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Low Pressure Heliox-based Rebreather System to Reduce Work of Breathing and Conserve Gas

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Conflict of Interest: S.P. has a patent for a home-based breathing system (US20160213879A1) that has been licensed by SaiOx, Inc. Currently S.P. does not have any investments in SaiOx, Inc and S.P. does not receive any royalties.

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Abstract

Background: To test the ability of a low-pressure, low-flow, Heliox-based rebreathing system to reduce work of breathing and conserve gas while preserving CO_2 concentration, temperature, and humidity at physiological levels in a bench study.

Methods: We performed a bench study of a novel low-pressure, low-flow, noninvasive Heliox rebreathing system with CO_2 scrubber that was connected to an artificial lung simulator with careful monitoring of flow, pressure, work of breathing, oxygen (O_2), carbon-dioxide (CO_2), temperature, and humidity levels. Multiple runs of breathing were performed while manipulating levels of resistance (5 – 30 cm H_2O/L/sec), gas mixtures (room air, 79% Helium 21% O_2, and 70% Helium and 30% O_2), and leak levels (ultra-low, low, and high).

Results: We found significant reductions in work of breathing (up to 64%) while conserving gas with estimates of up to 54-fold reduction in medical gas wastage ($P<0.001$). Specifically, at resistances of 5, 10, 20, and 30 cm H2O/L/sec we demonstrated 64%, 57%, 36%, and 7% reduction in work of breathing ($P<0.0001$). Gas wastage was reduced by 10- to 54-fold while the end-tidal CO_2 concentration, humidity, and temperature were maintained by the device at physiological levels.

Conclusions: In a bench-test, a low-pressure, low-flow, noninvasive Heliox rebreathing system with CO_2 scrubber reduced work of breathing and conserved gas while preserving CO_2 concentration, temperature, and humidity at physiological levels. Future studies in human subjects need to be performed to determine whether reduction of work of breathing and gas conservation can be achieved.

Keywords: Chronic obstructive pulmonary disease, sleep, emphysema, noninvasive ventilation, artificial respiration, heliox.

Introduction

Heliox has been used alone or in combination with non-invasive ventilation (NIV) for the treatment of acute respiratory failure due to asthma exacerbation, upper airway obstruction, bronchiolitis, and COPD [1-5]. One of the major barriers for the utilization of Heliox gas in the clinical setting is the cumbersome nature of administering the gas[6]. Specifically, the need for transferring large tanks into the intensive care unit (ICU) rooms and storage needs is both labor-intensive and time consuming for the respiratory therapist. Additionally, the respiratory therapists need to transport new tanks to replenish the supply every 8-12 hours in the ICU from the storage area. Moreover, Helium is a natural resource and gas wastage due to leaks incurred by using a simple nonrebreather or Venturi mask does not capture the exhaled or leaked gas and thereby increases costs and wastes a finite resource[7]. A system that uses a rebreathing circuit and low-pressure low-flow system can reduce the magnitude of air-leak and also help improve tolerability of the ventilatory support by avoiding a high-flow system that uses a conventional loose fitting face mask. There is a knowledge gap, however, as to whether such a rebreather system (CO_2 scrubber and rebreathing circuit) with Heliox and low-pressure, low-flow state, can reduce work of breathing and conserve gas.

To address the afore-mentioned knowledge gap, we devised and bench-tested a prototype device of a Heliox rebreathing system with CO_2 scrubber that conserves gas and assessed the impact on work of breathing with an artificial lung system. Specifically, our aims were to test the ability of a low-pressure, low-flow, Heliox-based rebreathing system to (a) reduce work of breathing [PRIMARY AIM] and (b) conserve gas while preserving CO_2 concentration, temperature, and humidity at physiological levels [SECONDARY AIM] in a bench study. If our aims are achieved, and human testing in patients with simulated airway obstruction are successfully performed to demonstrate efficacy [2] -- then the device can be further tested and made available in various clinical applications.

