

Invited Review

Development of Aerosol Drug Delivery with Helium Oxygen Gas Mixtures

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ABSTRACT

Aerosol drug delivery using helium-oxygen gas mixtures (heliox) is considered in terms of flow physics, atomization, and aerosol mechanics. Theoretical considerations are then related to past studies of the physiological effects of the inhalation of heliox and its potential use as a drug delivery medium. Past clinical trials of heliox investigating this use are reviewed and technical recommendations made for its successful development. It is proposed that improved peripheral lung drug delivery with heliox is highly dependent on proper administration, especially the inclusion of proper reservoir system for the gas.

Key words: aerosol drug, aerosol therapy, atomization gas, heliox, helium, nebulizer

INTRODUCTION

THE MEDICAL USE of helium-oxygen gas mixtures (heliox) dates back nearly 70 years. These mixtures are often used to provide improved gas exchange in subjects suffering from obstructive airway conditions. Heliox has also been investigated as a medium for aerosol drug delivery through a long series of clinical trials with the general hypothesis that the lower density gas would provide improved outcomes in subjects receiving treatments for obstructive disease conditions. These studies, including two recent meta-analyses,^{1,2} offer a mixed picture regarding the use of heliox for aerosol drug delivery.

The present paper reviews the physical and physiological aspects of aerosol drug delivery with heliox and considers how administration

technique may effect outcome. Previous trials investigating heliox for inhalation and aerosol drug delivery will be reviewed and interpreted, and recommendations proposed to maximize the benefits of heliox, and to facilitate its development as a medium for aerosol drug delivery.

FLOW PHYSICS OF HELIOX

In standard atmospheric conditions, helium has a density (ρ) of 0.17 kg/m³ compared to 1.33 for oxygen.³ The viscosities (μ) of these gases are, respectively, 197 and 204 μP (10^{-7} kg/(m · s)). The properties of a mixture of these gases can be estimated as:

$$B_{\text{mixture}} = C_1B_1 + (1 - C_1)B_2 \quad (1)$$

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where B is the density or viscosity, C is the mole fraction of the gas component, and the subscripts 1 and 2 refer to the two components of the mixture. Using this estimation, a 70/30 helium/oxygen mixture would be 2.3 times less dense than air and an 80/20 mix three times less (Table 1). Since the viscosities of these gases are similar, the differences in their flow properties are primarily related to density.

Reports on the clinical use of heliox predate any detailed consideration of the fluid mechanics involved with its inhalation. Typically, the respiratory improvements have been attributed to a change in the character of the flow from turbulent to laminar due to the lower density of heliox. Indeed, heliox will have a lower propensity for turbulent flow, as measured by the Reynolds number (Re):

$$\text{Re} = \frac{\rho U D}{\mu} = \frac{4\rho V}{\pi\mu D} \quad (2)$$

where U is a flow velocity (in m/sec), V is the flow rate, and D is a length representing the geometry of the flow (typically the diameter of the airway). Low values of Reynolds number are indicative of laminar flow and higher ones of turbulence. The propensity for turbulence can be vastly oversimplified through the consideration of Reynolds number alone, however. Flow geometry and surface conditions play a crucial role. Studying a model of the human larynx and trachea, Dekker found that turbulence was exhibited even at approximately 6.0 LPM/Re~560 during inhalation and 7.3 LPM/Re~684 during exhalation. These values are well below typical peak inhalation flow values: 34 LPM/Re~3173 for inhalation and 27 LPM/Re~2530 for exhalation.⁴ Even with the 2–3-fold reduction in Reynolds number associated with the lower density heliox, some amount of turbulence generation still appears likely.

