methods of ventilation. In addition, we quantify the efficacy of an 80% helium and 20% oxygen gas mixture (heliox [HE]) as a potential solution for lambs experiencing depressed ventilation during rigid bronchoscopy due to its decreased turbulence and airway resistance, as demonstrated in patients with upper airway obstruction.9-12

Materials and Methods

Computational Fluid Dynamics Analysis

A CAD model was created identical to the reported physical dimensions of the size 3.5 Doesel-Huzly rigid bronchoscope (Karl Storz, Tuttlingen, Germany) with SOLIDWORKS design software (Dassault Systemes, Vélizy-Villacoublay, France). Computational fluid dynamics (CFD) analyses were performed with the integrated Flow Simulation package within SOLIDWORKS software for room air (RA) and HE with pressure-controlled ventilation. The system simulated a full respiratory cycle with the proximal inspiratory pressure set to pressure-controlled ventilation. The system simulated a full respiratory cycle with the proximal inspiratory pressure set to pressure-controlled ventilation. The laminar and turbulent flow characteristics were calculated with the time-averaged Navier-Stokes equation as previously described.8

In Vivo Analysis

Six term purpose-bred lambs were used in a crossover study that evaluated the physiologic parameters during bronchoscopy, with and without spontaneous respiratory effort. Two additional lambs were used to optimize the experimental design at the beginning of the study. Lambs were chosen because the model has proven to be an excellent animal model for ventilation.13-15 The study protocol was approved by the University of Utah Institutional Animal Care and Use Committee (IACUC; protocol 15-12012). Conflicts of interest were disclosed to the University of Utah IACUC and the University of Utah Conflict of Interest Office.

The protocol was designed to simulate ventilation during foreign body removal. A 5-mm balloon catheter (NuMED, Hopkinton, New York) was used to simulate foreign body aspiration. General anesthesia was induced with 2% isoflurane (Abbott Laboratories, North Chicago, Illinois) and titrated to keep the lambs breathing spontaneously. A size 4.0 uncuffed endotracheal tube (Mallinckrodt, Covidien, Ireland) was used to intubate the lambs and was attached to the ventilator circuit (Draeger North America, Houston, Texas). The lambs were placed on 100% fraction of inspired oxygen (FiO2) while monitoring equipment was put into place. The neck was shaved and scrubbed with Betadine solution. Intravascular catheters were placed in the common carotid artery and external jugular vein to facilitate blood gas sampling and fluid administration, respectively. The lamb was then placed in a veterinary sling in the prone position to maximize comfort and physiologic stability. A radiant warmer was used to ensure that the lamb’s rectal temperature remained within normal physiologic parameters. An oximeter probe was placed on the lamb’s tail or ear to monitor oxygen saturation (SpO2) and heart rate. Heart rate, respiratory rate, tidal volumes, systolic and diastolic blood pressure, mean arterial pressure, partial pressure of oxygen (PaO2), partial pressure of carbon dioxide (PaCO2), arterial pH, and SpO2 were monitored. Ventilation settings were adjusted to achieve respiratory homeostasis while weaning to 21% FiO2 (RA) with a respiratory rate of 12 to 14 breaths per minute, positive end expiratory pressure of 5-cm H2O, and a peak inspiratory pressure of 20-cm H2O in all test subjects. Once the lamb was stable, an arterial blood gas was drawn to establish a baseline. The endotracheal tube was then removed. The vocal folds were anesthetized with 4 mg/kg of 1% lidocaine, and the bronchoscopy device was then introduced into the trachea.

The lambs underwent the following interventions: (1) bronchoscopy for 5 minutes, (2) suctioning for 2 minutes with a 7F rigid suction catheter (Karl Storz) introduced through the bronchoscope lumen, (3) introduction and inflation of a 5-mm catheter balloon within the trachea for 5 minutes, and (4) suctioning and inflation of the catheter balloon for 2 minutes (Figure 1). A 2.9-mm zero-degree Hopkins rod telescope was in place in the bronchoscope lumen during interventions that did not involve suctioning. Outcome parameters were documented every 60 seconds. At the beginning and end of each intervention, arterial blood gases were obtained. If the lamb became physiologically unstable with a concomitant drop in blood pressure and bradycardia (defined as heart rate <130 with a 20% drop in systolic blood pressure), the study was stopped and the lamb resuscitated. Once the animal completed evaluation with the study device, it was intubated again with a 4.0 endotracheal tube and supported by 100% oxygen and allowed to return to respiratory homeostasis. The same protocol was performed with HE being substituted for RA.