Materials and Methods

A bench study experimental set-up is shown in the schematic diagram in **Figure 1**. The device was tested with the mask interface attached to a manikin head with realistic upper airway structure. The dead space of the manikin airway is 150 mL with an airway resistance is 2.4 cm H2O/L/s. The furthest end of the manikin's tracheal airway was connected to a lung simulator (ASL 5000®; IngMar Medical, Pittsburg, PA, USA) that was programmed to simulate spontaneous breathing with various additional resistances [8, 9]. Measurements of flow (V in **Figure 1**; heated pneumotachograph, Fleisch, Lausanne, Switzerland) and airway pressure (P in **Figure 1**; Validyne, Northridge, CA) were made at the corresponding locations between the manikin mask interface and the device [8, 10, 11]. Data were collected and stored on a laptop after analogue to digital conversion and signal conditioning for subsequent review and analysis (Windaq, Akron, OH). An adjustable leak aperture (L in **Figure 1**) was placed between the mask interface and the device to facilitate known levels of leak [8]. Carbon-dioxide was entrained at the location (CO_2 in **Figure 1**) indicated between the lung simulator and mannequin head as indicated. Temperature was measured at two locations: A temperature probe was placed at a side port near the mask (T; in **Figure 1**) and an additional temperature probe was placed downstream to the CO_2 scrubber (T'; in **Figure 1**).

The device configuration is shown in **Figure 1**. The gas source was a tank containing mixed gas (80% Helium [He] and 20% Oxygen [O_2]) and another tank with 100% O_2. The device has an option for a wall source for 100% O_2 in addition to the tank. A Heliox blender enabled appropriate admixture of gases to the desired He:O_2 concentration levels. A closed circuit with CO_2 scrubber and monitoring devices for CO_2 and O_2 concentration was included (Nonin capnograph, Plymouth, MN). A reservoir bag enabled appropriate gas inspiratory flow and thereby prevented any situation during which a negative airway pressure – that can increase work of breathing -- would be created. A one-way valve enabled directionality of the flow as indicated in **Figure 1**.

Prevention of asphyxiation

To prevent asphyxiation there are three features. We incorporated both a O2 sensor (blue box on the inspiratory limb) and CO_2 sensor (green box on the expiratory limb) with preset limits that would alarm if either or both tanks (HeO_2 or O_2 tanks) were to become empty or if the CO_2 scrubber were to malfunction (**Figure 1**). Second, both tanks that serve as gas source contain O2 (100% Oxygen and an admixture of 80% Helium and 20% Oxygen (**figure 1**). Such a dual tank system is aimed at reducing chance for asphyxiation if either one of the tanks runs out of gas. Third, a solenoid valve that is on the face mask is shown in the inset, which, in the event of a system electrical failure will immediately open a trapdoor on the full-face mask (due to loss of electricity) and allow the patient to breathe room air and thereby prevent asphyxiation.

Work of breathing

During the simulation runs the airway resistance was varied between four different levels -- 5, 10, 20, or 30 cm H_2O/L/s. At each resistance level, the muscle pressure (Pmus) was set on the lung simulator to achieve a tidal volume of 500 ml for each run. In addition to varying the resistance level, there were three different gas admixtures of He:O_2 concentrations that were delivered: 0:21 (room air); 79:21 Heliox and 70:30 Heliox. In all, four runs were performed for 3 minutes each at each resistance and gas admixture level for a total of 48 runs. The rationale for the 3-minute runs was based upon our prior study in which we found that 3-minute runs of stable conditions in a bench testing model demonstrated reliable results and allowed stable and representative data of work of breathing and corresponding findings[11]. The inspiratory and expiratory work of breathing generated by the lung simulator device was recorded at the end of each 3-minute run.