TABLE 1. DIFFERENT GAS PROPERTIES IN STANDARD ATMOSPHERIC CONDITIONS (70°F AND 14.70 PSIA)

Gas	Density (kg/m ³)	Viscosity (μP)
Heliox 80/20	0.40	198
Heliox 70/30	0.52	199
Air	1.20	183
100% oxygen	1.33	204

Adapted from Raznjevic.³

In an idealized airway, the relationship between flow and pressure can be considered in terms of equations derived for pipe flows⁵:

$$V = \pi \sqrt{\frac{\Delta P D^5}{8L\rho f}} \quad (3)$$

where V is the flow rate, ΔP is the pressure differential to drive the flow, L is the length of the flow region, and f is a friction factor defined based on turbulence level. The friction factor can be approximated for the various flow regimes as follows⁵:

$$\begin{aligned} f &\sim 64/\text{Re} && \text{[laminar]} \\ f &\sim 2.2/\text{Re}^{1/2} && \text{[transitional]} \\ f &\sim \text{constant (function of surface roughness)} && \text{[fully turbulent]} \end{aligned} \quad (4)$$

For laminar flows, the above friction factor results in a flow-to-pressure relationship that is independent of density. For transitional or turbulent flows, however, higher flows will be attainable at a given pressure with a lower density gas. Inversely, less pressure (or work of breathing) is needed to generate a given flow rate with a lower density gas:

$$\begin{aligned} V &\propto \Delta P && \text{[laminar]} \\ V &\propto \sqrt[3]{\frac{\Delta P^2}{\rho}} && \text{[transitional]} \\ V &\propto \sqrt{\frac{\Delta P}{\rho}} && \text{[fully turbulent]} \end{aligned} \quad (5)$$

In the very deep lung, flows are likely to be laminar. Similar pressure to flow relationships will then occur for heliox and air. Flows into and out of this region, however, will be limited by conditions in the upper airways, mouth, and trachea. The upper airways have the highest flow resistance of any portion of the lung, even under healthy conditions.⁶ During obstructive lung disease states, the resistance in the upper airway region increases, affecting both inhalation and exhalation. Heliox will increase flow rate, not because it changes the flow from turbulent to laminar, but rather because in the large airways, the pressure differential needed to drive the flow will be less. Increased convective flows into the

peripheral lung promote increased diffusional flows, thus leading to more effective gas exchange.⁷

Papamoschou⁵ performed an analysis of flows in the lung based on Equations 3 and 4 and a simplified model of the human lung, and determined analytically that 80/20 heliox will provide a 50% higher delivery rate of oxygen compared to air. He extended his analysis to flows through an obstruction and obtained similar results. Ho et al.⁸ considered the delivery of heliox or pure oxygen through an obstructed airway and concluded that 100% oxygen is likely to provide better oxygen delivery to the lungs, while heliox is more likely to provide better CO₂ removal. However, these studies of single breath analyses are limited since they do not consider the potential effects of heliox inhalation on more macroscopic physiological parameters such as respiratory rate and tidal volume.

STUDIES ON HELIOX INHALATION

Esposito and Ferretti⁹ noted higher minute and alveolar ventilation when 79/21 heliox was inhaled versus air during normoxic and hypoxic exercise. During hypoxia, an increase in peak oxygen consumption was noted in the subjects breathing heliox versus air, along with increased arterial oxygen saturation, increased partial pressure of oxygen (p_{aO_2}), and decreased partial pressure of CO₂ (p_{aCO_2}). Babb et al.¹⁰ performed a study where senior runners inhaled either room air or heliox while performing exercise. The subjects inhaling 79/21 heliox had higher tidal volumes, higher respiratory rates, and consequently higher minute volumes at peak exercise. End tidal CO₂ was significantly lower when using heliox at all work rates considered. Pulmonary resistance was lower as well with heliox. When breathing heliox, the runners demonstrated higher mean expiratory flow rates, lower end expiratory lung volumes, and less expiratory flow limitation. Pedersen and Nielsen¹¹ have demonstrated that the maximum exhalational flow associated with flow limitation is inversely proportional to gas density. A decrease in flow limitation would allow for more effective exhalation, less gas trapping and hyperinflation, and consequently more effective total gas exchange.

