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J. A. S. Ball
R. J. Cusack
R. M. Grounds

The role of helium in the treatment of acute respiratory failure

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Dr. J. A. S. Ball (✉)
Lecturer in Intensive Care Medicine
Department of Anaesthesia
and Intensive Care
1st Floor, Grosvenor Wing
St George's Hospital, Blackshaw Road
London, SW17 0QT, UK
Tel.: +44 (0) 20 87 25 33 16
Fax: +44 (0) 20 87 25 31 35
E-Mail: j.ball@sghms.ac.uk

Dr. R. J. Cusack
Clinical Research Fellow

Dr. R. M. Grounds
Consultant and Reader in Anaesthesia
and Intensive Care Medicine

Summary Reducing the density of inspired gas by substituting helium for nitrogen should, in theory, enhance both oxygenation and carbon dioxide clearance. This review details and critically discusses the clinical trials of heliumoxygen therapy in patients with acute respiratory failure.

Key words Helium – respiratory failure – mechanical ventilation

Introduction

Following Ramsey's successful isolation of helium (He) in 1895, Barach first described its use in the treatment of acute respiratory failure in the 1930s (1, 2). As a result of advances in therapy and reduced availability, He largely disappeared from the therapeutic armoury until a resurgence of interest began in the late 1980s. This review outlines the theoretical reasons for utilising He in the treatment of acute respiratory failure; discusses, in detail, the clinical trials published to date; and briefly describes the technical problems related to its use.

Theoretical arguments

He is a colourless, odourless, gas with inert chemistry. It is insoluble in human tissues at atmospheric pressure (3). It is 7 times less dense than nitrogen, 8 times less dense than oxygen with comparable viscosity (see Table 1). As a result, a mixture of helium : oxygen ($He:O_2$) has a lower Reynolds (Re) number (4) and hence greater bulk flow, and a higher diffusion coefficient, than an equivalent nitrogen : oxygen ($N_2:O_2$) mixture. Thus, substituting He for N_2 in inspired gas should enhance both O_2 and CO_2 transport throughout the entire bronchial tree (5). Similarly, in disease states that rely significantly on collateral ventilation (6, 7) $He:O_2$ should significantly enhance this route of gas transport.

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Table 1 Physical properties of pure gases

Gas	Density (ρ) (Kg/m^3)		Viscosity (η) (μP)
	STP (72)	1 atm/37 °C	1 atm/37 °C (73)
Helium (He)	0.179	0.158	203.82
Nitrogen (N_2)	1.250	1.101	183.42
Oxygen (O_2)	1.429	1.258	212.64
Water vapour (H_2O)	0.600 [1]	0.722	103.47
Carbon dioxide (CO_2)	1.977	1.741	154.76
Air (79% N_2:21% O_2)	1.293	1.139	189.56
Heliox (79% He:21% O_2)	0.442	0.389	205.67

STP = at 273 °K and 1 atmosphere pressure; [1] = at 373 °K and 1 atmosphere pressure

Data from animal and normal human experiments

Long-term inhalation of He:O_2 mixtures has failed to show any deleterious effects in mice (2) or humans (8).

Altland and colleagues (9) examined the effects of hypoxia on rats by exposing them to mixtures of O_2 (FiO_2 0.05) in He, N_2, Ar, and SF_6 (ascending order of density). The rats exposed to He:O_2 had significantly higher arterial O_2 saturations and better survival rates than the others. Shanklin and Lester (10) investigated oxygen toxicity in neonatal rabbits, by comparing the effects of pure O_2 with those of O_2 diluted in a variety of carrier gases including He. Next to pure O_2, He:O_2 caused the greatest toxicity. Thus He appears to enhance O_2 transport through the lungs.

