Potential therapeutic strategies aimed at reducing the intensity of mechanical ventilation in ARDS
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Heliox improves carbon dioxide removal during lung protective mechanical ventilation

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Submitted
Abstract

Introduction: Helium is a noble gas with a low density. This allows lower driving pressures in mechanical ventilation and increased carbon dioxide (CO₂) diffusion. We hypothesized that heliox facilitates ventilation in adult patients during lung–protective mechanical ventilation using low tidal volumes.

Methods: Prospective observational cohort sub study of an open label single arm intervention study. Twenty four patients were included, who were admitted to the ICU after a cardiac arrest. Patients were mechanically ventilated for 3 hours with heliox (50% helium; 50% oxygen) during a fixed protective ventilation protocol (6 ml/kg), with prospective observation for changes in lung mechanics and gas exchange. Statistics by Bonferroni post correction with statistical significance set at P<0.02.

Results: During heliox ventilation, respiratory rate was decreased (25±4 vs. 23±5 L min⁻¹, P=0.01). Minute volume ventilation showed a trend to decrease compared to baseline (11.1±1.9 vs. 9.9±2.1 L min⁻¹, P=0.03), while reducing PaCO₂ levels (5.0±0.6 vs. 4.5±0.6 kPa, P=0.02) and peak pressures (21.1±3.3 vs. 19.8±3.2 cmH₂O, P=0.02).

Conclusions: Heliox improved CO₂ elimination while allowing reduced minute volume ventilation in adult patients without lung injury during protective mechanical ventilation.
Introduction

Helium is an inert gas with lower density than air (1), allowing for less turbulent flow through airways, leading to lower airway resistance. As a result, during mechanical ventilation with a helium/oxygen mixture (heliox), lower driving pressures are needed to distribute oxygen to the distal alveoli compared to ventilation with oxygen (2). Also, diffusion of carbon dioxide (CO₂) is increased during heliox, which in addition might facilitate ventilation. Due to these properties, there may be a rationale to use heliox in patients with severe pulmonary disease with respiratory failure in whom protective mechanical ventilation with low tidal volumes is not feasible due to the development of respiratory acidosis e.g. in acute respiratory distress syndrome (ARDS). Until date, use of heliox is clinically applied using high frequency ventilation in paediatric patients (3,4) and in patients with high airway resistance due to severe asthma, most often also in children (5,6). Clinical data on adult patients during conventional mechanical ventilation are limited.

The aim of this study was to investigate the effect of heliox on gas exchange as part of a safety and feasibility study on the potential of heliox ventilation to improve neurological outcome after cardiac arrest (7). We hypothesized that the use of heliox also allows for increased CO₂ elimination in adults during conventional mechanical ventilation with low tidal volumes.

Methods

The study was approved by the local medical ethics committee of the Academic Medical Center, University of Amsterdam, the Netherlands (protocol number NL 30466.018.09) and conducted in concordance with the principles of the declaration of Helsinki and good clinical practice. The study was registered with the Dutch Trial Registry (www.trialregister.nl) under NTR2257. From all patients or their legal surrogate written informed consent was obtained. It was a prospective observational cohort sub study of an open label single arm intervention study, performed in the mixed surgical-medical intensive care unit (ICU) of a tertiary referral center in Amsterdam, the Netherlands. From April 2010 to October 2011, patients admitted to the ICU after cardiopulmonary resuscitation (CPR) because of a witnessed out-of-hospital cardiac arrest, were included in the study after informed consent was given by their relatives. Inclusion criteria were return of spontaneous circulation within 30 minutes of arrest and coma on admission. Exclusion
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criteria were hypoxemia with a need for ventilation with a \( \text{FiO}_2 \) higher than 50% or more than 10 cmH\(_2\)O positive end–expiratory pressure (PEEP), pregnancy, severe disability, a neurological disorder or co–morbiditiy with life expectancy of less than 6 months.