Rodrigo et al.¹ and Ho et al.² review a series of studies involving heliox inhalation. In nine stud-

ies from these analyses, summarized in Table 2, heliox was used only as a means of improving ventilation and not to deliver aerosol drugs.^{7,12-19} Seven of these studies involved mask inhalation of heliox, and two involved mechanical ventilation.^{7,15} Of the seven mask studies, five demonstrated positive results based on peak expiratory flowrate (PEFR),^{12,13,16} PaCO₂^{14,19} pulsus paradoxus,^{12,16} blood pH,^{14,19} and dyspnea index.^{12,13} Two studies reported generally negative results. One study reported no significant change in one second forced expiratory volume (FEV1) with 70/30 heliox.¹⁷ The other reported no changes in forced vital capacity (FVC), FEV1, or indices of dyspnea, but did note small but significant improvements in PEFR and FEF25-75 with 70/30 heliox.¹⁸

Schaeffer et al.¹⁵ demonstrated an improved alveolar to arterial oxygen gradient (p_{A-a}) when mechanically ventilating asthmatic subjects with 80/20 heliox versus case-matched controls ventilated with room air. Gluck et al.⁷ utilized a crossover design, ventilating seven subjects intubated for severe asthma exacerbations, first with air and then subsequently with 60/40 heliox. Heliox ventilation increased blood pH and decreased PaCO₂ levels in all seven subjects. Levels of P_{aO₂} increased in five of the subjects who had initial levels of 96 mm Hg or below, and decreased in the two subjects with higher levels (120 and 102 mm Hg).

In addition to the studies reported by Rodrigo et al.¹ and Ho et al.,² Diehl et al. demonstrated that heliox facilitates ventilator weaning in subjects with chronic obstructive pulmonary disease (COPD).²⁰ Jaber et al. also concluded that heliox significantly improved comfort and decreased inspiratory effort after tracheal extubation.²¹ The same authors had also investigated the use of heliox in non-invasive ventilation in patients with acute exacerbations of COPD. They concluded that heliox significantly enhanced the ability to reduce patient effort and to improve gas exchange.²² In both studies, oxygen concentration in the mix was adjusted from 25% to 40% to maintain oxygen saturation at 90% or higher. Similarly, Jolliet et al. demonstrated better gas exchange when heliox was used during noninvasive pressure support ventilation (NIPSV) of subjects with COPD.²³ A later larger study by the same authors demonstrated similar gas exchange properties for heliox and air, but also reported shorter hospital stays and lower total costs when

TABLE 2. CLINICAL TRIALS USING HELIOX WITHOUT SPECIFIC NEBULIZATION^a

<i>Trial</i>	<i>Reference</i>	<i>n</i>	<i>Study treatment</i>	<i>Outcomes</i>
Shiue and Gluck (1989)	19	10	Heliox during 20 min after bronchodilator therapy	Reversal of acidosis. Reduction of dyspnea
Gluck et al. (1990)	7	7	Mechanical ventilation with heliox	Reduction of airway pressure. Reduction in CO ₂ retention Resolution of acidosis
Kass and Castriotta (1995)	14	12	Consecutive case study: 5 patients ventilated, 7 face mask	18% decrease in PaCO ₂ ($p < 0.005$) Increase in pH by 0.1 ($p < 0.001$)
Manthous et al. (1995)	16	27	Controlled study; breathing during 15 min	Reduction in pulsus paradoxus ($p < 0.01$) 35% increase in PEFR ($p < 0.001$)
Carter et al. (1996)	18	11	Crossover double-blind randomized study; 15 min breathing 70/30	No significant difference in FEV ₁ ($p = 0.36$) and FVC ($p = 0.5$) Improvement in PEFR ($p = 0.04$), FEF ₂₅₋₇₅ ($p = 0.006$)
Kudukis et al. (1997)	12	18	Double-blind randomized controlled trial; 15 min breathing	No effect on dyspnea score Significant decrease of pulsus paradoxus ($p < 0.001$) while breathing heliox Increase in PEFR ($p < 0.05$) Decrease in dyspnea index ($p < 0.0002$) Mechanical ventilation averted for 3 patients
Verbeek and Chopra (1998)	17	13	5 min of breathing heliox (70/30)	No significant improvement in FEV ₁ .
Kass and Terregino (1999)	13	23	Randomized controlled study; 8 h gas breathing	58.4% increase in PEFR in the first 20 min in the heliox group ($p < 0.001$) Rapid significant decrease in dyspnea score and RR ($p < 0.05$)
Schaeffer et al. (1999)	15	22	Retrospective case match for mechanically ventilated patients	Decrease in A—a gradient ($p < 0.0003$)

^aTrials from Rodrigo et al.¹ and Ho et al.²

heliox was utilized with NIPSV in COPD.²⁴ The significant reduction of work of breathing when using heliox was verified by Gainier et al.²⁵ in a randomized crossover study using heliox in sedated, paralyzed and mechanically ventilated patients with acute exacerbation of COPD.