Gas leak and gas conservation

Multiple simulation runs (n=3) were performed at different leak levels at the low-pressure state (mean airway pressure of 0.5 cm H_2O and range of 0-2 cm H_2O) – ultralow (0.53 $\underline{+}$ 0.35 lpm [Mean, standard deviation]), low (0.85 $\underline{+}$ 0.14 lpm) and high (1.3 $\underline{+}$ 0.02 lpm) -- set by an adjustable aperture to mimic real-world air leak from the face-mask interface with a diameter range of 10.7, 12 and 13.4 mm range respectively [12]. Such apertures at a conventional (higher) airway pressure setting of 15 cm H_2O would have resulted in air leaks of 16, 25, and 40 lpm, respectively. Considering that exhaled gas rich in oxygen is recirculated through the device CO_2 scrubber, the fraction of inspired oxygen (FiO_2) was maintained with very little loss of gas outside the rebreather system. A continuous background flow of gas of ~ 1 to 2 lpm as measured during the expiratory phase constituted the low-flow state. When the lung simulator switches to inspiratory cycle a sinusoidal inspiratory flowrate with a peak of 60 lpm was programmed into the lung simulator to mimic the human condition. In contrast the flow rate during exhalation for NIV ranges much higher (~40 lpm) for a full-face mask with bleeder valves at a pressure setting of 15 cm H_2O [13]. Three runs for 8 hours each were performed at each leak level (ultralow, low, or high) and for each gas admixture concentration of Heliox (70:30 and 79:21) for a total of 18 runs.

CO_2 elimination

CO_2 gas was entrained at 2-2.5 L/min between the lung simulator and the mannequin to simulate CO_2 gas production and to artificially raise the end-tidal CO_2 concentration in the breathing circuit to 46 mmHg (which is higher than normal range of 38-42 mmHg). Subsequently, an 8-hour run was performed to assess whether the exhaled CO_2 levels were normalized and maintained at normal levels. This run was repeated three times at a He:O2 blend of 70/30 and ultra-low leak level.

Humidity

An in-line humidifier and de-humidifier were introduced in the inspiratory and expiratory limbs of the device, respectively, to humidify and de-humidify the gas within the circuit at a He:O2 blend of 70/30 and ultra-low leak level. The exhaled humidity levels when compared to the ambient humidity levels in the laboratory was measured and reported over 8-hour period (3 runs).

Comparisons for work of breathing across various resistance levels and medical gas admixtures were performed using 2-way ANOVA with repeated measures (IBM SPSS, Armonk, NY). Means and standard deviations are reported unless otherwise specified. Coefficient of variation was measured as the proportion of standard deviation of mean values and expressed as percentage. All values are reported as statistically significant if P values are less than 0.05.

Results

Work of breathing

Work of breathing was consistently reduced at both Heliox concentrations and are shown in **Table 1** and **Figure 2**. The work of breathing was reduced by 64%, 57%, 36%, and 7% at resistances of 5, 10, 20, and 30 cm H_2O/L/sec, respectively ($P<0.0001$; 2-way ANOVA with repeated measures). There was negligible difference in reduction of work of breathing between 70/30 and 79/21 Heliox gas mixtures. There were very small differences in variability across the various runs and hence the standard deviation bars are not seen in **Figure 2**. The coefficient of variation was less than 0.02%.

Gas leak and conservation

Multiple simulation runs (n=3) were performed at different leak levels and the remaining time that was left in the tank at a certain flow (gas leak rate) was estimated for a M-tank (3200 L) using the remaining pressure (pressure gauge; **Table 2**). The gas loss was then used against the lifespan of a M-tank without the conservation system at 6 lpm to provide meaningful estimates of fold-increase in tank lifespan (**Table 2**). Depending on leak levels and Heliox concentration chosen, the tank would last from 5 to 27 days. A fold-change for increase in time based upon such an assumption are provided in **Table 2** for each Heliox admixture level and leak level. All fold changes were statistically significant ($P<0.001$).

