The Role of Helium in the Treatment of Acute Respiratory Failure

J. A. S. Ball, A. Rhodes, and R. M. Grounds

Introduction

Ramsey first isolated helium from the mineral cleavite in 1895 [1]. In the mid 1930s, Barach first described its use, in place of nitrogen, as the carrier gas for oxygen [2]. He recommended it as an adjunct to the treatment of respiratory failure, in particular, for obstructive lesions of the larynx, trachea, and airways [1, 3, 4]. Helium briefly enjoyed widespread use; however, with the outbreak of World War II, supplies became limited and this, coupled with pharmaceutical advances, especially in the field of aerosolized bronchodilators, led to its demise from the therapeutic armory. Over recent years there has been a small-scale resurgence in the experimental use of helium in a variety of patients with acute respiratory failure. The aim of this chapter is to present the theoretical reasons for its use, critically review the limited trial data, and briefly discuss some of the practical issues in utilizing helium in mechanical ventilators.

The Physics of Gas Flow in the Respiratory Tract

Gas flows from a region of high pressure to one of low pressure. The rate at which it does so is proportional to the pressure difference between the two regions. The constant of the equation that relates flow to pressure difference is called resistance, hence

$$V = \frac{\Delta P}{R} \tag{1}$$

where V = flow, ΔP = pressure difference and R = resistance. Resistance to gas flow through a conduit is determined not only by flow rate but also by conduit geometry and the physical properties of the gas. As resistance to gas flow increases, the characteristics of gas flow change from laminar to turbulent. Since resistance is a function of conduit geometry, directional change, changes in cross-sectional area, branching, and the magnitude of frictional forces exerted by the surface of the conduit can all increase resistance to flow and induce turbulence.

Two physical properties of a gas determine its flow characteristics through a conduit, its density and its viscosity. The flow characteristics of a gas in a tube can be predicted from the Reynolds number (Re) according to the following equation:

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$$Re = \frac{DV\rho}{A\eta} \tag{2}$$

where $D = \sqrt{A \cdot (4/\pi)}$, V= bulk flow at A, ρ = density, A = the cross sectional area and η = gas viscosity. In the lung Re $\geq$ 4000 predicts turbulent flow and Re $\leq$ 2000 predicts laminar flow. Between these values a combination of these two characteristics occurs, referred to as transitional flow.

If you consider the respiratory tract from trachea to alveoli, the effective cross sectional area increases with each division and the flow rate drops. Hence, from equation 2 if V falls and A increases, Re falls, and gas flow goes from predominantly turbulent in the trachea to predominantly laminar in the successive generations of the bronchial tree. For any gas, the level at which flow becomes laminar is determined by the flow rate, which in turn is determined by the respiratory effort. Thus for gas flow in the respiratory tract, the relationship between respiratory effort (generated pressure difference) and flow described in equation can be expressed in the following equation:

$$\Delta P = k\rho^{(i+x)}\eta^{-x}V^{(2+x)} \tag{3}$$

where ΔP = the pressure change, k is a constant related to airway geometry, ρ = the gas density, η = the gas viscosity and V = the flow rate. x = a number between minus 1 and 0 and represents the nature of flow, -1 representing laminar flow, 0 representing turbulent flow and values in-between representing transitional (or mixed) flow. The derivation of x is complex and reviewed elsewhere [5]. From equation 3 when flow is laminar and therefore x = minus 1, only gas viscosity and airway geometry determine resistance. As flow becomes transitional and then turbulent and therefore x becomes more positive, gas density increasingly determines resistance and the influence of gas viscosity wanes. The value of k is also affected by x but in a complex fashion such that in laminar flow, frictional forces exerted by the airway wall are effectively zero but increase as x increases.

In a normal subject breathing at rest, gas flow becomes laminar between the main and lobar bronchi. Exercise or any pathology that increases ventilatory requirements and/or airway resistance will shift this transition distally. As a larger proportion of the bronchial tree is subject to transitional and turbulent flow, so the value of x increases and so does the effect of gas density on flow. From equation 3 flow is inversely proportional to gas density hence, if all other conditions are constant, the lower the density of the gas the greater the flow.

As has been shown, the movement of gas from the upper airway to the alveoli is complex. Initially, gas flows down a pressure gradient causing convective mixing of inspired and airway gas. At some point in the distal generations of the bronchial tree, gas flow slows, and diffusive gas mixing predominates. Where this transition occurs, a sharp concentration gradient exits, at which mixing of inspired and alveolar gases predominates. The dissipation of energy at this 'front' enables facilitated diffusion [6]. Convective gas mixing is dependent on flow and hence gas density. Diffusive gas mixing is independent of flow but is also inversely proportional to gas density. Thus reducing gas density improves gas transport throughout the bronchial tree.

Theoretical Benefits of Helium

Helium is the second element in the periodic table with a molar mass of 4.0 g mol^{-1}. It is biologically inert and insoluble in human tissues at atmospheric pressure. Long-term inhalation of helium-oxygen (He-O_2) mixtures has failed to show any deleterious effects [7].

Helium is seven times less dense than nitrogen and eight times less dense than oxygen (Table 1). The density of a gas mixture is equal to the concentration weighted sum of its constituent parts, i.e.,

$$\rho_{gm} = (FA \times \rho_A) + (FB \times \rho_B) \quad (4)$$

where ρ_{gm} = the density of the gas mixture, FA = the proportion of gas A, FB = the proportion of gas B, and ρ_A and ρ_B = the densities of the two gases. Density decreases as temperature increases in a predictable fashion (Fig. 1) according to the equation:

$$\rho_T = \rho_{298\,K} \times \frac{298}{T} \quad (5)$$

where ρ_T = the density at temperature T (K) and ρ_{298} = the density at 298 K.

The viscosity of helium, nitrogen and oxygen are roughly equal, being 188 μP, 167 μP and 192 μP respectively, at 0°C [8]. The viscosity of a gas mixture can also be approximated to the concentration weighted sum of its constituent parts (see equation 4), such that He-O_2 mixtures are $<8\%$ more viscous than nitrogen-oxygen (N_2-O_2) mixtures. Viscosity of a gas increases with increasing temperature. The exact relationship is complex, but over the range of room temperature (inspired gas) 20–25°C to body temperature (intra-pulmonary and expired gas) 35–40°C the relationship can be approximated to a linear equation of the form:

$$\eta_T = \eta_0 + 0.5\,T \quad (6)$$

where η_T = the viscosity at temperature T (°C) and η_0 is the viscosity at 0°C [8]. Thus in the range 20–40°C the viscosity of a mixture of N_2-O_2 or He-O_2 will only change by $\sim 6\%$. Thus, in practical terms the differences in the viscosities of N_2-O_2 and He-O_2 mixtures can be ignored.