Katz et al.²⁶ demonstrated that heliox provided lower levels of PaCO₂ during high-frequency oscillatory ventilation (HFOV). A modest improvement in PaO₂ was also demonstrated with both 40/60 and 60/40 heliox. Katz et al. later determined that heliox did not alter gas exchange if tidal volume was kept constant during HFOV. Heliox did provide similar CO₂ removal at lower ventilator pressures.²⁷ Better CO₂ transport during HFOV has also been demonstrated in lab models²⁸ and in an animal model that utilized low bias flow oscillation.²⁹

These studies suggest a consistent pattern of lower resistance and improved ventilation with heliox, including larger tidal volumes and more complete exhalation, corresponding to improved pulmonary CO₂ removal. Similarly, a pattern of improved oxygenation compared to air is demonstrated in several of the trials.^{9,15,26,29} The role of diffusion in these studies must be considered. Higher diffusion coefficients are expected for CO₂ and O₂ in helium compared to nitrogen.³⁰ Under simplified conditions, this would provide increased transport of oxygen and carbon dioxide independent of convection. The overall effect of this difference in diffusion on whole-lung gas exchange is not as simple to determine. A previously reported study that held tidal volume constant demonstrated no improvement in gas exchange associated with heliox during HFOV.²⁷

Some models even indicate an inverse relationship between diffusivity and alveolar gas exchange under certain conditions.³¹ At any rate, heliox inhalation is likely to provide conditions under which convective effects will enhance diffusion, through the extended propagation of "concentration fronts" and decreased time constants within the lungs.⁷

HELIOX USE IN JET NEBULIZERS

Gas-driven medical nebulizers are primarily used to aerosolize liquid medications for inhalation. The gas flow provides the dynamic force needed to atomize the liquid medication and convey it to the patient. The Weber number is the ratio of the aerodynamic force delivered by a moving gas to the surface tension force of a liquid. It provides a measure of how effectively a gas flow will be able to atomize a given liquid. A larger Weber number would be indicative of more atomization force and the likelihood of a smaller aerosol.³²

$$\text{Weber} = \frac{\rho_{\text{gas}} U_{\text{gas}}^2 d}{\sigma} \quad (6)$$

where ρ_{gas} and U_{gas} are the gas density and velocity, d is a characteristic dimension of the atomizer, and σ is the liquid surface tension. The lower density of heliox related to air provides a smaller Weber number, or less atomization force. In a medical nebulizer, higher flow rates of heliox will therefore be required to produce aerosols with similar sizes to those generated with air. This property is clinically important because aerosol size is a primary determinant of effective pulmonary aerosol deposition.³³ Corcoran et al.³⁴ demonstrated direct relationships between aerosol respirability (size) and nebulizer flow rate for both air and heliox. In these studies 70/30 heliox generated a larger aerosol at all tested flowrates when compared to air. Piva et al. reported a similar result.³⁵ Hess et al. reported that both aerosol size and the amount of drug mass (albuterol) in respirable sizes decreased when 80/20 heliox was utilized compared to air at the same flowrate.³⁶ The difference in these studies is likely a consequence of the aerosol sizing methods used, that is, a drug concentration method for measuring size (Hess) versus an optical method that measures literal geometric size (Corcoran, Piva), and may be indicative of a drug concentrating effect.

When heliox is utilized with a medical nebulizer, the effects of room air dilution must also be considered. The volume of gas output by a medical nebulizer during the period of an inhalation is typically less than the volume inhaled by the subject, so room air will typically compose some part of the breath. Consider that a nebulizer driven at 12 LPM will provide 0.4 L of gas over a 2-sec inhalation. Assuming a tidal volume of 0.6 L, the density of 70/30 heliox would increase from 0.52 to 0.75 kg/m³ (a 44% increase) based on room air dilution. To avoid this, a closed system, typically including some kind of gas reservoir, should be used.