CO_2 elimination, temperature, and humidity

Considering that the system assumes adequate CO_2 elimination and that the CO_2 scrubber eliminates CO_2 through an exothermic reaction, the end tidal CO_2 levels and temperature levels were also measured at the level of the mask. An additional temperature probe was placed near the CO_2 scrubber. After entraining 3% CO_2 gas, over an 8-hour run, following an initially high CO_2 level there was an immediate and persistent normalization of the CO_2 levels in **Figure 3**. Moreover, the mask temperature (**Figure 3**) remained constant whereas the temperature at the CO_2 scrubber was mildly elevated and remain elevated over an 8-hour period ($P=0.01$). The humidity levels remained normal between 43-47% (Laboratory humidity level was 38-42%).

Discussion

In a bench testing experiment we have demonstrated that a novel rebreather system (CO_2 scrubber and rebreathing circuit) with Heliox and a low-pressure, low-flow state, can reduce work of breathing. We have also shown that the system can significantly conserve gas by reducing waste while preventing hypercapnia or adverse alterations in airway temperature and humidity levels.

Our system provides a novel approach at providing low-pressure, low-flow system that can alleviate the work of breathing due to the reduced density of the gas. We report our system as a low-flow system in comparison to the high flow nasal oxygen (HFNO) systems that are currently used in patients with acute respiratory failure[14]. Novel systems that do not use high-flow or high-pressure systems for reducing risk for intubation and mechanical ventilation when compared to conventional O_2 therapy are needed considering the morbidity associated with invasive mechanical ventilation. However, human studies aimed at demonstrating the ability of our device to reduce work of breathing needs to be performed.

Our gas conservation approach prolonged the lifespan of an M-size tank significantly and reduced wasteful exhalation of medical gases (Helium and Oxygen; see **Table 2**). Such an approach aimed at conserving Heliox can save significant time for the busy respiratory therapists and also enable smaller tanks that can facilitate ease of transport, storage, and occupy less space in the ICU room. Moreover, when used purely with 100% oxygen alone, and without any Heliox, our proposed system can significantly conserve precious oxygen supplies, although it may not reduce work of breathing due to lack of high airway pressure assistance or low-density gas (Heliox). Efforts need to be undertaken to bringing such simple technology to a strained infrastructure with lifesaving implications in both developed and developing countries [15].

Bench tests of our device demonstrated that our gas conservation approach with the Heliox rebreathing system with CO_2 scrubber would prolong the life of each tank to 27 days when compared to the life of a full tank of conventional Heliox systems of just 12 hours (half-a-day; **Table 2**). This is a 54-fold improvement in gas conservation that can, in turn, facilitate implementation of this intervention in both the hospital and possibly, in the future, even in the home setting for stable severe COPD with huge cost savings (**Table 2**). The gas cost of our proposed innovative system is only $650 to $1,680 per year if this device were used only nocturnally for 8-hours in hospitalized patients. Moreover, our gentle low pressure, low flow system brings forth innovation that addresses poor adherence to noninvasive mask ventilation that is engendered by conventional high-pressure and high-flow systems.

In summary, we performed a bench-test of a low-pressure, low-flow, noninvasive Heliox rebreathing system with CO_2 scrubber that reduced work of breathing and conserved gas while preserving CO_2 concentration, temperature, and humidity at physiological levels. This innovative low-pressure, low-flow, system needs further testing in humans.

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Conflict of interest statement: S.P. has a patent for a home-based breathing system (US20160213879A1) that has been licensed by SaiOx, Inc. Currently S.P. does not have any investments in SaiOx, Inc and S.P. does not receive any royalties.