During spontaneous breathing, the inhaled gas is warmed and humidified in the upper airway. In a mechanically ventilated patient this is achieved either through a heater humidifier or heat and moisture exchanger. Regardless of scenario, the in-

Table 1. Physical properties of pure gases

Gas	Density (ρ) at 298 K (25°C) [g cm^{-3}]	Viscosity (η) at 298 K (25°C) [μP]
Helium (He)	0.176	198.59
Nitrogen (N_2)	1.230	177.96
Oxygen (O_2)	1.405	206.39
Water vapour (H_2O)	1.092	99.10
Carbon dioxide (CO_2)	1.980	149.10

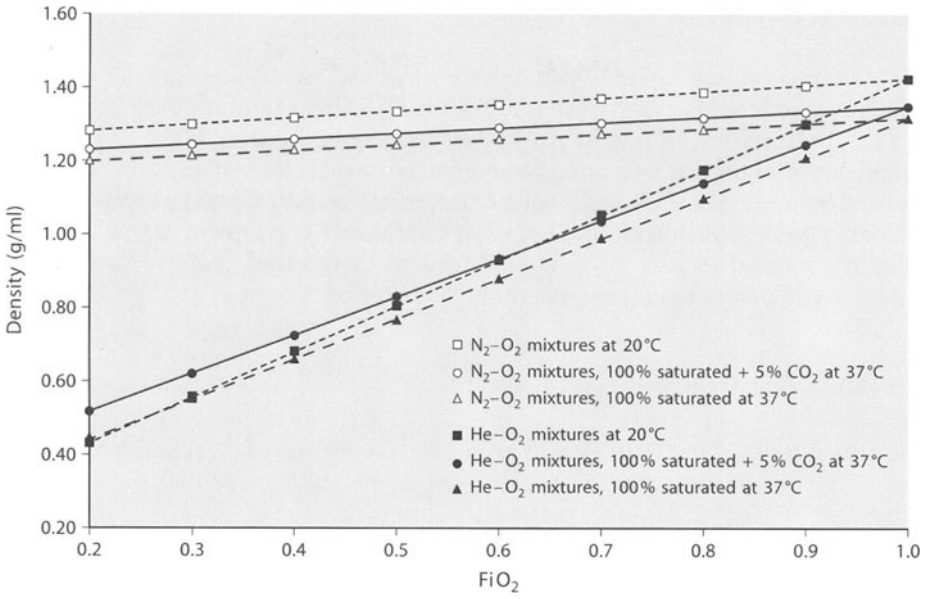

Fig. 1. Density variation with gas composition and temperature

spired gas mixture entering the trachea should be approaching core body temperature and has a relative humidity of near 100%, equivalent to 6% water vapor. Water vapor has a density of ~1 g/ml and a viscosity of ~100 µP at 25°C. Thus it has little effect on Re (see equation 2 and Fig. 1) and hence flow characteristics of N_2-O_2 or He-O_2 mixtures.

In addition to water vapor, expired gas contains a variable proportion of carbon dioxide (CO_2). CO_2 has a density of 1.98 g/ml and a viscosity of 149.10 µP at 25°C. This results in negligible change in the flow characteristics of N_2-O_2 mixtures and a small but important change on Re and hence flow characteristics of He-O_2 mixtures (Fig. 1). This increase almost certainly has no clinical significance but does have a significant effect on the calibration of monitoring equipment (see later).

Thus as a result of substituting He for N_2 in inspired gas there is a 10–300% decrease in Re for mixtures with a fraction of inspired oxygen (FiO_2) of 0.90–0.21 (see equation 2 and Fig. 1). Hence, for the same driving pressure a greater proportion of flow will be laminar or mixed, resulting in higher volumes per unit time [9]. As a consequence, the location of the convection diffusion front is shifted distally, enhancing alveolar gas mixing [6]. In addition to increasing gas flow via the bronchial tree, the substitution will enhance collateral ventilation, which is responsible for a significant proportion of alveolar ventilation in many disease states [10]. The net result should be significant alveolar unit recruitment and an improvement in ventilation perfusion matching in both airway and parenchymal lung pathology. Furthermore, oxygen and CO_2 will diffuse faster through He than N_2 leading to more complete diffusion equilibrium and a consequent fall in alveolar arterial oxygen difference [11, 12].

Effects of Helium in Experimental Animals

Altland and colleagues [13] examined the effects of hypoxia on rats by exposing them to mixtures of oxygen (FiO_2 0.05) in He, N_2, argon (Ar), and sulfur hexafluoride (SF_6) (ascending order of density). The rats exposed to He-O_2 had significantly higher arterial oxygen saturations and better survival rates than the others. Shanklin and Lester [14] investigated oxygen toxicity in neonatal rabbits, by comparing the effects of pure oxygen with those of oxygen diluted in a variety of carrier gases including He. Next to pure oxygen, He-O_2 caused the greatest toxicity. Thus, He appears to enhance oxygen transport through the lungs.

Effects of Helium in Normal Human Subjects

Breathing He-O_2 (79:21) at rest, has no significant effect on gas exchange in normal subjects [15]. There are at least eight studies that have compared the effects of breathing He-O_2 (79:21) to air in normal subjects during exercise [16–23]. The protocols, measurement techniques, and results of these studies vary significantly but a coherent message emerges and is perhaps best summarized in the study by Esposito and Ferretti [23]. They compared the respiratory parameters and gas exchange variables of eight subjects breathing four different gas mixtures, air, He-O_2 (79:21), N_2-O_2 (89:11), and He-O_2 (89:11), during maximal exercise. When breathing the normoxic gas mixtures, the expired minute volume (V_E) and the alveolar ventilation (V_A), were greater with He-O_2 than N_2-O_2 (V_E 139.1 versus 109.9 l/min; V_A 112.1 versus 95.1 l/min), though only the former was statistically significant. Despite these differences there was no difference in the partial pressure of arterial oxygen (PaO_2) or $PaCO_2$. When breathing the hypoxic gas mixtures, identical differences in V_E and V_A were observed between the two gas mixtures (V_E 141.3 versus 107.8 9 l/min; V_A 101.5 versus 82.1 l/min) though here both were statistically significant. As expected PaO_2 fell but was significantly greater for He-O_2 than N_2-O_2 (46.6 versus 40.0 mmHg). $PaCO_2$ also fell significantly for the hypoxic He-O_2 mixture, despite no difference in V_E (24.7 mmHg for He-O_2 [89:11] versus 27.3 mmHg for He-O_2 [79:21]). No fall was seen in $PaCO_2$ between the normoxic and hypoxic N_2-O_2 mixtures. Thus in hypoxic conditions He-O_2 increases the transport of oxygen and CO_2 through the lungs. The mechanism by which this is achieved is complex and incompletely understood, however, merely increasing V_E by the effective reduction in Re does not explain these findings.

Clinical Trials

To our knowledge, there are 12 case series and 14 controlled trials of He-O_2 utilization in patients with respiratory failure. Tables 2 and 3 summarize the patients studied and the result. Individual studies are discussed in the following section.