THE EFFECTS OF HELIOX ON AEROSOL DEPOSITION

The gas inhaled during an aerosol drug treatment affects the aerosol properties. Heliox does not change the particle conveyance by the gas medium, but the potential for deposition of the aerosol in the upper airways due to impaction increases with flow rate and aerosol size, and decreases with tidal volume (due to the associated expansion in airway caliber).³³ The inhalation of heliox causes increases in both inhalation flow rate and tidal volume,^{9,10} so its effect on impaction is difficult to speculate upon. The impaction rate may also be affected by the flow pattern and turbulent structures in the region. Using computational fluid dynamics, Comer et al.³⁷ computed the particle deposition patterns in the first two bifurcations of the lungs. They demonstrated that particle motions are directly related to the secondary flows, which are in turn directly dependent on the Reynolds number. For a low Reynolds number, the particles generally follow the bulk flow while an increase in Reynolds number generates secondary flow patterns that increase the deposition. Potentially the lower Reynolds numbers associated with heliox could limit early deposition by reducing the secondary flows.

Aerosol particles reaching the low-speed regions of the deep lung simply descend at their terminal velocity due to gravitational sedimentation. The terminal velocity of these small aerosols is affected by gas viscosity, but not appreciably by gas density since the associated Reynolds numbers in this region are very low. Deposition due to sedimentation will increase with aerosol

size, terminal velocity and residence time in the lung (time between breaths).³³ The increased respiratory rate that is associated with heliox¹⁰ may allow for less settling time for these particles in the deep lung. However, heliox flows are likely to drive the aerosols further into the peripheral lung because of less momentum loss in the upper airways. The larger heliox tidal volumes will contain more drug, and will be delivered into lungs that are essentially more expanded to accommodate them. When exhalation occurs, it will be more complete due to decreased air trapping that may limit the ability of the patient to refill their lungs with gas and aerosol. Aerosols progressing into the peripheral lung during inhalation (but not depositing) will have an increased chance of depositing on exhalation as well.

Scintigraphy has been used in several studies to evaluate the efficiency of aerosol drug delivery with heliox. Anderson et al.³⁸ delivered 3.6 μm radiotagged particles to 10 subjects breathing either 80/20 heliox or air. The subjects inhaled the particles on four different days using the different gases at two flowrates each. Particle deposition in the periphery of the lung (based on 24-h counts) increased when heliox was used while deposition in the mouth and throat and tracheobronchial region decreased. Peripheral deposition demonstrated a linear relationship with airway resistance (R_{aw}) for both air and heliox, with lower airway resistances resulting in higher levels of peripheral deposition. The study was performed at set inhalation flow rates limiting the ability to predict deposition effects in the upper airways during an uncontrolled inhalation with heliox. In a double-blinded randomized study, Piva et al.³⁵ administered radioisotope aerosols via nebulizer to 20 children with lower airway obstructions using either 80/20 heliox or oxygen. Overall, the subjects who utilized heliox deposited the aerosols at a higher rate in the lungs. The effect was most pronounced in subjects with the highest degree of obstruction (based on pulmonary function), and not demonstrated in subjects with only moderate obstruction.

STUDIES OF HELIOX FOR AEROSOL DRUG DELIVERY

Heliox has been utilized as a driving gas for medical jet nebulizers in a series of clinical trials. Typically, these studies have hypothesized that

the lower density gas would provide more effective delivery of aerosol medications to and beyond sites of obstruction. Most of these studies evaluate the effectiveness of the treatments by comparing changes in pulmonary function or other clinical scores when taking a nebulized drug with heliox vs. air or oxygen (Table 3).

Henderson et al.³⁹ performed a single-blinded trial of nebulized albuterol delivery in 205 adult subjects with asthma exacerbations using 70/30 heliox or oxygen. Both treatments were given at a reported delivery rate of 10 LPM. Three doses were given to each subject at 15-min intervals. Peak expiratory flowrate (PEFR) and one-second forced expiratory volume (FEV1) were measured before the first treatment and after each successive treatment. The two groups demonstrated similar improvements in pulmonary function after bronchodilator use, and no difference in rate of hospital admission. No information was given on the delivery apparatus.

