Helium:oxygen versus air:oxygen noninvasive positive-pressure ventilation in patients exposed to sulfur mustard

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Exposure to sulfur mustard (SM) causes a variety of respiratory symptoms, such as chronic bronchitis and constrictive bronchiolitis. This study assessed the effectiveness of noninvasive positive-pressure ventilation, adjunct with 79:21 helium:oxygen instead of 79:21 air:oxygen, in 24 patients with a previous exposure to SM presenting with acute respiratory failure. Both air:oxygen and helium:oxygen significantly decreased systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse rate, respiratory rate, dyspnea, and increased oxygen saturation (*P* values: .007, .029, .002, <.001, <.001, <.001, and .002 for air:oxygen, respectively, and <.001, .020, .001, <.001, <.001, <.001, and .002, for helium:oxygen, respectively). Moreover, helium:oxygen more potently improved systolic pressure, mean arterial pressure, pulse rate, respiratory rate, and dyspnea (*P* values: .012, .048, <.001, <.001, and .012, respectively). The results of our study support the benefit of using helium:oxygen adjunct with noninvasive positive-pressure ventilation in patients exposed to SM with acute respiratory decompensation. (Heart Lung® 2011;40:e84–e89.)

During acute decompensation of diseases, such as chronic obstructive pulmonary disease (COPD) and bronchiolitis, increased work of breathing would be a major risk of respiratory muscle fatigue,[1,2] the main factor requiring intubation and mechanical ventilation.[2-4] Noninvasive ventilation reduces the respiratory muscle load during respiratory decompensation and has been shown to decrease the work of breathing[5] and the need for intubation in these patients.[4]

Noninvasive positive-pressure ventilation (NIPPV) is defined as any form of ventilatory support applied without the use of endotracheal intubation. NIPPV includes continuous positive airway pressure with or without inspiratory pressure support and adjuncts, such as the use of helium-oxygen mixture,[6] and is now considered for patients with stable but severe COPD.[7]

Heliox, a mixture of helium and oxygen, is a biologically inert gas with a density one third that of air. Because of its low density, heliox flows more efficiently through constricted airways with less turbulence and resistance than oxygen or air–oxygen mixtures, which results in an improved laminar air movement.[8] Literature to date supports the use of helium:oxygen to treat obstructive conditions of the upper airway. Some studies have suggested that use of helium:oxygen inhalation in patients with obstructive lung disease decreases airway resistance[9,10] and successfully reverses airway obstruction in patients who are unresponsive to conventional therapy.[11] Helium:oxygen improves breathing in patients with critical upper airway obstruction.[12,13] Helium:oxygen has been shown to improve exercise endurance capacity in patients

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with moderate-to-severe COPD and may be helpful particularly in patients with severe airflow limitation.[14] It has been shown to increase oxygenation, carbon dioxide elimination, and expiratory flow, possibly through decreasing the work of breathing and enhancing the delivery of aerosolized medications to the peripheral alveoli.[11,15-18] Helium:oxygen has also been found to be beneficial in bronchiolitis.[19]

In patients with COPD, using helium:oxygen during NIPPV has been shown to decrease dyspnea and work of breathing, reduce intrinsic positive end-expiratory pressure and dynamic hyperinflation,[20] increase expiration time and carbon dioxide elimination,[21,22] and shorten duration of post-intensive care unit hospitalization.[23]

However, to date, no study has evaluated the effect of helium:oxygen in patients exposed to mustard gas. Sulfur mustard (SM) has been the most widely used chemical warfare agent in the past century. SM was extensively used during World War I[24] and the Iran–Iraq war, in which it was extensively used against both Iranian militants and civilians by Iraqi forces.[25] SM is responsible for a variety of respiratory symptoms, the most common of which are chronic bronchitis[26,27] and constrictive bronchiolitis.[26,28] The pathology in these patients is centered in the airways, mostly the small airways, rather than parenchyma and septum in chronic bronchitis and emphysema. Therefore, any treatment targeting resistance should show benefits in these patients. In fact, because obstruction of the small airways is a major contributing factor in these patients, we can expect that treatments that reduce airway resistance would alleviate symptoms in these patients. The purpose of this study was to examine whether NIPPV using 79:21 helium:oxygen instead of 79:21 air:oxygen could reduce dyspnea and improve ventilatory variables, gas exchange, and hemodynamic tolerance in these patients.