Table 2. Case series of $He\text{-}O_2$ utilization

Author	Patients	Result
Duncan and McClellan [25]	UAO; mixed	Significant benefit
Nelson et al. [26]	Croup; infants	Significant benefit
Rodeberg and Biros [27]	Post extubation stridor; children	Significant benefit
Smith and Gluck [24]	UAO; mixed	Significant benefit
Shiue et al. [33]	Asthma; adults	Significant benefit
Gluck and Castriolta [6]	Asthma; adults	Significant benefit
Kass et al. [34]	Asthma; adults	Significant benefit
Swidwa et al. [46]	COPD; adults	Significant benefit
Hollman et al. [52]	Bronchiolitis; infants	Significant benefit
Gross et al. [53]	Bronchiolitis; infants	No benefit[a]
Tatsuno et al. [54]	Post cardiac surgery; infants	Significant benefit
Yahagi et al. [56]	Post cardiac surgery; adults	Significant benefit

[a] see text
UAO: upper airway obstruction; *COPD:* chronic obstructive pulmonary disease

Table 3. Controlled trials of $He\text{-}O_2$ vs. $N_2\text{-}O_2$

Author	Patients	Result
Kemper et al. [28]	Post extubation stridor; children	Significant benefit
Terregino et al. [29]	Mild croup; infants	No benefit
Kass and Terregino [35]	Asthma; adults	Significant benefit
Schaeffer et al. [36]	Asthma; adults	Significant benefit
Manthous et al. [37]	Asthma; adults	Significant benefit
Kudukis et al. [38]	Asthma; children	Significant benefit
Carter et al. [39]	Asthma; children	No benefit
Verbeek and Chopra [40]	Asthma; adults	No benefit
Jolliet et al. [47]	COPD; adults	Significant benefit
Jaber et al. [48]	COPD; adults	Significant benefit
Tassaux et al. [49]	COPD; adults	Significant benefit
Wolfson et al. [50]	BPD; infants	Significant benefit
Elleau et al. [51]	RDS; neonates	Significant benefit
Petros et al. [55]	Post cardiac surgery; infants	Significant benefit

COPD: chronic obstructive pulmonary disease; *BPD:* bronchopulmonary dysplasia; *RDS:* respiratory distress syndrome

Laryngeal, Tracheal, and Major Bronchi Obstruction

Upper airway obstruction remains the leading indication for $He\text{-}O_2$ therapy. The literature in this area has recently been thoroughly reviewed by Smith and Biros [24]. They report a case series of six patients and review 12 original case studies and three other series [25–27], documenting the dramatic relief of upper airway obstruction

by He-O_2. In addition there are two small randomized trials of He-O_2 in upper airway obstruction [28, 29] which add further evidence to the efficacy of this intervention. Smith and Biros draw three important conclusions from their experience and literature review: First, that the greater the severity of upper airway obstruction, the more dramatic the benefit of He-O_2. Second, that contrary to the unsubstantiated opinion of many authors, He-O_2 can still be highly efficacious even at comparatively low concentrations of He (FiHe < 0.6). Third, that the efficacy of this intervention is poorly appreciated and not widely available.

Also of potential interest to intensivists is the reported efficacy of He-O_2 as an adjunct to ventilation in situations of iatrogenic upper airway obstruction. Bronchoscopy performed via the patient's airway or via small diameter endotracheal or tracheostomy tubes can be associated with ventilatory compromise. This can be prevented/treated by employing He-O_2 [30]. Similarly, surgery on the larynx and/or trachea can be facilitated by He-O_2 [31, 32].

Asthma

The first case series of helium in acute asthma was published in 1989 by Shiue and Gluck [33]. They enrolled 10 adult patients who had presented with acute severe asthma and a respiratory acidosis. All patients had received nebulized β_2 agonist, intravenous steroids, and aminophylline but failed to improve. All then received a He-O_2 mixture (FiO_2 25–40%) via a partial rebreathing face mask. Most patients reported a rapid improvement in dyspnoea. Five patients normalized their arterial $PaCO_2$ and pH by 20 minutes, the remainder by 60 minutes. No patient required intubation or mechanical ventilation during their admission.

The following year Gluck and colleagues published a second case series [6] in which they reported the effects of He-O_2 mixtures on seven adult, acute asthmatic patients who had been intubated and mechanically ventilated for acute respiratory failure. All patients had received maximal medical therapy including subcutaneous ephedrine, and been ventilated for 1 hour without significant improvement. These patients were then ventilated with 60–80% He. All seven patients exhibited a dramatic and rapid improvement. After a mean duration of He therapy of only 2.5 minutes the average peak airway pressure (PIP) fell by 32.86 cmH_2O. After a mean of 22.2 minutes the average $PaCO_2$ had fallen by 35.7 mmHg (4.76 kPa). There was no statistically significant change in PaO_2, although hypoxia ($PaO_2 < 60$ mmHg, 8 kPa) was an exclusion criteria and the mean PaO_2 at study entry was 94 mmHg (12.5 kPa). All seven patients were successfully weaned and extubated within 24 hours. Mean duration of He-O_2 therapy was 6.3 hours.

In 1995, Kass and Castriotta reported a case series of 12 adult, acute asthmatics treated with He-O_2 [34]. All had a persistent respiratory acidosis despite maximal medical therapy. Seven patients received He-O_2 via non-rebreathing face mask, whilst the remaining five were intubated and mechanically ventilated with He-O_2. Eight patients responded to He-O_2, defined as normalization of $PaCO_2$ or $\geq 15\%$ fall in $PaCO_2$ within ~ 60minutes. The four non-responders, three of the face mask treated group and one of the intubated group, improved, but not sufficiently to meet these criteria. Oxygenation, as measured by alveolar arterial ratio improved in all

patients but this was not statistically significant. Intensive care unit (ICU) and hospital stay was shorter in the responders; 1.3 vs. 3.1 days and 3.8 vs. 7.3 days respectively but only the latter reached statistical significance. Average duration of treatment was 16.8 hours. The responders had a significantly lower pre-intervention arterial pH and a significantly shorter duration of symptoms at time of presentation 17.8 hours vs. 78 hours.

Following this series Kass and colleagues conducted a randomized controlled trial (RCT) in adult acute asthmatics, none of whom had respiratory failure [35]. Entry criteria was a peak expiratory flow (PEF) of <200 l/min. Both groups received standard therapy, with the control group receiving N_2-O_2 70:30 and the treatment group receiving He-0_2 70:30. Although 28 patients were recruited, one patient in the control group deteriorated necessitating intubation and mechanical ventilation, and two patients in each group improved to such an extent that they were discharged prior to the end of the study at 8 hours. Of the remaining 23 patients, 11 were randomized to He-O_2. Nine of the treatment group had a $>25\%$ improvement in PEF at 20 minutes compared to only two in the control group. Indeed, parity between the two groups was not reached until 6 hours. Surprisingly, the treatment group showed a further, significantly greater improvement over the last two hours of the trial.