DeBoisblanc et al.⁴⁰ used 80/20 heliox to deliver four treatments of albuterol and ipratropium bromide to adult subjects with acute exacerbations from COPD. *In vitro* experiments were performed prior to these studies to quantify the respirable dose of aerosol being generated with each gas. The authors used a heliox flow rate of 11 LPM to produce an aerosol with a similar respirability to one generated with 8 LPM of air. The heliox group demonstrated slightly better improvement in FEF25-75, but the authors attributed little real clinical significance to this result. A small volume nebulizer was used with no mention of a reservoir to prevent room air dilution.

Dorfman et al.⁴¹ administered albuterol and ipratropium via oxygen-driven nebulizer to 39 adult subjects, with either 80/20 heliox or air connected to the inhalation circuit proximal to the nebulizer and delivered at 10 LPM. No difference in post-treatment PEFR was noted between the groups. Five heliox subjects were admitted to the hospital versus none in the air group. The use of an oxygen-driven nebulizer with the heliox test case likely resulted in significantly lower concentrations of helium in the inhaled gas mixture.

Rose et al.⁴² delivered aerosol bronchodilators continuously via large volume nebulizer to 36 asthmatic adult subjects using either 70/30 heliox or air (30% oxygen) in a double-blinded, randomized trial. Both groups demonstrated similar rates of improvement in FEV1, PEFR, and oxygen

TABLE 3. CLINICAL TRIALS OF HELIOX USED AS A MEDIUM FOR AEROSOL DRUG DELIVERY

<i>Trial</i>	<i>Reference</i>	<i>n</i>	<i>Subject group (ages)</i>	<i>Reservoir used?</i>	<i>Primary results</i>
Trials using a nebulizer with a reservoir or a large volume nebulizer					
Rose et al. (2002)	42	36	Asthma exacerbations (18–55)	Large volume nebulizer	Improvement in Borg dyspnea scale with heliox vs. O ₂ . No improvement in RR, O ₂ Sat, PEFr, FEV ₁ .
Kress et al. (2002)	43	45	Asthma exacerbations (<50)	Yes	Better improvement in FEV ₁ with heliox vs. air.
Kim et al. (2003)	46	30	Asthma exacerbations (2–18)	Yes	Better improvement in pulmonary index and lower rate of hospital admission with heliox.
Bag et al. (2002)	44	31	Stable asthma (18–44)	Yes	Better improvement in FEV ₁ , FVC, PEFr with heliox.
Trials using a standard nebulizer without a reservoir or with an unknown delivery system					
Henderson et al. (1999)	39	205	Asthma exacerbations (18–65)	Unknown	No differences in improvement—PEFr or FEV ₁ .
Dorfman et al. (2000)	41	39	Asthma exacerbations (8–55)	No ^a	No difference in PEFr, more admissions in heliox group.
Lanoix et al. (2003)	45	94	Asthma (19–55)	Unknown	No difference in PEFr, FEV ₁ , time to best PEFr/FEV ₁ , length of ED stay, admission rate, with heliox vs. oxygen
deBoisblanc et al. (2000)	40	50	Acute COPD exacerbations	No	No difference in FEV ₁ improvement with heliox vs. air delivery. Slight improvement in FEF _{25–75} .
Studies based on scintigraphy					
Anderson et al. (1993)	38	10	Asthma (27–59)	Yes	Better peripheral deposition with heliox.
Piva et al. (2002)	35	20	Lower airways obstr. (5–15)	Yes	Better peripheral lung deposition in subjects with severe peripheral obstruction. No difference in subjects with only moderate obstruction.

^aStudy gas added to inhalation circuit at 10 LPM proximal to oxygen driven nebulizer.

saturation. Respiration rates were the same in the two groups. There was a difference in the Borg scale of perceived dyspnea favoring heliox delivery. The large volume nebulizer would likely accumulate a substantial amount of heliox internally that would largely negate room air dilution.