MATERIALS AND METHODS

The study was performed from February 2007 to June 2007 at a major university hospital that provides tertiary medical care for patients exposed to chemical warfare agents. All patients signed an informed consent before participating in the study, and all procedures were conducted in accordance with the principles of Declaration of Helsinki and approved by local ethical committees. The patients included in this study were exposed to SM approximately 20 years previously. They had severe dyspnea, and NIPPV was used. Criteria for initiating NIPPV follow our usual practice guidelines and require at least 2 of the following: worsening dyspnea during the previous 10 days, respiratory rate > 25 breaths/min, arterial pH < 7.35, $Paco_2$ > 50 mm Hg, and Pao_2 < 50 mm Hg.[4] Exclusion criteria include recent pneumothorax (<1 month), severe respiratory failure or hemodynamic instability with forthcoming intubation, Fio_2 of < .4, impaired consciousness or absence of patient cooperation, and facial lesions precluding NIPPV.[23]

A total of 24 patients entered this study. Before initiating the study, all patients underwent spirometry, body plethysmography, and blood gas analysis. Patients received either 79% helium:21% oxygen mixture or air:oxygen mixture for 45 minutes. After a 45-minute period, the other mixture (air:oxygen or helium:oxygen) was prescribed for the patients. Twelve patients received helium:oxygen and 12 patients received air:oxygen first. All subjects were randomly assigned to either of the 2 treatment sequences. The randomization was performed by a physician blinded to the groups using a random number table. The sequence was masked until interventions were allocated to the patients. Patients were blind to the type of gas. Physiologic variables included blood pressure, pulse rate, respiratory rate, oxygen saturation, and dyspnea on a Borg scale, performed before initiating and immediately after discontinuing the NIPPV trial. The Borg scale is an analog scale that subjectively assesses the perceived severity of dyspnea on a scale from 1 to 10.[29]

The NIPPV device selected was the BiPAP Pro Instrument (Respironics Inc., Murrysville, PA, USA), which functions as a standard continuous positive airway pressure flow generator. One of 2 levels (bilevel positive airway pressures) is controlled by a pressure valve that delivers expiratory positive airway pressure or inspiratory positive airway pressure. The ventilator was set in spontaneous mode, at the maximal tolerated inspiratory positive airway pressure, and at an expiratory positive airway pressure tolerated in the range of 2 to 5 cmH_2O. Oxygen was added to the mask side-port at a flow able to achieve a target Sao_2 greater than 90%. The nasal mask used in this study is a lightweight and solid shell rubber that conforms to a patient's nose. On each side of the plastic shell were 2 inlet connection adapters that accommodated gas supply tubing. The nasal mask was secured firmly by head straps that minimized gas leaks between the face and the mask. Oxygen connection tubing was attached to 1 of 2 nasal mask gas connection outlets and to a flowmeter. Helium was administered by connecting a tank, containing a 79:21 mixture of helium and oxygen pressurized

Table I
Baseline data of patients

	Mean ± SD (range)
Age	44.54 ± 5.70 (38-59)
FVC	2.33 ± .72 (1.05-3.87)
FVC %	50.50 ± 16.73 (25.0-89.0)
FEV_1	1.05 ± .34 (.57-1.96)
FEV_1%	29.27 ± 7.97 (17.0-46.0)
FEV_1/FVC	47.70 ± 13.20 (20.00-81.00)
MMEF	.51 ± .21 (.21-.93)
VC	2.44 ± .75 (1.29-4.08)
RV	4.45 ± 1.63 (2.04-9.86)
RV %	212.02 ± 86.29 (48.0-481.0)
TLC	7.25 ± 1.45 (5.27-12.76)
TLC %	115.92 ± 29.68 (81.0-201.0)
RV/TLC %	60.36 ± 12.97 (29.17-81.05)
pH	7.36 ± .045 (7.22-7.43)
Pco_2	43.59 ± 10.28 (35.00-81.60)
Po_2	61.01 ± 13.54 (32.30-90.00)
Oxygen saturation	86.55 ± 10.54 (57.40-96.10)
Hco_3	24.12 ± 4.15 (19.00-39.60)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; MMEF, mean maximum expiratory flow; TLC, total lung capacity; VC, vital capacity; SD, standard deviation.

at 200 bars (BOC Special Gases Company, Manchester, UK) to a helium:oxygen reducing valve and flowmeter (regulator) and placed on standby. Oxygen connecting tubing was attached to the helium:oxygen regulator and the second nasal-mask gas connection outlet.

All data were analyzed by SPSS software version 13.0 (SPSS Inc, Chicago, IL). The data were analyzed after helium:oxygen or air:oxygen administration using 2-tailed paired *t* tests. P values less than .05 were considered statistically significant.