Upon completion, the lamb was again intubated with an endotracheal tube, provided 100% FiO2, and returned to respiratory homeostasis. The lamb was then paralyzed with 100 mcg/kg of pancuronium and ventilation settings adjusted to achieve respiratory homeostasis on 21% FiO2.
with a tidal volume of 5 to 7 mg/kg and the same peak inspiratory pressure, positive end expiratory pressure, and respiratory rate as before. The protocol was then repeated to simulate loss of respiratory drive.

Statistical Analysis

Descriptive statistics were determined with the Mann-Whitney U test for mean comparisons of variables with 2 groupings. For variables with groupings of 3, 1-way analysis of variance was used. Because starting points for variables were different in each intervention, statistical analysis was done for the mean change from start to finish for each. Survival analysis was based on the Kaplan-Meier survival curve with log-rank test. Statistical analyses were conducted with SPSS 21 (IBM, Armonk, New York). All tests were 2-tailed, and results were considered significant at \( P \leq .05 \).

Results

CFD Analysis

CFD analysis of the 3.5 Doesel-Huzly rigid bronchoscope utilizing HE demonstrated that turbulence increased throughout the entire respiratory cycle as compared with RA. This was especially accentuated during peak flow, which corresponded to the beginning of the ventilator cycle (inspiration). In particular, the HE CFD analysis had a 20%-31% increase in turbulent energy (J/kg) than RA, with the former occurring at the end of inspiration and the latter occurring at peak flow rate (beginning of the inspiration; Figure 2).

In Vivo Analysis

Term lambs weighed between 4.6 and 6.8 kg (mean = 6.2 kg), with 4 females and 2 males. The age at the time of the experiment ranged from 1 to 4 days (mean = 2.2 days).

During spontaneous ventilation (SV), initial SpO\(_2\), respiratory rate, heart rate, mean arterial pressure, systolic blood pressure, PaCO\(_2\), PaO\(_2\), and pH were not statistically different between study groups (RA vs HE), and values were within normal physiologic ranges for term lambs. No differences were detected in the initial physiologic parameters or arterial blood gas measurements between SV and MV. Mean starting PaCO\(_2\) was 53 mm Hg in the SV group versus 61 mm Hg in the MV group. Because we were measuring change in PaCO\(_2\) and not absolute value, we believe that this did not affect the outcomes of our study.

Spontaneous vs Mechanical Ventilation

All lambs during SV on RA completed the trial without resuscitation for physiologic instability (100%), as compared with only 2 lambs during MV (33%, \( P = .004 \); Figure 3). Two lambs during MV required resuscitation after 4 minutes, while 2 more required resuscitation after 5 minutes. Because the interventions were done sequentially in each lamb, we were able to compare outcomes in SV and MV during only the first 3 minutes. After 3 minutes, PaO\(_2\) (–196 vs –190, \( P = .94 \)), systolic blood pressure (–6.7 vs –3, \( P = .34 \)), and diastolic blood pressure (–0.8 vs 1.7, \( P = .99 \)) were not different between the SV and MV groups. Mean change in PaCO\(_2\) was significantly less after 3 minutes (–6.7 vs 13, \( P = .01 \)) during SV versus MV. Mean change in heart rate was less during SV (–1 beat per minute) as compared with MV (–44 beats per minute) and was not significantly different (\( P = .17 \)). Mean change in SpO\(_2\) was significantly less during SV (–4.7%) than MV (–24.2%; \( P = .01 \); Figure 4). The mean O\(_2\) saturation nadir was 92.8% in the SV group and 68.6% in the MV group. The final mean CO\(_2\) after 3 minutes was 49 and 76.7 mm Hg in the SV and MV groups, respectively, although the difference was not significant (\( P = .06 \)).

Room Air vs Heliox

During SV, SpO\(_2\) decreased more following all interventions in the HE group as compared with the RA group; however, this was not statistically significant (Figure 5). The mean SpO\(_2\) nadir was 81% with RA and 63% with HE. No
significant difference was seen between RA and HE in the mean change in systolic and diastolic blood pressure, PaCO₂, or PaO₂ in any of the interventions during SV (Figures 6 and 7). The final mean PaCO₂ was 49.2 and 51.2 mm Hg in the RA and HE trials, respectively. All animals remained physiologically stable and did not require early resuscitation in the HE trials during SV. We were unable to collect HE results during MV, as the study was terminated prior to this intervention in all but 1 lamb due to physiologic instability.