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Figure Legends

Figure 1 The bench set-up of the device, mask interface, and the manikin head with realistic upper airway structure is shown. The manikin's tracheal airway was connected to a lung simulator programmed to simulate spontaneous breathing with various additional resistances. Measurements of flow (V), airway pressure (P), temperature near the mask (T) and downstream to the CO2 scrubber (T'), CO_2, and O_2 levels were made and the data was collected and stored on a laptop after analogue to digital conversion (A/D converter) for analysis. An adjustable leak aperture (L) was placed between the mask interface and the device to facilitate known levels of leak. Carbon-dioxide was entrained at the location (CO_2) indicated between the lung simulator and mannequin head as indicated. The device involved a one-way valve (Valve), reservoir bag, CO_2 scrubber, Heliox blender, and medical gas sources (Heliox; HeO_2 at 80% Helium and 20% O_2 and 100% O_2) as well as a wall source for O_2 at 100%. The upper left inset reveals the mask with a solenoid valve that would automatically open if there were an electrical failure due to demagnetization of an electrical magnet. An image of the compact device without the shell cover is shown in the lower bottom inset.

Figure 2 Work of breathing (Y-axis) is plotted for various levels of resistance (X-axis) for 79%:21% Helium:Oxygen (Heliox 79/21; left panel) and 70%:30% Helium:Oxygen (Heliox 70/30; right panel). There is significant reduction in work of breathing that ranges from 7% to 64%. The Standard Deviation across multiple runs are not apparent as the coefficient of variance (proportion of standard deviation of the mean values) is less than 0.02%.

Figure 3 Breathing runs that lasted for 8-hours demonstrate that the device was able to maintain CO_2 and temperature levels at the site of the mask at normal physiological levels. Measurement of temperature distal to the CO_2 scrubber is also shown revealing the exothermic reaction of CO_2 removal.

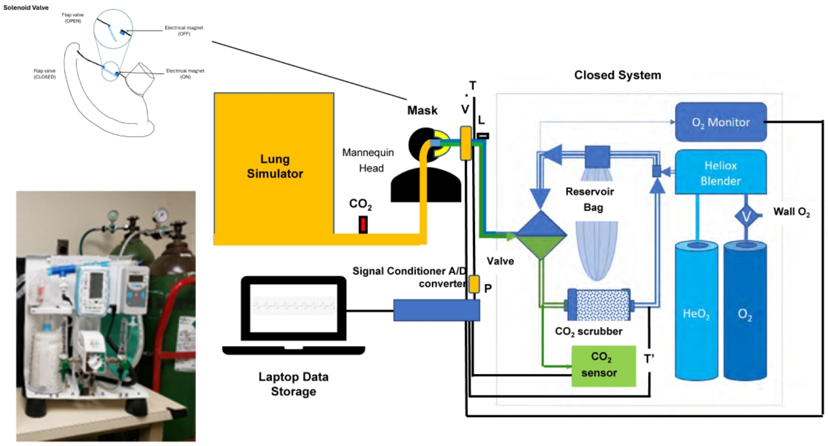
Quick look

Current Knowledge

Current methods of administering Heliox in clinical settings suffer from barriers to delivery such as large and difficult to transport tanks needed due to a high-flow delivery system that is associated with significant gas wastage. Gas waste can be reduced by rebreathing systems but such a rebreathing system with CO_2 scrubbers can create an exothermic reaction with heat and be adversely affected by moisture. The combination of Heliox and rebreather system with CO_2 scrubber has not been shown in laboratory evaluations to reduce work of breathing while preserving temperature, CO_2 concentration, and humidity levels.

What This Paper Contributes To Our Knowledge

In a laboratory bench evaluation using an artificial lung simulator, a novel low-pressure, low-flow, noninvasive Heliox rebreathing system with CO_2 scrubber that reduced work of breathing and conserved gas while preserving CO_2 concentration, temperature, and humidity at physiological levels.