Schaeffer and colleagues also retrospectively reported a series of 11 severe, adult, acute asthmatics whom they had mechanically ventilated with He-O_2 [36]. Due to the widespread use of He-O_2 in their hospital, these cases were matched with historical controls. Despite the obvious flaws in the comparison of these two groups the improvement at 90 minutes in alveolar-arterial oxygen gradient in those patients who had received He-O_2 was very marked in comparison to the controls; 216 to 85 torr in the He-O_2 group versus 226 to 181 torr in the controls. All 11 He-O_2 patients demonstrated a significant improvement in oxygenation compared to only six of the 11 controls. In addition, the magnitude of the improvement was significantly greater in the He-O_2 group. Most strikingly, the improvement in oxygenation was achieved despite a very high FiO_2 (mean 0.81) at the outset of He-O_2 treatment. Notably, there was a reduction in $PaCO_2$ in seven of the 11 He-O_2 group but only three of the eleven controls. These differences between the two groups were not statistically significant. No outcome data were presented.

There are four other published trials of He-O_2 in acute asthma, which in our opinion add little if anything to the above studies. Manthous et al. [37] investigated the effects of He-O_2 in 16 acute adult asthmatics, by measuring their PEF and pulsus paradoxus. They measured these variables at three time points: after 30 minutes of medical therapy, after 15 minutes He-O_2, and after a further 15 minutes of N_2-O_2. In addition they monitored the same variables in 11 control patients who received only standard therapy. Both groups showed an improvement in both variables over the 30 minute study period, however, the improvement in the treatment group was significantly greater after the 15 minutes He-O_2.

In a nearly identical design, Kudukis et al. [38] performed a blinded RCT of He-O_2 in 18 children with acute asthma. Subjects received 15 minutes of their randomly allocated gas (8 N_2-O_2, 10 He-O_2). PEF and pulsus paradoxus were measured before treatment, after 15 minutes of treatment, and 15 minutes after cessation of treatment. All of the subjects who received He-O_2 showed a significant improvement af-

ter He-O_2, which reversed within 15 minutes. No changes were seen in the control group.

Carter et al. [39] performed a double blind randomized cross-over trial in 11 children. Entry to trial took place 1–3 days following admission to hospital and initiation of medical therapy. Spirometry and dyspnea score were measured after 15 minutes of breathing He-O_2 70–30 and N_2-O_2. No changes were found.

In a poorly conceived study by Verbeek and Chopra [40], 13 acute asthmatics were administered He-O_2 for 5 minutes, prior to any bronchodilator therapy and forced expiratory volume in one second (FEV_1) measured before and after. No improvement was seen in any of these patients.

The nine published clinical trials of helium in acute asthma, feature only 132 very heterogeneous patients and 11 historical controls. Of the 132 patients, 101 received helium, although in four of the nine trials this was for only 5–15 minutes. Only 23 patients were mechanically ventilated. Only two studies were randomized controlled trials, enrolling 18 and 23 patients respectively. Seven of the trials report a positive benefit of helium treatment, although very variable outcome measures were employed. Overall, though the data are extremely limited it appears that the sicker the patient and the earlier helium is used, the greater the benefit. Indeed in our experience He-O_2 ventilation can result in dramatic improvements in acute asthmatics and should be available in all ICUs. However, the precise role of He therapy in acute asthma remains to be defined, in particular, whether its administration might prevent the need for intubation and mechanical ventilation.

He-O_2 as the Driving Gas for Updraft Nebulization

In several of the asthma trials the issue of nebulized bronchodilator delivery is discussed. The question of whether He-O_2 exerts its beneficial effects by enhancing the delivery of these drugs is raised but left unanswered. There are three studies in the literature which examine the theory behind this question and two recent published RCTs, one in acute asthmatics and the other in acutely decompensated chronic obstructive pulmonary disease (COPD) patients.

Svartengren and colleagues estimated the proportion of 3.6–3.8 μm teflon particles labeled with Tc^{99m} that are deposited in the mouth and throat, and in the alveoli, when inhaled in air or He-O_2 (80: 20) [41]. They employed nine healthy human subjects with or without bronchoconstriction, created by aerosolized methacholine bromide, and delivered the particles with a flow of 0.5 l/s. Deposition in the mouth and throat did not differ between air and He-O_2 delivery. The proportion deposited in the alveoli was larger in the unconstricted subjects and significantly greater in the constricted subjects when inhaled with He-O_2.

The same group investigated alveolar particle deposition in 10 stable asthmatic subjects [42]. They used 3.6 μm particles labeled with In^{111}. These they delivered using either air or He-O_2 (80:20) at 0.5 and 1.2 l/s. Measurements were taken immediately following inhalation and at 24 hours. The measurements taken at 24 hours (Ret24) were considered to represent alveolar deposition. For both flow rates Ret 24 was significantly higher when with He-O_2. The difference seen between air and He-O_2 inhalation was larger than seen in the normal subjects in their previous study.

Hess and colleagues evaluated the particle size and inhaled mass of albuterol nebulized with air and He-O_2 (80:20) at several flow rates using a lung model [43]. Particle size and inhaled mass was significantly reduced by He-O_2. Increasing the flow rate of He-O_2 reduced this effect. Doubling the concentration of the albuterol solution increased the inhaled mass without affecting particle size. The authors concluded that flow rates should be increased when He-O_2 is employed to drive nebulizers.

In the clinical setting, however, the issue appears less clear cut. Henderson and colleagues performed a RCT in asthmatics with mild to moderate acute exascerbations [44]. The control group received three nebulized doses of albuterol 5 mg delivered by oxygen at 10 l/min, at 15 minute intervals. The treatment group received identical therapy but delivered by He-O_2 (70:30) at 10 l/min. PEFR and FEV_1 were used as outcome measures. Both groups showed a 70% improvement over the 45 minute trial with no difference between the groups. In a similar trial in 50 COPD patients, with mild to moderate decompensations, deBoisblanc and colleagues made identical findings [45]. The only major methodological difference was that in the COPD study spirometry was performed after 60 and 120 minutes. The authors of the second paper [45] argue that the absence of an effect may well have been due to the effective overdose of bronchodilator delivered by conventional gas such that any increase in drug delivery achieved by He-O_2 could not have a clinically measurable effect. Overall, it appears that enhanced delivery of bronchodilators is unlikely to be the explanation for the positive findings in the asthma trials.

COPD

In 1985, Swidwa and colleagues investigated the effects of He-O_2 in 15 severe (FEV_1 < 1 l) but stable COPD patients [46]. After 15 minutes inhalation of He-O_2 they noted a modest reduction in $PaCO_2$ and a significant reduction in functional residual capacity (FRC), which they argued indicated a significant reduction in intrinsic positive end-expiratory pressure (PEEPi).

Jolliet and colleagues investigated the effects of He-O_2 in a group of 19 acutely decompensated COPD patients [47]. Hypoxic patients were excluded. Each patient was stabilized on non-invasive pressure support ventilation (NIPSV), a process which took a mean of 17 hours. NIPSV was withdrawn for 2 hours and baseline arterial blood gas, ventilatory and cardiovascular parameters recorded. The patients then received NIPSV with either N_2-O_2 or He-O_2 for 45 minutes, the choice of gas mixture being randomly allocated. NIPSV was again stopped for a 45 minute period following which a second period of NIPSV was undertaken with the alternative gas mixture. As expected NIPSV caused a decrease in respiratory rate; an increase in both tidal and minute (Vmin) volume; and an increase in PaO_2 regardless of gas mixture, with no statistically significant difference between the two. NIPSV also reduced inspired time and $PaCO_2$ with both gas mixtures, but for these variables the effects of He were significantly greater. Notably the reduction in $PaCO_2$ was proportional to the baseline value. The authors suggest that the reduction in inspired time, is the crucial factor and explains the decrease in $PaCO_2$. They argue that a shorter inspired time coupled with an increase in tidal volume, facilitates expiratory lung emptying.