**Discussion**

Hypoxia and hypercarbia have been shown in multiple studies to occur in as many as 1 in 4 patients undergoing rigid bronchoscopy; however, very few published studies have evaluated the rigid bronchoscope as an airway device. We recently demonstrated highly turbulent flow in the Doesel-Huzly Pediatric Bronchoscope (Karl Storz) as compared with a similar-sized outer-diameter endotracheal tube in a CAD model. One of the limitations of that study was the use of Poiseuille law to calculate resistance, which assumes laminar flow in a system that is known to have turbulent airflow. The current study provides an in vivo model to consider turbulent airflow.

The lamb model is currently the only large animal physiologic model of neonatal chronic lung disease, having replaced the baboon model over a decade ago. Lambs tolerate prolonged ventilatory support, which facilitates physiologic studies and allows repeated blood sampling because of their large size. A number of studies used term lambs as healthy control subjects. The airway of a term...
lamb (~6-8 mm) accommodates a size 4.0 uncuffed endotracheal tube and size 3.5 ventilating bronchoscope, the most common sizes used in the pediatric population. Smaller or larger sizes could be accommodated by using preterm or older lambs, respectively.

We recently reviewed the cases of >300 pediatric patients who underwent rigid bronchoscopy for airway foreign body, and found that the average duration of the procedure was 29 minutes. All lambs tested tolerated a minimum of 45 minutes of rigid bronchoscopy with various interventions prior to needing any resuscitation secondary to physiologic instability: >50% longer than the average in vivo procedure length. In lambs undergoing bronchoscopy while spontaneously ventilating, 33% experienced hypoxia across the various interventions, similar to the published rate of 25%. Many pediatric anesthesiologists prefer to maintain SV during induction to maintain respiratory drive and prevent converting a partial obstruction to a complete obstruction when a proximal foreign body is present. However, cessation of respiratory effort due to fatigue or improper depth of anesthesia is not uncommon, thereby necessitating a switch to MV. Chen et al found that 16 of 44 patients (36%) aged <5 years undergoing bronchoscopy for airway foreign body who were maintained on spontaneous or assisted ventilation were switched to controlled ventilation. In a prospective study of 36 children undergoing bronchoscopy for aspirated foreign bodies who were randomized to either spontaneous or controlled ventilation, Soodan et al found that all patients in the SV group had to be switched to controlled ventilation owing to inadequate depth of anesthesia. In the current study, lambs undergoing bronchoscopy during SV tolerated all interventions without requiring resuscitation because of desaturations, hypoxia, hypercarbia, or deviation of physiologic measurements outside of normal range. This is in stark contrast to lambs undergoing bronchoscopy during MV, where all but 2 lambs required early termination of the study because of desaturations, bradycardia, and hypotension (Figure 3), demonstrating rapid decompensation once respiratory drive is lost.

Our CAD modeling analysis demonstrated turbulent flow directed toward the tracheal wall in the bronchoscope, which may explain why the device produces a compromised airway during MV. The difference between SV and MV suggests that breathing around the bronchoscope during SV may be beneficial in maintaining respiratory homeostasis during rigid bronchoscopy. Notably, FiO₂, positive end expiratory pressure, and peak inspiratory pressure were held constant in this study to prevent masking the deficiencies in the bronchoscope as an airway device. In a true clinical scenario, an astute anesthesiologist would make adjustments to the FiO₂ and peak inspiratory pressure to maintain tidal volumes prior to clinical demise and might often be able to...
compensate for the challenges of ventilation with a rigid bronchoscope. In a patient who is difficult to ventilate because of a challenging foreign body or an underlying pulmonary disease, these interventions may be insufficient.

Our study design required intervention with the onset of bradycardia and hypotension, making it unlikely to identify statistical significance in these outcome measures. Hypoxia with a trending drop in heart rate strongly implicates impending cardiopulmonary arrest due to hypoxemia. The Kaplan-Meier log-rank test did show a statistically significant difference in need for intervention owing to physiologic instability during MV as compared with SV. During the first 3 minutes, the mean physiologic parameters during MV trended toward worse clinical outcome. These physiologic trends were notably absent during SV. However, for practical reasons of large animal studies, sample size was not sufficient to detect statistical differences.

