Intensive Care Med (2003) 29:1666–1670
DOI 10.1007/s00134-003-1911-z

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Helium-oxygen reduces work of breathing in mechanically ventilated patients with chronic obstructive pulmonary disease

Received: 9 December 2002
Accepted: 13 June 2003
Published online: 25 July 2003

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Abstract *Objective:* To evaluate whether helium-oxygen mixture reduces inspiratory work of breathing (WOB) in sedated, paralyzed, and mechanically ventilated patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). *Design and setting:* Open, prospective, randomized, crossover study in the medical intensive care unit in a university hospital. *Patients and participants:* 23 patients admitted for acute exacerbation of COPD and mechanically ventilated. *Measurements:* Total WOB (WOBt), elastic WOB (WOBel), resistive WOB (WOBres), and WOB due to PEEPi (WOBPeepi) were measured. Static intrinsic positive end expiratory pressure (PEEPi), static compliance (Crs), inspiratory resistance (Rins), inspiratory (*t*insp) and expiratory time constant (*t*exp) were also measured. These variables were compared between air-oxygen and helium-oxygen mixtures. *Results:* WOBt significantly decreased with helium-oxygen (2.34±1.04 to 1.85±1.01 J/l, $p<0.001$). This reduction was significant for WOBel (1.02±0.61 J/l to 0.87±0.47, $p<0.01$), WOBPeepi (0.77±0.38 J/l to 0.54±0.38, $p<0.001$), and WOBres (0.55±0.19 J/l to 0.44±0.24, $p<0.05$). PEEPi, Rins, *t*insp and *t*exp significantly decreased. Crs was unchanged. *Conclusions:* Helium-oxygen mixture decreases WOB in mechanically ventilated COPD patients. Helium-oxygen mixture could be useful to reduce the burden of ventilation.

Keywords Chronic obstructive pulmonary disease · Helium · Work of breathing · Dynamic hyperinflation · Mechanical ventilation

Introduction

Acute respiratory failure in patients with chronic obstructive pulmonary disease (COPD) is a frequent cause of admission in the intensive care unit. Whatever the precipitating cause, the respiratory failure is due to an imbalance between the respiratory load and the capacity of the respiratory muscles [1]. The load of the respiratory muscles is increased generally because of increased airway resistance and dynamic hyperinflation [1]. Both increase the total inspiratory work of breathing (WOBt). Thus in anesthetized, paralyzed, and mechanically ventilated COPD patients with acute respiratory failure WOBt is markedly higher than in normal subjects [2]. Elastic (WOBel) and resistive (WOBres) work of breathing account for, respectively, 53% and 47% of the overall increase in WOBt [2]. Apart from causal treatment, breathing helium-oxygen mixtures improves breathing pattern during spontaneous and under noninvasive mechanical ventilation [3, 4]. Helium is a low-density inert gas without any biological effect. A helium-oxygen mixture has a lower density than air-oxygen mixture. The magnitude of difference is proportional to helium concentration. Using lower gas density decreases the resistance of the airways and dynamic hyperinflation in intubated and mechanically ventilated COPD patients [5]. The consequences on the main physiological parameter, WOB, has been tested in only one study [3] with a limited number of patients during noninvasive ventilation. Thus the aim of this prospective study was to test whether helium-oxygen mixture reduces WOBt in COPD patients undergoing invasive mechanical ventilation.

Materials and methods

Study design

We performed a clinical, open, prospective, randomized, and interventional study using a crossover design. All patients received air-oxygen or helium-oxygen in random order. Measurements were obtained after 45 min of inhalation of each of the two gas mixtures. Tidal volume (Vt), respiratory rate, inspiratory flow rate, and Ti/Ttot did not differ between air-oxygen and helium-oxygen periods (Table 2). This study was approved by the local ethics committee of our institution, and informed written consent was obtained from next of kin. All patients completed the experimental protocol without any adverse effect.