The authors fail to report the level of PEEP set on the ventilator, which could also represent a significant factor.

Jaber and colleagues performed a similar study in 10 acutely decompensated COPD patients [48]. Again, hypoxic patients were excluded. They compared the effects of a minimal level of NIPSV (equivalent to spontaneous breathing) with a therapeutic level; with both N_2-O_2 and He-O_2. Zero PEEP (ZEEP) was set on the ventilator. As in the previous study, PaO_2 tidal volume, and Vmin increased with NIPSV whilst RR, inspired time and $PaCO_2$ fell. He-O_2 alone reduced PEEPi, $PaCO_2$ and work of breathing (WOB). All of these effects were enhanced by NIPSV. Yet again, the more severe the abnormalities in these parameters the greater the response. The authors [48] suggest that in patients who fail a trial of NIPSV, He-O_2 should be considered as an adjunctive intervention that might prevent intubation.

Tassaux and colleagues investigated the effects of He-O_2 in 23 acutely decompensated COPD patients who had been intubated and mechanically ventilated for ≥ 36 hours [49]. Yet again, hypoxic patients were excluded. The patients were ventilated in a mandatory volume control mode with ZEEP. Patients' hemodynamic and respiratory variables were measured at baseline, after 45 minutes of He-O_2 and 45 minutes after resumption of N_2-O_2. No effect on arterial blood gases, mixed venous oxygen tension, cardiovascular parameters, tidal volume, or respiratory system compliance were seen. He-O_2 did however, produce significant reductions in peak and plateau airway pressures, PEEPi, and the volume of trapped gas above FRC.

Taken together these trials demonstrate the benefits of He-O_2 on the respiratory mechanics of decompensated COPD patients. He-O_2 consistently improves both inspiratory and expiratory flow producing a reduction in dynamic hyperinflation with a consequent improvement in gas exchange, the magnitude of which is proportional to the degree of derangement. Whether He-O_2 would increase the success rate of NIPSV and/or reduce its duration remains speculative.

Bronchopulmonary Dysplasia (BPD)

Wolfson and colleagues investigated the effects of He-O_2 on 12 spontaneously breathing infants with BPD [50]. A cross-over design was employed (N_2-O_2 then He-O_2 then N_2-O_2) and measurements of respiratory mechanics and work of breathing made at each stage. FiO_2 was kept in the range 0.21–0.33. He-O_2 reduced the average PIP by 28%; the average inspiratory and expiratory resistances by 29 and 37% respectively; the resistive WOB by 53%; and the mechanical power of breathing (work per unit time) by 40%. The authors predict the overall effect of He-O_2 would be to reduce the overall WOB by 50% and energy requirement for breathing by 1.87 kcal/kg/day. This significant saving should result in improved growth for such infants at this vital stage in their development.

Neonatal Respiratory Distress Syndrome (RDS)

Elleau and colleagues performed a RCT of He-O_2 versus N_2-O_2 in 27 premature neonates with RDS [51]. Of note, none of these neonates received surfactant. The maxi-

mum duration of treatment was 8 days. The groups though small were well matched. Neonates in the He-O_2 group had significantly better PaO_2/FiO_2 ratios by day 2 and required significantly less respiratory support by day 4. 10/13 in the He-O_2 group versus 5/14 in the control group were extubated by day 8. Final outcome was also better in the treatment group in whom BPD developed in 2/13 versus 7/14. Taking death and BPD together the treatment group suffered 3/13 cases verses 10/14 cases amongst the controls.

Bronchiolitis

There are two published trials of He-O_2 in infants with respiratory syncitial virus (RSV) bronchiolitis. Hollman and colleagues administered He-O_2 to 18 spontaneously breathing infants and assessed their response using a clinical asthma score [52]. Thirteen of the patients had mild to moderate disease, five of whom showed improvement after 20 minutes of He-O_2. Five patients with severe disease all showed significant improvement after 20 minutes therapy. Two of these patients were rescored after 40 minutes and both showed a further significant improvement. The reduction in clinical asthma score correlated well with baseline score, that is, the sickest patients showed the greatest improvement. Nine of the patients were continued on He-O_2, for between 7 hours and 6 days. Six of these children required face mask continuous positive airway pressure (CPAP) but only one of the six, required intubation.

In contrast Gross and colleagues, who studied ten mechanically ventilated infants with RSV bronchiolitis, found no statistically significant improvement with He-O_2 [53]. They ventilated each patient with four successive gas mixtures, N_2-O_2 50:50, He-O_2 50:50, He-O_2 60:40, and He-O_2 70:30. Each mixture was administered for 15 minutes following which arterial blood gas analysis was performed. Despite the lack of statistically significant improvement in gas exchange, a close inspection of the data reveals a pattern of responders and non responders. Three of the patients had hypercapnia $PaCO_2 > 45$ mmHg, but only one of them and one of the normocapnic infants showed a reduction in $PaCO_2$. Six of the infants showed a significant improvement in PaO_2/FiO_2 (increase by >40 mmHg). Of the remaining four, three were very hyperoxic at the beginning of the trial with PaO_2s of 176, 198, and 243 mmHg, respectively, and therefore unsurprisingly showed no improvement. The remaining non-responder maintained a near constant PaO_2/FiO_2 ratio throughout the trial.

These trials are not comparable but when examined in the light of the asthma studies, largely conform to the same picture.

Post Cardiac Surgery

Tatsuno and colleagues reported a case series of 11 infants, who having failed to wean from mechanical ventilation following corrective cardiac surgery, were given a trial of He-O_2 (60:40) CPAP via endotracheal tube [54]. In nine of the patients there was an improvement in PaO_2 during the first 24 hours, which returned towards base-

line over successive days. $PaCO_2$ gradually increased over the weaning period. Respiratory rate was initially elevated on starting He-O_2 CPAP but settled within 1–2 hours with the authors commenting that respiratory distress lessened day by day. All 11 patients were successfully weaned to extubation without requiring re-initiation of mechanical ventilation. Average duration of He-O_2 CPAP was 2.7 days. The authors conclude that He-O_2 CPAP is an effective weaning strategy in such patients.

Petros and colleagues published the results of their pilot study in post cardiac surgery infants who had persistent pulmonary hypertension and required inhaled nitric oxide (NO) [55]. Nine infants were entered into this study. Six received N_2-NO for 30 minutes, followed by He-NO for 30 minutes and then returned to N_2-NO. The remaining three received the adjunctive gas mixture in the opposite order. Average starting FiO_2 was 0.75. N_2-NO (commenced at 40 ppm) caused a small but significant increase in PaO_2 (average increase 0.4 kPa) but no other effects. He-NO caused a significantly greater increase in PaO_2 (average increase 4.2 kPa), a significant increase in tidal volume (pressure controlled ventilation, settings maintained, average increase 0.7 ml/kg) and a consequent significant decrease in $PaCO_2$.