Breathing He:O_2 (79:21) at rest has no significant effect on gas exchange in normal human subjects (11). 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 (12–19). The protocols, measurement techniques and results of these studies vary significantly but a coherent message emerges and is perhaps best summarised in the study by Esposito and Ferretti (19). They compared the respiratory parameters and gas exchange variables of 8 subjects breathing normoxic (79:21) and hypoxic (89:11), N_2:O_2 and He:O_2 gas mixtures 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^{-1}; V_A 112.1 versus 95.1 L min^{-1}), though only the former was statistically significant. Despite these differences there was no difference in the partial pressure of arterial O_2 (PaO_2) or $PaCO_2$. When breathing the hypoxic gas mixtures, similar differences in V_E and V_A were observed between the two gas mixtures (V_E 141.3 versus 107.8 9 L min^{-1}; V_A 101.5 versus 82.1 L min^{-1}) though here both were statistically significant. As expected oxygenation fell with the hypoxic mixtures, but PaO_2 was significantly greater with He:O_2 than N_2:O_2 (46.6 versus 40.0 mmHg). $PaCO_2$ also significantly fell 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 O_2 and CO_2 through the bronchial tree. The authors discuss that 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.

Although inert, one physical property of helium might be deleterious to humans, especially children. He has a thermal conductivity that is approximately 6 times that of N_2 and it enhances the diffusivity of water vapour to a similar extent (20). However, no clinically significant sequelae have ever been demonstrated. Dromer and colleagues (20) investigated the effects of He:O_2 on the temperature of expired gas in 6 normal adults. They found that thermal inertia of the airways and their surrounding tissues was the limiting factor in heat loss and that this was unaffected by inspired gas composition.

Clinical trials

We have conducted a detailed literature search using a variety of databases and pursued all trials referenced in the identified trials and reviews. From these sources there are 14 case series and 22 controlled trials of He:O_2 utilisation in patients with respiratory failure. Tables 2 and 3 summarise the patients studied and the authors' results. Individual studies are discussed in the following sections.

Laryngeal, tracheal and major bronchi obstruction

Upper airway obstruction (UAO) remains the leading indication for He:O_2 therapy. The literature in this area has recently been thoroughly reviewed by Smith and Biros (21). They report a case series of 6 patients and review 12 original case studies and 3 other series (22–24), documenting the dramatic relief of UAO by He:O_2. In addition there are three randomised trials of He:O_2 in UAO (25–27) that add further evidence to the efficacy of this intervention. Smith and Biros draw three important conclusions from their experience and literature review: Firstly, that the greater the severity of UAO, the more dramatic the benefit

of He:O_2. Secondly, 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). Thirdly, that the efficacy of this intervention is poorly appreciated and not widely available. Further evidence of the efficacy of He:O_2 has been provided by Jaber et al. (28) in the setting of elective extubation post >48 hours mechanical ventilation. They demonstrated a significant reduction in inspiratory effort with no change in gas exchange.

There is also evidence which demonstrates the efficacy of He:O_2 as an adjunct to ventilation in situations of iatrogenic UAO. 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 (29).

Asthma

The first case series describing the use of He:O_2 in acute asthma was published in 1989 by Shiue and Gluck (30). They enrolled 10 adult patients who had presented with acute severe asthma and a respiratory acidosis. All patients had received nebulised 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 normalised their arterial $PaCO_2$ and pH after 20 minutes, the remainder by 60 minutes. No patient required intubation and MV during their admission.

The following year, Gluck and colleagues published a second case series (5) in which they reported the effects of He:O_2 mixtures on 7, 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 hours without significant improvement. These patients were then ventilated with 60–80% He. All 7 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 cm H_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 h. Mean duration of He:O_2 therapy was 6.3 h.

In 1995 Kass and Castriotta reported a case series of 12 adult, acute asthmatics treated with He:O_2 (31). All had a persistent respiratory acidosis despite maximal medical therapy. Seven patients received He:O_2 via non-rebreathing face mask, whilst the remaining 5 were intubated and mechanically ventilated with He:O_2. Eight patients responded to He:O_2, defined as normalisation of $PaCO_2$ or ≥15% fall in $PaCO_2$ within ~60 minutes. The four non-respon-