Kress et al.⁴³ delivered aerosol albuterol to 45 adult subjects using either 80/20 heliox or oxygen, in a randomized but non-blinded manner. A small volume medical nebulizer equipped with a reservoir bag was used. Both the nebulizer and the reservoir bag received separate flows at 10 LPM for oxygen or 18 LPM for heliox. Subjects received three treatments and had pulmonary

function evaluations after each. Improvements in FEV₁ were demonstrated with heliox at all three assessment points. This group very specifically allowed for 15 min of washout prior to the performance of any pulmonary function tests after heliox use, to ensure that exhalational flows were not improperly measured based on the lower density helium contained in the breath.

Bag et al.⁴⁴ delivered aerosol albuterol to 31 clinically stable asthma adult subjects using 80/20 heliox or air. A small volume nebulizer driven at 8 LPM and a reservoir bag were used. In this single-blinded study all subjects received a treatment with each gas on two separate days

thus allowing them to serve as their own controls. Improvements in FEV1, FVC, PEFR and FEF25-75 were noted with heliox. This study utilized a volume-based spirometer to ensure that exhalation flows containing heliox were properly characterized.

Lanoix et al.⁴⁵ delivered albuterol to 94 subjects suffering from exacerbations of asthma using either 80/20 heliox or oxygen. The authors reported no statistical differences in PEFR, FEV1, time to best values of PEFR and FEV1, length of ED stay, admission rates, inability to complete study, and return visits when comparing delivery with 80/20 heliox versus oxygen. This trial was reported in abstract form, and therefore no detail on administration technique was available.

Kim et al.⁴⁶ delivered nebulized albuterol to 30 children suffering from asthma exacerbations using either 70/30 heliox or oxygen through a large volume nebulizer with a reservoir. Pulmonary index (PI; a combined scale of patient symptoms) was evaluated every half-hour over 240 min or until patient discharge. Subjects using heliox for delivery demonstrated better improvement in PI and a higher rate of discharge from the emergency room. This group utilized a volume-based spirometer for all PFT measurements.

In an *in vitro* study of aerosol drug delivery during mechanical ventilation, Goode et al.

demonstrated increased aerosol delivery from a metered dose inhaler (MDI) and a nebulizer when heliox was utilized. With the MDI, the increased delivery was due to decreased deposition within a spacer in the ventilator circuit. With the nebulizer, oxygen was used as the driving gas and greater aerosol delivery was achieved when the circuit was filled with heliox versus oxygen.⁴⁷

CONCLUSION

Heliox provides higher flow rates for a given pressure difference (i.e., less resistance) when compared to air or oxygen, for turbulent or near-turbulent flows, as would be expected in the upper airways during most breathing conditions. The upper airways provide the dominant component of flow resistance during inhalation and exhalation in the healthy lung,⁶ and would be expected to provide even more resistance in subjects with obstructive lung diseases. The lower resistance heliox gases would sustain more momentum while flowing through the upper airways providing increased flow into the deep lung that would carry proportionally more aerosol drug into this region. Increased convection into the deep lung will likely provide improved diffusion as well. Scintigraphy studies have con-