A non-comparable study in adult post cardiac surgery patients was performed by Yahagi and colleagues [56]. They studied 12 patients who had persistent hypoxia ($PaO_2/FiO_2 < 150$ mmHg with $FiO_2 > 0.6$) despite a PEEP of 10 cmH_2O. All of their patients were normocapnic. After a 90 minute observation period, patients were switched from N_2-O_2 to the equivalent ratio of He-O_2. FiO_2 was then decreased to maintain a constant arterial oxygen saturation (SaO_2). After 90 minutes, the patients were reassessed. On average, PaO_2/FiO_2 had increased from 113 to 174 mmHg, shunt fraction had decreased from 29 to 19%, and dynamic compliance (Cdyn) had increased from 60 to 65 ml/cmH_2O. The authors suggest that the improvement in Cdyn is largely due to increased flow in the smaller airways and may have led to significant recruitment of collapsed and/or poorly ventilated areas. They also comment that due do its very low solubility, He will prevent absorption atelectasis more effectively than N_2 and hence more effectively retain recruited units. This in turn facilitates a reduction in FiO_2 and results in further benefit. The authors also suggest that in these patients, in whom extrinsic PEEP levels > 10 cmH_2O can result in cardiovascular compromise, He-O_2 could effectively be used intra-operatively to prevent at least a proportion of such cases.

These last two studies, taken together with those of Schaeffer et al. [36] and Elleau et al. [51] refute the widely stated contention that in order to be of benefit, He-O_2 mixtures must be administered in ratios where the FiHe ≥ 0.6. Indeed, regardless of primary pathology, the evidence presented here supports the notion that the greater the degree of respiratory failure, the greater the benefit from He-O_2 administration. In light of the growing body of evidence [57, 58] that minimizing the lung injury caused by mechanical ventilation in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) has a major impact on morbidity and mortality there is a compelling argument to consider He-O_2 in the treatment of these patients.

Indeed, in a pilot study performed in our center (unpublished work, Dr J Fennell) six ARDS patients were ventilated for 4 hours with He-O_2. The trial was a cross-over design and the protocol aimed at increasing the FiHe until the $PaO_2 \leq 8$ kPa (60 mmHg). One patient, who became hemodynamically unstable shortly after initiation of He-O_2, showed no benefit. In the other five patients, three showed signifi-

cant improvement in both PaO_2/FiO_2 ratio and $PaCO_2$ (tidal volume and Vmin held constant). In the remaining two patients, one showed an improvement in PaO_2/FiO_2 ratio but a deterioration in $PaCO_2$ and in the other no change was seen in the PaO_2/FiO_2 ratio but a significant improvement in $PaCO_2$ was seen. There were a number of technical problems with the ventilator during this study which led us to investigate the administration of He-O_2 on our unit, before proceeding with a larger study.

Technical Considerations in Utilizing He-O_2 with Mechanical Ventilators

Currently, no commercially available mechanical ventilator is specifically designed for use with He-O_2 mixtures. However, many ventilators can safely use He by simple substitution of a 79:21 He-O_2 mixture for air. He-O_2 should be used in preference to 100% He to avoid the possibility of delivering hypoxic gas mixtures. The performance of all ventilators is affected to a variable extent by the physical properties of the intrained gases. The major issues are the accuracy of gas mixing, pressure delivery/monitoring, and volume delivery/monitoring. The only significant published work that addresses these questions was produced by Tassaux and colleagues [59].

Gas Mixing

Different manufacturers have adopted a number of approaches to this technical question. The type and positioning of the proportional inspiratory valves have a marked effect on the FiO_2 delivered when He-O_2 is sustituted for air. In their com-

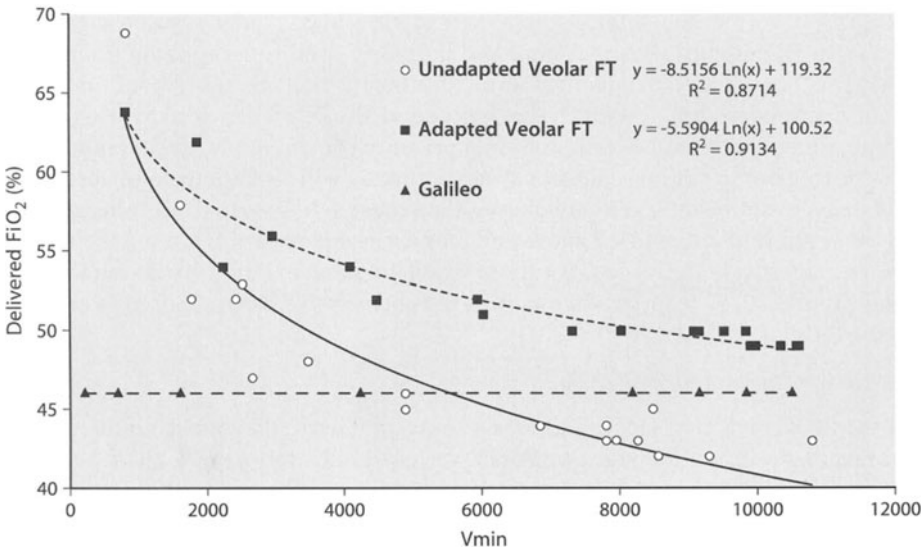

Fig. 2. Delivered FiO_2 versus minute volume (Vmin) for three different ventilators, set FiO_2 50%

prehensive assessment of seven of the most commonly employed ventilators, Tassaux and colleagues found reliable delivery from the Veolar FT, Galileo (Hamilton Medical, Rhäzuns, Swizerland), the Servo 900C and Servo 300 (Siemens-Elema, Solna, Sweden). Significant deviation from set FiO_2 was found in the Evita 2, Evita 4 (Drägerwerk, Lübeck, Germany), and the 7200 Series (Nellcor Puritan Bennett, Pleasanton, CA). Work in our center however, differs from Tassaux and colleagues' findings and showed a marked deviation of delivered FiO_2 from set FiO_2 in the Veolar FT [60] (Fig. 2) but not the Galileo. The deviation varied in a predictable fashion with both tidal volume and Vmin. On the advice of the manufacturers, the pressure regulator for the 'air' input was lowered from 1.5 to 0.4 bar whilst that for the 'O_2' input was increased from 1.75 to 3.2 bar, with considerable improvement (Fig. 2). In essence, as long as the FiO_2 delivered is continuously monitored, and adjustments to the ventilator settings altered appropriately, this problem can be overcome.