Table 2 Case series of He:O_2 utilisation

1st Author	Patients	Result
Duncan (22)	7 SB patients with UAO	Significant benefit. None required intubation
Nelson (23)	14 SB infants with viral croup who had failed standard treatment	Significant benefit. None required intubation
Rodeberg (24)	8 SB children with post extubation stridor	Significant benefit. Only one patient re-intubated
Smith (21)	A heterogeneous group of 6 SB patients with UAO	Significant benefit.
Shiue (30)	10 SB acute severe adult asthmatics	Significant benefit
Gluck (5)	7 MV'd adults with acute severe asthma	Significant benefit. Rapid fall in peak Paw and $PaCO_2$
Kass (31)	12 acute severe adult asthmatics; 7 SB and 5 MV	Significant benefit
Verbeek (37)	13 SB adults with acute asthma	No benefit
Swidwa (45)	15 SB adults with severe stable COPD	Significant benefit
Hollman (51)	18 SB infants with bronchiolitis	Significant benefit
Tatsuno (74)	11 infants who'd failed to wean from MV post cardiac surgery received heliox (60:40) as CPAP via endotracheal tube	Significant benefit
Yahagi (55)	12 MV'd adult patients with persistent hypoxia post-cardiac surgery	Significant benefit
Michael (75)	3 MV'd paediatric patients with high PIPs and inadequate ventilation	Significant benefit
Winters (60)	5 children with severe respiratory failure received heliox HFOV	Significant benefit

SB = spontaneously breathing; MV'd = mechanically ventilated

Table 3 Controlled trials of $He:O_2$

1st Author	Patients	Result
Butt (56)	Cross-over trial of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 6 preterm infants with BPD and subglottic stenosis, 5 normal infants and 6 infants on CPAP	Fall in $tcPO_2$ in 1st & 2nd groups. Fall in resp. rate with no change in $tcPCO_2$
Kemper (25)	Randomised cross-over trial of $N_2:O_2$ (70:30) vs $He:O_2$ (70:30) in 15 episodes of post extubation stridor in 13 SB children	Significant benefit
Terregino (26)	RD-BCT of $N_2:O_2$ (70:30) vs $He:O_2$ (70:30) in 15 SB children 4/12-6 yrs with mild croup	No benefit
Weber (27)	RCT of $He:O_2$ (70:30) vs nebulised epinephrine in 29 SB infants with croup	Equal benefit
Jaber (28)	Cross-over trial of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) immediately post-tracheal extubation (>48 hrs of MV)	Significant reduction in inspiratory effort and improved comfort
Kass (32)	RCT of $N_2:O_2$ (70:30) vs $He:O_2$ (70:30) in 23 mild-moderate SB acute asthmatics	Significant benefit
Schaeffer (33)	Historical case control study of 11 mechanically ventilated adults with acute severe asthma	Significant benefit
Manthous (34)	Controlled cross-over trial of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 16 SB adults with acute asthma compared to 11 similar control subjects	Significant benefit
Kudukis (35)	RCT of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 18 SB children with acute asthma	Significant benefit
Carter (36)	Complex cross-over trial of 11 SB child asthmatics 24–72 h post-hospitalisation	No benefit
Dorfman (38)	RCT of $He:O_2$ (80:20) vs $N_2:O_2$ (79:21) in 39 SB adults with acute asthma	No benefit
Henderson (43)	RCT of $N_2:O_2$ vs $He:O_2$ driven updraft nebulisation of bronchodilators in 205 SB adults with acute asthma	No benefit
deBoisblanc (44)	RCT of $N_2:O_2$ vs $He:O_2$ driven updraft nebulisation of bronchodilators in 50 SB adults with acute exacerbations of COPD	No benefit
Jolliet (46)	Randomised cross-over trial of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 19 adults with acute exacerbations of COPD receiving NIPSV	Significant benefit
Jaber (47)	Cross-over trial of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 10 adults with acute exacerbations of COPD receiving NIPSV	Significant benefit
Tassaux (48)	Cross-over trial of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 23 MV'd adults with acute exacerbations of COPD	Significant benefit
Wolfson (49)	Cross-over trial of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 12 SB infants with BPD	Significant benefit
Elleau (50)	RCT of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 27 MV'd neonates with RDS	Significant benefit
Gross (52)	Cross over trial of $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 10 MV'd infants with bronchiolitis	No benefit [1]
Petros (54)	Cross-over trial of iNO in $N_2:O_2$ vs $He:O_2$ (variable FiO_2) in 9 MV'd infants with pulmonary hypertension post-cardiac surgery	Significant benefit
Cros (59)	Cross-over trial of heliox (60:40) and nitrox (69:40) for intra-operative HFJV in 10 adults	Significant benefit
Pizov (76)	Cross-over trial of He and O_2 TGI (various flow rates) in 7 MV'd adults with acute respiratory failure	Significant benefit. He more efficient than O_2

RCT = randomised control trial; SB = spontaneously breathing; MV'd = mechanically ventilated

ders, 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 gradient (A-a O_2) improved in all patients but this was not statistically significant. 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 h. 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 h.