During heliox treatment patients were mechanically ventilated in a pressure controlled mode, using a Servo–I ventilator, which was adjusted and calibrated for heliox ventilation. Helium (Linde Gas Therapeutics, Eindhoven, the Netherlands) was mixed with oxygen to achieve a concentration of 50% helium and 50% oxygen. Respiratory settings were modified using a study protocol. Respiratory rate was adjusted to target pH of 7.35 – 7.45 and \( \text{PaCO}_2 \) of 4.5 –5.5 kPa, with an inspiration to expiration (I:E) ratio of 1:2, while maintaining a tidal volume of 6 ml/kg predicted body weight. No changes were made to I:E ratio, \( \text{FiO}_2 \) and PEEP levels during heliox treatment. After 3 hours, heliox was switched back to oxygen in air and patients were ventilated according to our standard ICU protocol with tidal volumes of 6 ml/kg predicted body weight. All patients were treated with therapeutic hypothermia (32°C–34°C) as part of standard care in patients with decreased consciousness after CPR. Target temperature had been reached by the time heliox ventilation was initiated and was maintained during heliox ventilation. For sedation, propofol and opiates were used. Neuromuscular relaxants were given as a bolus, but only during shivering.

Respiratory parameters were measured over time, starting just prior to heliox ventilation (\( T=-1 \)), within 15 minutes after start heliox (\( T=0 \)), during heliox treatment (\( T=1 \) – \( T=3 \)) and until 3 hours after heliox was switched back to oxygen in air (\( T=4 \) – \( T=6 \)). Dynamic compliance was measured during heliox ventilation (\( T=1 \) – \( T=3 \)), as this was a read–out at the Servo–I ventilator only. Resistance was calculated by dividing the pressure difference by air flow per minute and \( \text{PaCO}_2 \) / end tidal \( \text{CO}_2 \) gradient by dividing the difference between \( \text{PaCO}_2 \) and end tidal \( \text{CO}_2 \) by \( \text{PaCO}_2 \). Arterial blood gas analysis was determined hourly (Alpha stat, RAPIDLab 1200, Siemens, Deerfield, USA).

Statistical analysis

Data are expressed by mean and SEM. Time points within the same subjects were compared using paired \( T \)–test or Wilcoxon signed rank test, depending on distribution of the data. A total of three comparisons were made between several time points (\( T=-1 \) vs. \( T=0 \); \( T=0 \) vs. \( T=3 \); \( T=3 \) vs \( T=6 \)). Using Bonferroni post correction, statistical significance was set at \( P<0.02 \).
Results

106 patients were screened, of whom 29 were eligible. Of these, informed consent was refused in 4 cases. Of 25 included patients, heliox was discontinued within 15 minutes in one patient due to hypoxemia, requiring a PEEP level above 10 cm H₂O. This patient was excluded from further analyses. In the remaining 24 patients, of whom 83% was male with a mean age of 64.9±12.3 years, no acute infections were present at start of the study, 1 patient suffered from COPD, no other lung pathology was reported. During the study protocol, no changes in hemodynamics were observed.

Due to the switch of ventilation gas mixture from oxygen (T=–1) to heliox (T=0), respiratory settings needed adjustment according to the study protocol with limited tidal

Figure 1: Respiratory parameters during heliox ventilation for 3 hours (T=0 to T=3) and after switch to normal oxygen in air mixture (T3 to T6). Measurements started prior to heliox administration (T=–1). Data are MEAN ± SEM. (A) Minute volume ventilation (L min⁻¹); (B) respiratory rate (breaths min⁻¹); (C) peak pressure (cm H₂O); (D) PaCO₂ / end tidal CO₂ gradient (mmHg); (E) airway resistance (cm H₂O mL⁻¹ sec⁻¹) and (F) lung compliance (ml cm⁻¹ H₂O). *: P < 0.02
volume ventilation. Minute volume ventilation slightly rose after switching from oxygen to heliox, but no significant difference was found between before and right after the start of heliox ventilation (figure 1). Thereafter, during heliox ventilation, respiratory rates were adjusted to targeted pH and PaCO₂ levels, in accordance with the study protocol. This resulted in a significant decrease in respiratory rate and tended to decrease minute volume ventilation (figure 1). Tidal volumes remained stable at 6 ml/kg according to study and standard ICU protocol and did not change over time (data not shown). Peak pressures could be decreased during heliox ventilation (figure 1). PaCO₂ / end tidal CO₂ gradient increased immediately after start of heliox ventilation, but showed no effect over time (figure 1). Airway resistance and dynamic compliance by the ventilator did not change during heliox ventilation (figure 1).