Pressure and Volume Delivery/Monitoring

Most ventilators employ some form of differential pressure pneumotachograph to monitor pressures, flows, and volumes. These sensors provide vital feedback to the control centers and provide the vital safety alarms. The current technologies have been reviewed by Jaffe [61]. In essense, changing the physical properties of the gas mixture has little or no effect on pressure monitoring but a profound effect on flow/volume monitoring. Tassaux and colleagues [59] explain the derivation of a theoretical correction factor (CF) for these later two variables, such that:

$$CF = \sqrt{\frac{\rho_{air}}{\rho_{gm}}} \tag{7}$$

where CF = correction factor, ρ_{air} = density of air, and ρ_{gm} = density of the gas mixture, note that identical temperature and humidity conditions apply to both measurements (see above). In practical terms this means that the ventilators underestimate delivered volumes, with the magnitude of the discrepancy increasing as the proportion of inspired He increases. In a pressure control mode, this merely affects monitoring but in volume control mode, ventilators will attempt to compensate and will deliver significantly greater volumes than those set. Tasseaux and colleages tested the seven ventilators listed above and found variable results. However, their paper has two significant omissions. For those ventilators that exhibit a linear deviation of quantity measured from actual quantity, the correction from measured to actual is of the form:

$$\text{actual} = (\text{measured} \times CF) + K \tag{8}$$

where CF = correction factor and K is a constant. Firstly, they make no mention of the fact that even within their own data K varies significantly from -15 to $+64$. Secondly, they make no comment about the variability of CF or K within a particular ventilator. We have addressed these issues and examined the variability of the disposable, differential pressure, variable orifice pneumotachograph employed by the Veolar FT, Amadeus, and Galileo ventilators and that of an independent disposable,

fixed orifice, Pitot tube pneumotachograph, the MCVOX (Datex-Ohmeda, Finland) [62, 63]. Correction of expired tidal volume is complicated by the variability of gas composition and thus to minimise error, we recommend using inspired tidal volume. We have derived CFs and Ks for both devices. CF variability was up to 5% but K variability was more complex with ranges between −20 and +70. This necessitates calibrating each sensor prior to use, which significantly improves accuracy, though is rather laborious.

Conclusion

The physical properties of helium make it a highly attractive addition to the conventional treatment of patients with respiratory failure. Although there are some technical problems in monitoring its administration these can be relatively easily overcome. The cost is significant but not prohibitive, especially if its use shortens the duration of respiratory support. There is a growing body of clinical evidence to support its use, especially in patients with the most severe disease. The exact mechanisms by which He-O_2 improves the respiratory mechanics and gas exchange in such patients, remains contentious. Three scenarios warrant further investigation: First, the role of He-O_2 in preventing the need for intubation and mechanical ventilation, especially in patients with acute severe asthma and decompensated COPD. Second the role of He-O_2 in the management of mechanically ventilated patients with acute respiratory failure, especially those with ARDS. Third the role of He-O_2 in patients who fail to wean from mechanical ventilation. Large, multi-center studies, designed and powered to consider the effects of He-O_2 on patient outcome, are required.

References

1. Barach AL (1935) The use of helium in the treatment of asthma and obstructive lesions in the larynx and trachea. Ann Intern Med 9:739–765
2. Barach AL (1934) Use of helium as a new therapeutic gas. Proc Soc Exp Biol Med 32:462
3. Barach AL (1935) The use of helium as a new therapeutic gas. Anesth Analg 14:210–215
4. Barach AL (1936) The therapeutic use of helium. JAMA 107:1273–1280
5. Drazen JM, Loring SH, Ingram RH Jr (1976) Distribution of pulmonary resistance: effects of gas density, viscosity, and flow rate. J Appl Physiol 41:388–395
6. Gluck EH, Onorato DJ, Castriotta R (1990) Helium-oxygen mixtures in intubated patients with status asthmaticus and respiratory acidosis. Chest 98:693–698
7. Strauss RH (1979) Diving medicine. Am Rev Respir Dis 119:1001–1023
8. Turner MJ, MacLeod IM, Rothberg AD (1989) Effects of temperature and composition on the viscosity of respiratory gases. J Appl Physiol 67:472–477
9. Papamoschou D (1995) Theoretical validation of the respiratory benefits of helium-oxygen mixtures. Respir Physiol 99:183–190
10. Terry PB, Traystman RJ, Newball HH, Batra G, Menkes HA (1978) Collateral ventilation in man. N Engl J Med 298:10–15
11. Erickson BK, Seaman J, Kubo K, et al (1994) Mechanism of reduction in alveolar-arterial PO2 difference by helium breathing in the exercising horse. J Appl Physiol 76:2794–2801
12. Erickson BK, Seaman J, Kubo K, et al (1995) Hypoxic helium breathing does not reduce alveolar-arterial PO2 difference in the horse. Respir Physiol 100:253–260

13. Altland PD, Brubach HF, Parker MG (1968) Effects of inert gases on tolerance of rats to hypoxia. J Appl Physiol 24:778–781
14. Shanklin DR, Lester EP (1972) On the pulmonary toxicity of oxygen. II. The effect of the second gas. Biol Neonate 20:140–158
15. Christopherson SK, Hlastala MP (1982) Pulmonary gas exchange during altered density gas breathing. J Appl Physiol 52:221–225
16. Murphy TM, Clark WH, Buckingham IP, Young WA (1969) Respiratory gas exchange in exercise during helium-oxygen breathing. J Appl Physiol 26:303–307
17. Nemery B, Nullens W, Veriter C, Brasseur L, Frans A (1983) Effects of gas density on pulmonary gas exchange of normal man at rest and during exercise. Pflugers Arch 397:57–61
18. Maillard D, Ben Jebria A, Hatzfeld C (1986) Effect of He-O_2 breathing on blood gases and ventilation during exercise in normal man. Bull Eur Physiopathol Respir 22:107–113
19. Bowers RW, Fox EL (1967) Metabolic and thermal responses of man in various He-O-2 and air environments. J Appl Physiol 23:561–565
20. Brice AG, Welch HG (1983) Metabolic and cardiorespiratory responses to He-O2 breathing during exercise. J Appl Physiol 54:387–392
21. Robertson WG, McRae GL (1966) Study of man during a 56-day exposure to an oxygen-helium atmosphere at 258 mm. Hg total pressure. VII. Respiratory function. Aerosp Med 37:578–582
22. Spitler DL, Horvath SM, Kobayashi K, Wagner JA (1980) Work performance breathing normoxic nitrogen or helium gas mixtures. Eur J Appl Physiol 43:157–166
23. Esposito F, Ferretti G (1997) The effects of breathing He-O2 mixtures on maximal oxygen consumption in normoxic and hypoxic men. J Physiol (Lond) 503:215–222
24. Smith SW, Biros M (1999) Relief of imminent respiratory failure from upper airway obstruction by use of helium-oxygen: a case series and brief review. Acad Emerg Med 6:953–956
25. Duncan PG (1979) Efficacy of helium–oxygen mixtures in the management of severe viral and post-intubation croup. Can Anaesth Soc J 26:206–212
26. Nelson DS, McClellan L (1982) Helium-oxygen mixtures as adjunctive support for refractory viral croup. Ohio State Med J 78:729–730
27. Rodeberg DA, Easter AJ, Washam MA, Housinger TA, Greenhalgh DG, Warden GD (1995) Use of a helium-oxygen mixture in the treatment of postextubation stridor in pediatric patients with burns. J Burn Care Rehabil 16:476–480
28. Kemper KJ, Ritz RH, Benson MS, Bishop MS (1991) Helium-oxygen mixture in the treatment of postextubation stridor in pediatric trauma patients. Crit Care Med 19:356–359
29. Terregino CA, Nairn SJ, Chansky ME, Kass JE (1998) The effect of heliox on croup: a pilot study. Acad Emerg Med 5:1130–1133
30. Pingleton SK, Bone RC, Ruth WC (1980) Helium-oxygen mixtures during bronchoscopy. Crit Care Med 8:50–53
31. Pashayan AG, Gravenstein JS, Cassisi NJ, McLaughlin G (1988) The helium protocol for laryngotracheal operations with CO2 laser: a retrospective review of 523 cases. Anesthesiology 68: 801–804
32. Cros AM, Guenard H, Boudey C (1988) High-frequency jet ventilation with helium and oxygen (heliox) versus nitrogen and oxygen (nitrox). Anesthesiology 69:417–419
33. Shiue ST, Gluck EH (1989) The use of helium-oxygen mixtures in the support of patients with status asthmaticus and respiratory acidosis. J Asthma 26:177–180
34. Kass JE, Castriotta RJ (1995) Heliox therapy in acute severe asthma. Chest 107:757–760
35. Kass JE, Terregino CA (1999) The effect of heliox in acute severe asthma: a randomized controlled trial. Chest 116:296–300
36. Schaeffer EM, Pohlman A, Morgan S, Hall JB (1999) Oxygenation in status asthmaticus improves during ventilation with helium-oxygen. Crit Care Med 27:2666–2670
37. Manthous CA, Hall JB, Caputo MA, et al (1995) Heliox improves pulsus paradoxus and peak expiratory flow in nonintubated patients with severe asthma. Am J Respir Crit Care Med 151: 310–314
38. Kudukis TM, Manthous CA, Schmidt GA, Hall JB, Wylam ME (1997) Inhaled helium-oxygen revisited: effect of inhaled helium-oxygen during the treatment of status asthmaticus in children. J Pediatr 130:217–224
39. Carter ER, Webb CR, Moffitt DR (1996) Evaluation of heliox in children hospitalized with acute severe asthma. A randomized crossover trial. Chest 109:1256–1261