Patients

Were studied 23 patients admitted to the medical intensive care unit, Hôpital Ste Marguerite, in Marseille, France, for management of acute exacerbation of their COPD. The baseline characteristics of the patients are shown in Table 1. The diagnosis of COPD was based on standard criteria [6, 7], clinical history, physical examination, and chest radiography combined, in three patients, with previous pulmonary functional tests. The precipitating cause of acute respiratory failure was acute pneumonia in three cases and was thought to be primarily related to respiratory tract infections in the others 20. All the patients were mechanically ventilated for 1–3 days using volume-controlled mode with constant flow, without positive end-expiratory pressure (PEEP). All patients needed an inspired oxygen fraction (FIO_2) less than 0.5. This limit of FIO_2 was chosen so that a highly inspired fraction of helium could be set. Patients received no cathecholamine or bronchodilator therapy during the day before the study. The patients were sedated with midazolam (Roche-Neuilly, Seine, France) and sufentanil (Janssen Cilag, Issy les Moulineaux, France) and paralyzed with cisatracurium (Glaxo-Smith-Kline, Marly le Roi, France). The attending physicians, who were not involved in the research project, established the initial setting of the ventilator according to the protocol of our ICU in this situation (Vt 7–8 ml/kg, constant flow, respiratory rate 12–15 cycles/min, inspiratory to expiratory ratio 20–25%) to limit PEEPi without impaired gas exchange.

Table 1 Characteristics of patients at inclusion (*n*=23)

Age (years)	70±10
Sex: F/M	5/18
Body mass index	23±3.6
Simplified Acute Physiology Score II	38±13
Internal diameter of the endotracheal tube (mm)	8±0.5
Days of mechanical ventilation before inclusion	2.8±2.2
PaO_2/FIO_2 (mmHg)	254±67
$PaCO_2$ (mmHg)	49±13
pH	7.35±0.07
Mean arterial pressure (mmHg)	79±14
Cardiac frequency (b/min)	83±18

Procedures and measurement techniques

All patients were ventilated with a Siemens 300 Servo Ventilator (Siemens-Elema, Solna, Sweden), which appears to be the safest to use with helium-oxygen mixture [8, 9]. The patients were ventilated with the same FIO_2 in volume-controlled mode with constant flow without PEEP throughout the study. The initial settings of the ventilator were not modified. Helium was delivered from a 50-l canister pressurized at 200 bar (AGA, Toulouse, France) through a pressure regulator into the normal air inlet. The canister contains a 78-22 mixture of helium and oxygen (Heliox), to avoid the accidental administration of a hypoxic mixture. As previously reported, the Servo 300 was unaffected by the use of helium. Whatever the FIO_2, the delivered tidal volume was equal to the Vt set [8, 9]. The inspired delivered Vt was checked by a pneumotachograph calibrated for the use of helium. To compute respiratory mechanics an integrated data acquisition system was used (Visionair, Erime, Saint Michel en L'Herm, France). This system includes a pressure transducer and a pneumotachograph (Fleish no.2) and their respective amplifiers. The signals were digitized and sampled at 200 Hz. All data were stored on a personal computer for further analysis. The pneumotachograph and pressure transducer were inserted between the endotracheal tube and the Y-piece of the ventilator circuit. The pneumotachograph was linear over the experimental range of flow. The software of the data acquisition system allows correction of gas viscosity. Before each series of measurements the pneumotachograph was checked with a 1-l supersyringe full of the gas mixtures studied. In all cases the difference between the effective and the measured volume was less than 5%. Vt was obtained by integrating the flow signal. The equipment dead space was 150 ml. To limit dead space the filter was omitted, and a heated humidifier was used on the inspiratory line. Special care was taken to avoid gas leaks in the equipment. All the measurements were carried out in body temperature and pressure conditions.

Plateau pressure (Pplat) and static PEEPi (PEEPi) were obtained by an end-inspiration and end-expiration occlusion using the hold buttons on the ventilator. Occlusions were maintained for 5 s to ensure that a plateau in airway pressure could be identified in all cases [10]. Five separate end-inspiration and end-expiration occlusions were performed per patient for each gas, leaving ten regular mechanical ventilatory cycles between them. Static compliance of the respiratory system (Crs) was determined from Pplat, Vt, and PEEPi according to the standard equation: Crs=Vt/(Pplat–PEEPi). Pulmonary flow resistance (Rins) was determined from peak dynamic pressure (Ppeak), Pplat, and inspiratory flow ($\dot{V}$) according to the equation: Rins=(Ppeak–Pplat)/$\dot{V}$: Inspiratory time constant (*t*ins) was calculated by the product of Crs and Rins. Expiratory time constant (*t*exp) was measured by the time required to exhale 63% of the tidal volume from the beginning of expiration [11, 12].