Switch of oxygen in air to heliox ventilation resulted in a rapid decrease in PaCO₂ levels, which increased again at discontinuation of heliox (figure 2). Also end tidal CO₂ decreased immediately after applying heliox ventilation and increased again after heliox discontinuation (figure 2). Both PaCO₂ levels and end tidal CO₂ showed no changes during the 3 hours of heliox ventilation (figure 2). In agreement with an increased CO₂ elimination, an increase in pH to 7.37 was seen shortly after the application of heliox.

Figure 2: Gas exchange during ventilation with heliox for 3 hours (T=0 to T=3). Measurements started just prior to heliox administration (T=−1) until 3 hours after heliox discontinuation (T=3 to T=6). Data are MEAN ± SEM. (A) PaCO₂ (kPa); (B) end tidal CO₂ measurements (kPa); (C) pH measured hourly and (D) PaO₂/FiO₂ ratio (mmHg). *: P < 0.02; **: P < 0.01; ***: P < 0.001.
Heliox improves carbon dioxide removal during lung protective mechanical ventilation (figure 2). In the course of heliox ventilation, pH tended to increase further. Oxygenation was not altered significantly after start of heliox or after switching back to oxygen (figure 2).

**Discussion**

In adult patients ventilated with protective mechanical ventilation strategy according to current ventilation guidelines (8), use of heliox improved ventilation, by allowing lower minute volume ventilation while PaCO₂ levels decreased.

The use of heliox ventilation has been mostly investigated in respiratory conditions such as upper–airway obstruction, asthma, bronchiolitis and croup. Results indicate that heliox improves gas exchange and reduces work of breathing (4-6). Most of the studies were performed in the pediatric population. In this study we focussed on adult patients. Cardiac arrest patients are obviously not the patients who are expected to benefit most from lowering minute volume ventilation, because these patients do not have obstructed airflow. Nevertheless this population was studied, since the feasibility study investigating neuroprotective properties of heliox (7), enabled us to investigate the response to long-term heliox ventilation in adult patients ventilated with pressure controlled ventilation modes and currently recommended protective settings. The reduction of respiratory rate and the decrease of peak pressures during heliox ventilation are promising results. However, it remains to be determined whether heliox is beneficial in patients with respiratory failure in whom protective ventilation is hampered by the development of respiratory acidosis.

Our study has several limitations. As this study was a secondary analysis of a safety and feasibility study on the use of heliox in cardiac arrest patients, the number of patients was not primarily powered to investigate the effects of heliox on ventilation. This may explain observed trends but absence of statistical significance. However, our data clearly show an increased CO₂ removal and improved ventilation, starting immediately after start of heliox ventilation. Long term effects could not be studied as heliox ventilation was limited to 3 hours. Another limitation may be that all patients received therapeutic hypothermia, which is known to decrease PaCO₂ levels (9). However, throughout the whole study period, temperatures were in the range of therapeutic induced hypothermia. Thereby, observed effects could not be due to hypothermia.
Furthermore, the capnography was not adjusted for heliox ventilation, which may have resulted in underestimation of end tidal CO₂ (10) and increase in PaCO₂ / end tidal CO₂ gradient after start of heliox. However, as PaCO₂ levels decreased and end tidal CO₂ remained stable during heliox ventilation, we believe increased CO₂ removal can be endorsed to the use of heliox.

Conclusions

Heliox ventilation improved CO₂ elimination and allowed for decreased minute volume ventilation, in patients ventilated in a pressure controlled mode according to the guidelines of the ARDS network (8). Results suggest that heliox may be a therapeutic possibility in patients in whom protective mechanical ventilation is hampered by the development of respiratory acidosis.
Reference list

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