40. Verbeek PR, Chopra A (1998) Heliox does not improve FEV1 in acute asthma patients. J Emerg Med 16:545–548
41. Svartengren M, Anderson M, Philipson K, Camner P (1989) Human lung deposition of particles suspended in air or in helium/oxygen mixture. Exp Lung Res 15:575–585
42. Anderson M, Svartengren M, Bylin G, Philipson K, Camner P (1993) Deposition in asthmatics of particles inhaled in air or in helium- oxygen. Am Rev Respir Dis 147:524–528
43. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA Jr (1999) The effect of heliox on nebulizer function using a beta-agonist bronchodilator. Chest 115:184–189
44. Henderson SO, Acharya P, Kilaghbian T, Perez J, Korn CS, Chan LS (1999) Use of heliox-driven nebulizer therapy in the treatment of acute asthma. Ann Emerg Med 33:141–146
45. deBoisblanc BP, DeBleiux P, Resweber S, Fusco EE, Summer WR (2000) Randomized trial of the use of heliox as a driving gas for updraft nebulization of bronchodilators in the emergent treatment of acute exacerbations of chronic obstructive pulmonary disease. Crit Care Med 28: 3177–3180
46. Swidwa DM, Montenegro HD, Goldman MD, Lutchen KR, Saidel GM (1985) Helium-oxygen breathing in severe chronic obstructive pulmonary disease. Chest 87:790–795
47. Jolliet P, Tassaux D, Thouret JM, Chevrolet JC (1999) Beneficial effects of helium: oxygen versus air: oxygen noninvasive pressure support in patients with decompensated chronic obstructive pulmonary disease. Crit Care Med 27:2422–2429
48. Jaber S, Fodil R, Carlucci A, et al (2000) Noninvasive Ventilation with helium-oxygen in acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161: 1191–1200
49. Tassaux D, Jolliet P, Roeseler J, Chevrolet JC (2000) Effects of helium-oxygen on intrinsic positive end-expiratory pressure in intubated and mechanically ventilated patients with severe chronic obstructive pulmonary disease. Crit Care Med 28:2721–2728
50. Wolfson MR, Bhutani VK, Shaffer TH, Bowen FW Jr (1984) Mechanics and energetics of breathing helium in infants with bronchopulmonary dysplasia. J Pediatr 104:752–757
51. Elleau C, Galperine RI, Guenard H, Demarquez JL (1993) Helium-oxygen mixture in respiratory distress syndrome: a double-blind study. J Pediatr 122:132–136
52. Hollman G, Shen G, Zeng L, et al (1998) Helium-oxygen improves Clinical Asthma Scores in children with acute bronchiolitis. Crit Care Med 26:1731–1736
53. Gross MF, Spear RM, Peterson BM (2000) Helium-oxygen mixture does not improve gas exchange in mechanically ventilated children with bronchiolitis. Crit Care 4:188–192
54. Tatsuno K, Imai Y, Konno S (1976) Therapeutic use of helium-oxygen mixture in continuous positive airway pressure for early weaning from mechanical ventilation after cardiovascular surgery in infants. J Thorac Cardiovasc Surg 72:119–122
55. Petros AJ, Tulloh RM, Wheatley E (1996) Heli-NO: enhanced gas exchange with nitric oxide in helium. Anesth Analg 83:888–889
56. Yahagi N, Kumon K, Haruna M, et al (1997) Helium/oxygen breathing improves hypoxemia after cardiac surgery. Artif Organs 21:24–27
57. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
58. Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N Engl J Med 342: 1334–1349
59. Tassaux D, Jolliet P, Thouret JM, Roeseler J, Dorne R, Chevrolet JC (1999) Calibration of seven ICU ventilators for mechanical ventilation with helium-oxygen mixtures. Am J Respir Crit Care Med 160:22–32
60. Ball JAS, Mitchell F, Rhodes A, Grounds RM (2000) Calibration of an adapted ventilator for use with helium oxygen mixtures. Intensive Care Med 26:S353 (Abst)
61. Jaffe MB (1998) Flow measurement with Novametrix Series 3 flow sensors – technical issues. Novametrix Medical Systems Inc, Wallingford, pp 1–8
62. Ball JAS, Rhodes A, Grounds RM (2000) Comparison of two methods for measuring tidal volumes in patients mechanically ventilated the helium-oxygen ($He-O_2$) mixtures. Br J Anaesth (Abst in press)
63. Ball JAS, Rhodes A, Grounds RM (2001) Calibration of a Pitot tube flowmeter for monitoring respiratory variables in pateints mechanically ventilated with helium-oxygen ($He-O_2$) mixtures. Crit Care Med (Abst in press)