WOBinsp, which is the sum of WOBel and WOBres, was obtained by integration of the pressure-volume product during inspiration (WOBinsp=∫ Pdyn×dV) using the software of the data acquisition system. The values of Paw at point of zero flow were determined as the beginning and the end of inspiration. WOBel was calculated according to the following equation: WOBel=Vt/2×(Pplat–PEEPi). WOBres was obtained by substrating WOBel from WOBinsp that correspond to the integration of the product (Pdyn-Pplat) by the volume change [WOBres=∫(Pdyn-Plat).×dV] [12, 13, 14]. WOB to overcome PEEPi (WOBPeepi) was computed as the product of Vt and PEEPi [2]. WOBt was equal to the sum of WOBel, WOBres, and WOBPeepi. WOB is expressed in joules per liter of ventilation.

For each variable the mean value of five sequential breaths was determined. Standard five-lead monitoring electrodes and an indwelling arterial (radial or femoral) catheter continuously monitored heart rate and systemic arterial pressures, respectively. Arterial oxygenation was continuously monitored by pulse oxymetry (Nellcor, Hayward, Calif., USA). During the study a physician not involved in the experiment was present to provide patient care. The airway was suctioned 5 min before each collection of data, and this was repeated as needed during the study.

Analysis of data

Data were analyzed using a statistical software (SigmaStat 2.0–SPSS Science). Differences between the gas mixtures were analyzed using the paired *t* test. Statistical significance was set at $p<0.05$. Values are given as mean ±SD.

Results

The following decreases were observed with the helium-oxygen mixture (Fig. 1):

- WOBt from 2.34±1.04 to 1.85±1.01 J/l ($p<0.001$)
- WOBel from 1.02±0.61 to 0.87±0.47 J/l ($p<0.01$)
- WOBPeepi from 0.77±0.38 to 0.54±0.38 J/l ($p<0.001$)
- WOBres from 0.55±0.19 to 0.44±0.24 J/l ($p<0.05$)

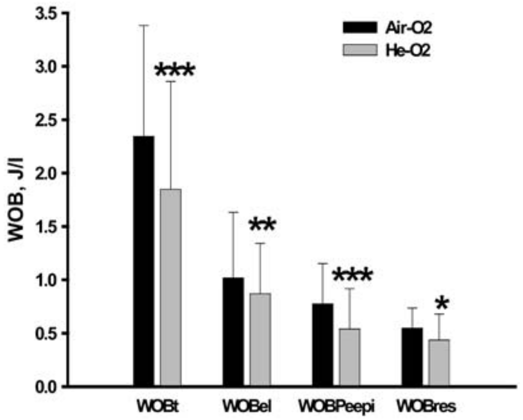

Fig. 1 Total (*WOBt*), elastic (*WOBel*), WOB due to PEEPi (*WOBPeepi*) and resistive (*WOBres*) inspiratory work of breathing with air-oxygen and helium-oxygen mixture in the 23 patients. Values are mean ±SD. Air-O2 vs. He-O2 ***$p<0.001$, **$p<0.01$, *$p<0.05$ air-oxygen vs. helium-oxygen

Each of these variables was reduced in all patients. All patients exhibited a PEEPi while ventilated with air-oxygen and helium-oxygen. PEEPi, Ppeak, and Pplat were significantly reduced when helium-oxygen was administered (Table 2). Rins and *t*ins were significantly reduced with helium-oxygen. Crs was not significantly modified. Peak expiratory flow increased with the use of helium-oxygen. *t*exp was significantly reduced with helium-oxygen (Table 2).

Discussion

The main finding of this study is that replacing air-oxygen with helium-oxygen during volume-controlled invasive ventilation in COPD patients decreases WOBt. This reduction concerns all the main determinants of the WOBt, namely WOBel, WOBPeepi and WOBres.

Several limitations of the present study should be pointed out. First, the study was performed under controlled mechanical ventilation in sedated and paralyzed patients. The extrapolation of the results to spontaneously breathing patients remains to be determined. Second, the measured WOB included the resistive work due to the endotracheal tube. However, this additional work was not corrected for since it reflects the true conditions of clinical practice. Third, the measured WOB did not consider gas compression. Volume was measured at the airway opening which may differ from the actual thoracic volume change, especially in the case of airway obstruction [12]. This effect overestimates the WOB and may have slightly overestimated the magnitude of difference between air-oxygen and helium-oxygen. Fourth, the pneumotachograph was calibrated to measure the inspired gas at body temperature. The expired gas had a slightly lower viscosity due to the presence of carbon dioxide. According to Hagen-Poiseuille's law, the expired flow may have been underestimated. The magnitude of error is about 8% [15]. This effect does not change the main result, namely the decrease in WOBt, but only peak expiratory flow measurements. Because the experimental