HE has long been a safe and effective therapy for conditions causing upper airway obstruction, such as asthma, post-extubation stridor, and respiratory distress syndrome, due to propensity for laminar flow and thus generally decreasing resistance and increasing flow rates.\(^\text{9-12}\) The density of the HE mixture in this study was 0.43 g/L, while that of air is 1.3 g/L. Typically, the rate of turbulence is proportional to the density of the gas. The Reynolds number reflects the propensity for a gas to have turbulent or laminar flow:

\[
Re = \left(\frac{pv}{\eta}\right) / \eta,
\]

where \(\rho\) is the density of the gas, \(v\) is the velocity, \(r\) is the cross-sectional area, and \(\eta\) is the viscosity. As shown here, HE has a density 3 times lower than air and, with a similar viscosity, a Reynolds number 3 times lower than air, which favors laminar flow. The gas is readily available in most tertiary pediatric hospitals where bronchoscopic procedures on children are performed. While the effect of HE on ventilation has been evaluated during MV and flexible bronchoscopy in various patient populations, no previous studies have evaluated the utility of HE during rigid bronchoscopy.\(^\text{26-28}\) Contrary to what is expected on the basis of the gas density, performing our CFD analysis of the rigid bronchoscope with HE demonstrated greater turbulence during inspiration, especially peak inspiration, with HE as compared with RA (unpublished data). We hypothesize that this is a result of HE being much lighter than air and, as such, being deflected when forced through a small angulated tube, similar to a ping-pong ball. As this finding appeared to contradict previous studies evaluating HE use for airway obstruction in children, we attempted to confirm or disprove these results by conducting the same flow analysis in vivo in lambs and assessing the specific respiratory physiologic effects.

The mean final SpO\(_2\) was more negative in the HE group (−31% change) than the RA group (−20% change) throughout the intervention, although this was not statistically significant (\(P = .3;\) Figure 5). Physiologic parameters of heart rate, systolic blood pressure, and diastolic blood pressure also showed no difference in mean change between the RA and HE groups, and all trended upward, which would be expected because of the highly stimulatory effect of bronchoscopy. Furthermore, arterial blood gas measurements were not different, and the PaCO\(_2\) remained within the normal range for each group (Figures 6 and 7). Lack of improvement with HE is not entirely clear; however, we suspect that this is likely due to lambs breathing around the bronchoscope during SV. Importantly, CFD analysis demonstrated more turbulence during MV with HE than RA, suggesting that ventilation would not improve with HE. Unfortunately, we are unable to create an accurate CFD model for SV, which requires creating a CAD model of a compliant trachea. In addition, HE results during MV in the in vivo model did not allow us to draw meaningful comparisons, as the study was terminated early, after 3 minutes, owing to physiologic instability.

Limitations in the study include the small sample size, likely making the study underpowered. Additionally, it would have been ideal to alternate between starting with MV and SV. However, for ethical reasons, the IACUC required that euthanasia occur immediately following the portion of the experiment utilizing paralysis to avoid undue discomfort for the animals during reversal of neuromuscular blockade. Note that this model does not account for (1) the common clinical scenario in which a foreign body has been present for a period of time and (2) the potential decreased gas exchange and intrapulmonary shunting that may result.

**Conclusion**

This study is the first to use term lambs as a model for pediatric rigid bronchoscopy. Lambs undergoing MV show rapid decompensation secondary to hypoxia and bradycardia when compared with lambs undergoing SV, likely secondary to turbulent airflow directed toward the tracheal wall, as shown on CFD analysis. In addition, substituting HE for RA did not improve in respiratory outcomes during rigid bronchoscopy. While CFD analysis showed increased turbulence of HE as compared with RA during MV, further studies utilizing HE in vivo are needed to determine its applicability to pediatric airway analysis.

**Author Contributions**

Justin C. Sowder, study design, acquisition, analysis, interpretation of data, wrote manuscript, final approval; Mar Janna Dahl, study design, acquisition of data, revised manuscript, final approval; Kaitlin R. Zuspan, acquisition of data, revised manuscript, final approval; Kurt H. Albertine, study design, analysis and interpretation of data, revised manuscript, final approval; Donald M. Null, study design, acquisition of data, revised manuscript, final approval; Mitchell D. Barneck, acquisition, analysis, interpretation of data, revised manuscript, final approval; J. Fredrik Grimmer, study design, revised manuscript, final approval.

**Disclosures**

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complex for reducing lung and brain injury in chronically ventilated preterm lambs (no bearing on this study); Kaitlin R. Zuspan, active research contract with Shire pharmaceuticals to test an IGF1 complex for reducing lung and brain injury in chronically ventilated preterm lambs (no bearing on this study); Kurt H. Albertine, active research contract with Shire pharmaceuticals to test an IGF1 complex for reducing lung and brain injury in chronically ventilated preterm lambs (no bearing on this study); Donald M. Null, speaker/honoraria for Mallinckrodt (speaker’s bureau, symposia, expert witness); Mitchell D. Barneck, cofounder of Airway Design, LLC; holds financial interest and a pending patent on a prototype rigid bronchoscope; J. Fredrik Grimmer, cofounder of Airway Design, LLC; holds financial interest and a pending patent on a prototype rigid bronchoscope.

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