RESULTS

The baseline data of the patients are shown in Table I. The study outcomes, before and after interventions, are shown in Table II. Our results showed that administering air:oxygen significantly decreased systolic and diastolic blood pressures, mean arterial pressure, pulse rate, respiratory rate, dyspnea, and increased oxygen saturation (P = .007, .029, .002, <.001, <.001, <.001, and .002, respectively). Helium:oxygen also significantly improved these variables (P = <.001, .020, .001, <.001, <.001, <.001, and .002, respectively). We further compared the 2 mixtures in this regard. Helium:oxygen in comparison with air:oxygen was more potent in improving systolic and mean arterial pressures, pulse rate, respiratory rate, and dyspnea (P = .012, .048, <.001, <.001, and .012, respectively) but not in improving diastolic blood pressure and oxygen saturation (P = .295 and .77, respectively). All patients tolerated and completed the procedure, and no complications or side effects were observed in the patients.

DISCUSSION

The present trial is the first to address outcome issues during the use of helium/oxygen with NIPPV in patients previously exposed to mustard gas. A beneficial effect of helium/oxygen was demonstrated in terms of blood pressure, pulse rate, respiratory rate, and dyspnea compared with air/oxygen.

Our results are in accordance with previous studies that showed helium:oxygen to be beneficial in the treatment of patients with obstructive conditions of the airways. Since its introduction, helium:oxygen has been widely used in upper airway obstructive disorders. Most of these studies have evaluated the effect of helium:oxygen mixture in acute episodes of asthma. The results, however, have been controversial. Helium:oxygen has been shown to improve at least 1 spirometry measure, such as forced expiratory volume in 1 second or peak expiratory flow rate, during asthmatic attacks in children[30] or adults.[17,31] This benefit, however, is not sustained beyond the first hour in most studies. Some suggest that patients with severe acute asthma may benefit more from helium:oxygen compared with patients with less severe acute asthma. Overall, helium:oxygen rapidly improves airflow obstruction and dyspnea in patients with acute severe asthma and may be useful as a therapeutic bridge until the corticosteroid effect occurs.[31]

Helium:oxygen has also been applied in patients with COPD. Grape et al[9] found a significant decrease in pulmonary resistance with helium:oxygen, and Swidwa et al[18] found a substantial decrease in functional residual capacity. Palange et al[32] showed that breathing helium:oxygen, by reducing airflow limitation, dynamic hyperinflation, and dyspnea sensation, is capable of improving high-intensity exercise endurance capacity in patients with moderate-to-severe COPD. It was suggested that helium:oxygen may be helpful, particularly in patients with severe airflow limitation.[31,32] However, Wouters et al[33] found no change in total respiratory resistance. The results of another study[34] indicated

Table II
Effect of helium:oxygen or air:oxygen on physiologic variables

	Before	After air:oxygen	After helium:oxygen
SBP	117.92 ± 10.62 (113.58-122.25) (105-140)	115.42 ± 11.03 (110.92-119.92) (100-145)†	112.71 ± 11.51 (108.01-117.41) (100-145)‡‡‡,*
DBP	78.75 ± 10.45 (74.48-83.02) (60-105)	77.08 ± 9.88 (73.05-81.12) (60-105)†	76.25 ± 9.00 (72.58-79.92) (70-100)‡
MAP	91.79 ± 10.07 (87.68-95.90) (75-116.7)	89.85 ± 10.02 (85.75-93.94) (73.3-118.3)††	88.12 ± 9.60 (84.20-92.04) (80-115)‡‡,*
PR	87.33 ± 12.94 (82.05-92.62) (68-125)	80.38 ± 12.91 (75.10-85.65) (60-112)†††	76.04 ± 11.55 (71.33-80.76) (59-102)‡‡‡,***
RR	24.79 ± 5.82 (22.41-27.17) (16-39)	21.79 ± 4.93 (19.78-23.80) (14-33)†††	19.75 ± 4.96 (17.72-21.78) (14-32)‡‡‡,***
Oxygen saturation	86.63 ± 9.96 (82.56-90.69) (52-95)	91.17 ± 5.78 (88.81-93.52) (70-98)††	91.38 ± 5.90 (88.97-93.78) (70-98)‡‡
Borg scale	8.00 ± .89 (7.64-8.36) (6-9)	5.29 ± 1.20 (4.80-5.78) (3-8)†††	4.75 ± 1.68 (4.07-5.43) (1-8)‡‡‡,*