Table 2 Mechanical characteristics of the respiratory system with air-oxygen and helium-oxygen

	Air-oxygen	Helium-oxygen	*p*
FIO_2 (%)	32±4	32±4	NS
Tidal volume (ml)	559±119	565±136	NS
Respiratory frequency (cycle/min)	14±2.3	14±2.3	NS
Inspiratory flow (l/s)	0.65±0.18	0.68±0.18	NS
Ti/Ttot (%)	21±5	21±5	NS
Peak pressure (cmH_2O)	34±10	28±9	<0.001
Plateau pressure (cmH_2O)	17±5	14±5	<0.001
Static intrinsic PEEP (cmH_2O)	8±4	6±4	<0.001
Static compliance (ml/cmH_2O)	62±17	65±17	NS
Inspiratory resistance ($cmH_2O\ s^{-1}\ l^{-1}$)	26±6	19±5	<0.001
Inspiratory time constant (s)	1.58±0.50	1.24±0.44	<0.001
Peak expiratory flow (l/s)	0.60±0.20	0.66±0.27	<0.01
Expiratory time constant (s)	1.14±0.57	1.05±0.54	<0.001

set-up was the same in the two study conditions, it is reasonable to assume that the observed differences between air-oxygen and helium-oxygen were due to the difference in gas mixture.

In COPD patients the WOB is usually increased because of an increase in the respiratory system resistance and PEEPi [16, 17]. The presence of an endotracheal tube contributes markedly to the increase in resistance. PEEPi represents an inspiratory load especially if the patient breathes spontaneously or attempts to trigger the ventilator [18]. To reduce WOB, therapy must concentrate to decrease respiratory system resistance and PEEPi. The use of helium-oxygen mixture instead of air-oxygen is equivalent to decreasing airway resistance [4, 19]. Thus, helium-oxygen mixture should: (a) decrease Rins and WOBres, (b) increase expiratory flow with a better lung emptying and a decrease in PEEPi, and (c) by the reduction in dynamic hyperinflation WOBel may decrease. This is indeed what we observed in our patients. The mean initial level of 2.34 J/l of WOBt was generally in line with other results obtained in COPD patients [2, 17]. The level of PEEPi that we observed in our patients was similar to that recorded in decompensated COPD on the third day of mechanical ventilation [20]. Tassaux et al. [5] and Broseghini et al. [21] measured a higher PEEPi, but measurements were carried out earlier in the course of mechanical ventilation. Finally, the level of minute ventilation and the breathing pattern used are important determinants of the level of PEEPi measured.

As shown in Table 2, PEEPi was reduced by the use of helium-oxygen. This finding is explained by a faster emptying of the lung, attested to by an increased peak expiratory flow and a decreased *t*exp. Consequently WOBPeepi was reduced with the use of helium-oxygen. Crs was not significantly modified by the use of helium-oxygen. In spite of this, WOBel was significantly reduced. WOBel depends mainly on the elastic forces but also on the viscoelastic forces and distortion of the chest wall. Viscoelastic forces are independent of gas density in COPD patients [22]. Hence the work due to distortion of the chest wall is negligible with relaxed respiratory muscles [23]. Indeed the lungs are not homogeneous in COPD [24]. Thus the decrease in WOBel without a significant increase in Crs may be explained by a different distribution of Vt. Table 2 shows a decrease in Rins with the use of helium-oxygen mixture. This is consistent with predictions made from the physics of airway flow dynamics, namely that for a given flow, driving pressure is lower with a gas of lower density which explains the decrease in WOBres.

Tassaux et al. [5] measured a decrease in PEEPi and end expiratory lung volume in ventilated decompensated COPD patients. Our results confirm their findings and add the measurement of the effect of helium-oxygen mixture on the WOBt during mechanical controlled ventilation. Jaber et al. [3] investigated the use of helium-oxygen in combination with noninvasive pressure support ventilation in decompensated COPD patients. They observed a reduction in the pressure-time index, WOBel, WOBres, and WOBt. Taken together these studies show a favorable effect of helium-oxygen on WOBt in COPD. However, considering the price of helium-oxygen mixture these findings are not sufficient to recommend its use in decompensated COPD patients. Prospective studies are needed to evaluate the impact of helium oxygen on the patient outcome and the duration of hospital stay.

Acknowledgements This study was conducted in the Medical Intensive Care Unit of Hôpital Sainte-Marguerite, Marseille, France, and was supported by “L’Assistance Publique–Hôpitaux de Marseille.”

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