The bench set-up of the device, mask interface, and the manikin head with realistic upper airway structure is shown. The manikin's tracheal airway was connected to a lung simulator programmed to simulate spontaneous breathing with various additional resistances. Measurements of flow (V), airway pressure (P), temperature near the mask (T) and downstream to the CO2 scrubber (T'), CO2, and O2 levels were made and the data was collected and stored on a laptop after analogue to digital conversion (A/D converter) for analysis. An adjustable leak aperture (L) was placed between the mask interface and the device to facilitate known levels of leak. Carbon-dioxide was entrained at the location (CO2) indicated between the lung simulator and mannequin head as indicated. The device involved a one-way valve (Valve), reservoir bag, CO2 scrubber, Heliox blender, and medical gas sources (Heliox; HeO2 at 80% Helium and 20% O2 and 100% O2) as well as a wall source for O2 at 100%. The upper left inset reveals the mask with a solenoid valve that would automatically open if there were an electrical failure due to demagnetization of an electrical magnet. An image of the compact device without the shell cover is shown in the lower bottom inset.

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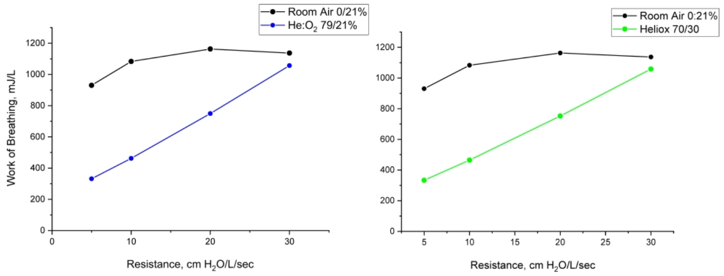

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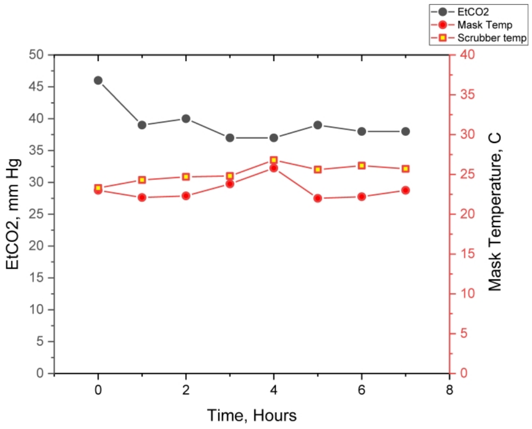

Breathing runs that lasted for 8-hours demonstrate that the device was able to maintain CO2 and temperature levels at the site of the mask at normal physiological levels. Measurement of temperature distal to the CO2 scrubber is also shown revealing the exothermic reaction of CO2 removal.

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Table 1: Effect of Heliox on Work of Breathing

Resistance (cm/H_2O/L/Sec)	Work of breathing (in mJ/L) * for various gas admixtures (Helium : Oxygen; percentage)			Reduction of work of breathing
	0:21	**79:21**	**70:30**	**(%)**
5	930 ± 0.2	331.8 ± 0.3	333.3 ± 0.2	- 64%
10	1083 ± 3.4	462.3 ± 0.4	464.7 ± 0.2	- 57%
20	1163.1 ± 1.5	749.6 ± 0.4	752.2 ± 0.2	- 35%
30	1136.9 ± 0.6	1056.6 ± 0.3	1058.2 ± 0.4	- 7%

± Standard deviation

* Work of breathing was reduced to various extent by the Heliox gas admixtures and at various settings of resistance.

Table 2: Estimations of Tank Lifespan at Various Leak levels

Leak levels	**Lifespan of a M-tank used with the device (days) for various Heliox gas admixtures**			
	79:21	**Fold-increase**	**70:30**	**Fold-increase**
Ultra-low	27	54-fold	12	24-fold
Low	17	34-fold	6	12-fold
High	11	22-fold	5	10-fold

Assumptions are based upon a standard M-tank last for 0.5 days in a hospital setting without the rebreathing system. Ultralow (0.53 ± 0.35 lpm [Mean, standard deviation]), low (0.85 ± 0.14 lpm) and high (1.3 ± 0.02 lpm) were preset by adjusting the leak aperture in the circuit.