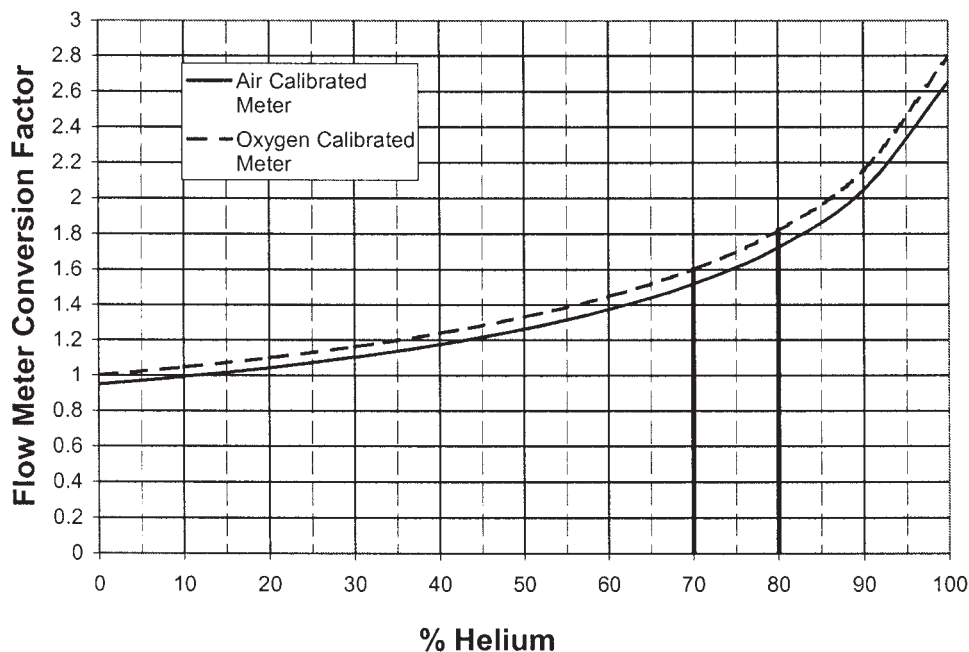


FIG. 1. Flow meter conversion chart for measuring heliox flows with air or oxygen meters. $V_{heliox}/V_{gas} = \sqrt{\rho_{gas}/\rho_{heliox}}$. Based on Equations 1 and 3.

firmed that aerosol drug deposition in the peripheral lung increases proportionally with decreased resistance.³⁸ Exercise studies have demonstrated that subjects breathe at higher rates and with higher tidal volumes when inhaling heliox versus air,^{9,10} which under ideal delivery conditions would allow for more inhaled drug to be delivered to the lungs as well based on volume alone.

The evidence currently available indicates that the ability of heliox to deliver aerosol drugs will be largely determined by the system used to deliver the aerosol and the gas. The inclusion of a reservoir device is suggested for any experimental or clinical investigations using medical nebulizers driven by heliox to prevent the dilution of the gas by room air. Of the trials considered on Table 3, five out of five studies that carefully utilized a gas reservoir demonstrated a positive result for heliox. One trial that utilized a large volume nebulizer that essentially acted as a reservoir demonstrated positive outcomes as well. It is important that this reservoir be large enough to accommodate the increased tidal volumes that would be expected with heliox inhalation.

When using gas driven nebulizers, higher heliox flow rates will likely be required to produce aerosols of similar sizes as those produced by air or oxygen flows.³⁴ Since aerosol size is an important determinant in the location and quantity of aerosol deposited in the lungs,³³ size evaluation for clinical applications, and size matching for comparative trials is suggested. Only one of the clinical trials considered herein reported data to substantiate that the aerosols being delivered in comparative trials of air or oxygen vs. heliox were of similar size.⁴⁰ Proper metering of heliox should be performed to avoid later confusion when reporting the results as well. The flowrate of heliox is underestimated by an air or oxygen meter unless a conversion is performed. (Ballfloat meters are calibrated for one gas at one pressure, typically air or oxygen at 50 psig.) A conversion chart is provided in Figure 1.

A decrease in deposition within aerosol delivery equipment has been noted in several studies where heliox was utilized.⁴⁷⁻⁴⁹ This must be considered as a potential confounding factor if aerosol behavior within the lungs is the sole consideration of a study, since heliox may be providing more drug at the mouthpiece. In clinical use this may provide the simple advantage of more efficient drug delivery.

Finally, if reporting pulmonary function data, proper attention should be paid to the effect of heliox in the exhalation of the subjects. If the physiologic effects of heliox inhalation alone are being considered, the investigators should assess pulmonary function when the lungs actually contain heliox. This necessitates the use of either a volume-based spirometer or a flow-based spirometer specifically calibrated for heliox. Assessment of pulmonary function to gauge the effectiveness of aerosol drug delivery is probably best performed after the subjects have washed the heliox out of their lungs so that the effects of gas inhalation can be differentiated from the effects of the deposited drug. Previous studies have speculated that approximately 5-15 min would be required for this washout to occur. It should be noted that the washout of helium may be delayed in subjects exhibiting poor ventilation.

The clinical and experimental investigation of heliox for aerosol drug delivery requires careful attention to the system used for drug delivery and the outcomes to be assessed. Simple clinical endpoints may not provide sufficient information to fully determine the effectiveness of this treatment. They are certain not to provide enough information to fully define the mechanisms behind the clinical response. The more detailed assessments provided in the exercise studies reported herein, or the use of an imaging technique such as scintigraphy may be a consideration for future trials.

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