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PR, pulse rate; RR, respiratory rate.
Data represent mean ± standard deviation (95% confidence interval).
†$P < .05$.
††$P < .005$.
†††$P < .001$ for after air:oxygen and before test comparisons.
‡$P < .05$.
‡‡$P < .005$.
‡‡‡$P < .001$ for after helium:oxygen and before test comparisons.
*$P < .05$.
**$P < .005$.
***$P < .001$ for helium:oxygen and air:oxygen comparisons.

that the breathing of helium:oxygen had no significant effect on dynamic hyperinflation in stable patients with COPD, regardless of the presence or absence of expiratory flow limitation during air breathing. This discrepancy in the response to helium:oxygen may reflect differences in the COPD populations studied.

Studies that used helium:oxygen mixture in combination with noninvasive ventilation have been more promising in this regard. Helium-oxygen introduced through NIPPV has shown a marked improvement in arterial blood gases and a reduction in respiratory rate and accessory muscle within 20 minutes of therapy.[22] Jolliet et al[21] applied helium:oxygen to patients with exacerbated COPD by NIPPV, reporting significantly decreased dyspnea scores, $Paco_2$, and shortened inspiratory time. These results suggest that this combination may reduce the need for intubation. In a study[23] that addressed outcome and cost issues during the use of helium/oxygen with NIPPV, but failed to show a significant reduction in the intubation rate or decrease in intensive care unit stay in patients with COPD with helium/oxygen instead of air/oxygen, a shorter duration of post-intensive care unit hospitalization was demonstrated in those in whom intubation was avoided. Moreover, a significant reduction in total hospitalization costs was documented in these patients.

Our study was performed in patients exposed to SM approximately 20 years previously. Several studies have shown that these patients have slow-evolving respiratory complications, such as bronchiolitis, chronic bronchitis, and bronchiectasis even 20 years after exposure. Some suggest that all aspects of different disorders addressed before are various presentations of bronchiolitis, which is the original nature of the pathology in these patients.[35] In these patients, the pathology is centered in the airways, primarily in the small airways, which may be responsible for the increased resistance and hyperinflation observed in these patients. Therefore, any treatment reducing resistance should be beneficial in these patients. In fact, the different underlying pathology in these patients stands for the beneficial effect of helium:oxygen adjunct with NIPPV observed in our study. The main physiopathologic finding in patients who have respiratory impairment due to exposure to mustard gas is obstruction of the bronchiole. Because the obstruction is irreversible, the current medications failed to have a proper effect. In such a circumstance, a modality such as NIPPV may be significantly effective. We showed that breathing helium:oxygen by NIPPV alleviated dyspnea and improved respiratory and pulse rates in patients who were exposed to mustard gas and had acute respiratory decompensation. Moreover, it had beneficial effects on blood pressure. Nevertheless, helium:oxygen failed to show superiority over air:oxygen in improving oxygen saturation, which was also shown by some other studies.[13] This study, however, had a major limitation. Even though patients were blinded to the gas mixture they were receiving, the investigators were not. Thus, the possibility of enrollment bias exists. However, true blinding is difficult to achieve because both the sound made by the ventilator when helium is used and a patient's voice have a different pitch, which is easily recognized by experienced staff members.[13,23]

The dyspnea in these patients is partly due to pulmonary hyperinflation, which is defined as an increase in functional residual capacity, residual volume, and total lung capacity above the predicted normal ranges. This may be a consequence of increased relaxation volume as a result of dynamic hyperinflation, which can occur whenever the expiratory flow is impeded (increased airway resistance). The increased airway resistance, however, can be overcome by decreasing the density of the inhaled gas. As density of a gas decreases, the flow increases. The density of helium is one third the density of ambient air. If during air breathing, the flow within the airways is not laminar, airway resistance should decrease using helium:oxygen mixtures.[36] As a result, inspiratory and expiratory flow are increased, enhancing carbon dioxide elimination and decreasing hyperinflation.[15] Helium:oxygen is useful in decreasing the work of breathing and the $PaCo_2$. Hypoxemic patients are not suitable for helium:oxygen therapy.[13] In addition, helium:oxygen may show further therapeutic benefits because there are no reported side effects with helium:oxygen.[16] Further studies are needed to address this issue.

CONCLUSIONS

The results of our study revealed the effectiveness of using helium:oxygen adjunct with NIPPV in mustard gas-exposed patients with acute respiratory decompensation. This combination has the advantage of avoiding intubation. The observed therapeutic benefit may be due to a decrease in the work of breathing and hyperinflation.

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