Following this series Kass and colleagues conducted a randomised controlled trial in adult acute asthmatics, none of whom had respiratory failure (32). Entry criteria was a peak expiratory flow (PEF)

of <200 L min^{-1}. Both groups received standard therapy, with the control group receiving N_2:O_2 70:30 and the treatment group receiving He:O_2 70:30. Although 28 patients were recruited, one patient in the control group deteriorated necessitating intubation and mechanical ventilation, and 2 patients in each group improved to such an extent that they were discharged prior to the end of the study at 8 h. Of the remaining 23 patients 11 were randomised to He:O_2. Nine of the treatment group had a >25% improvement in PEF at 20 minutes compared to only 2 in the control group. Indeed, parity between the two groups was not reached until 6 h. 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 (33). 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 A-aO_2 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 statistically significant improvement in oxygenation compared to only 6 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 7 of the 11 He:O_2 group but only 3 of the 11 controls. These differences between the two groups were not statistically significant. No outcome data were presented.

There are a further 5 published trials of He:O_2 in acute asthma, which in our opinion add little if anything to the above studies. Manthous et al. (34) 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 of He:O_2.

In a nearly identical design Kudukis et al. (35) performed a blinded, randomised control trial 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 after He:O_2, which reversed within 15 minutes. No changes were seen in the control group.

Carter et al. (36) performed a double blind, randomised cross-over trial in 11 children. Entry to the trial took place 1–3 days following admission to hospital and initiation of medical therapy. Spirometry and dyspnoea scores 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 (37) 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. In view of the short duration of therapy and the fact that these patients appear to have had relatively mild disease the negative findings of this trial are unsurprising.

A third negative study was published by Dorfman and colleagues (38). Using a randomised control design they recruited 39 adult patients with acute asthma, from 60 consecutively screened individuals. Study patients were then randomised to receive either air or He:O_2 (80:20) at 10 L min^{-1} for one hour. During this time, all patients received bronchodilators nebulised with O_2 and systemic steroids. The two groups were well matched at baseline but of note, none were hypoxic and the mean duration of symptoms was $\sim$40 h, with a very wide range. After one hour, both groups had shown a significant improvement in PEF but there was no difference between the groups. Indeed the only significant difference between the two groups was in heart rate after one hour (121 in the He group vs 96 in the control group). Whether this reflects a increase in the systemic dose of albuterol delivered is not discussed (see below). Overall, although the authors describe their patients as moderate to severe and their mean PEF pre-treatment was only 43% of predicted, the other data supplied together with the high response rate to treatment implies that this group of asthmatics was well compensated, hence unsurprisingly He:O_2 was no better than standard therapy alone.

The 10 published clinical trials of helium in acute asthma feature only 172 very heterogeneous patients and 11 historical controls. Of the 172 patients, 121 received helium, although in 4 of the 10 trials this was for only 5–15 minutes. Only 23 patients were mechanically ventilated. Only 3 studies were randomised controlled trials, enrolling 18, 23 and 39 pa-

tients respectively. Seven of the trials report a positive benefit of helium treatment, although very variable outcome measures were employed. Overall, though the data is extremely limited, it appears that the sicker the patient and the earlier helium is used the greater the benefit. 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 nebulisation

In several of the asthma trials the issue of nebulised 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 4 studies in the literature which examine the theory behind this question and 2 randomised control trials, one in acute asthmatics and the other in acutely decompensated chronic obstructive pulmonary disease (COPD) patients.

Svartengren and colleagues measured the quantity of 3.6–3.8 μm teflon particles labelled with Tc^{99m} that are deposited in the mouth and throat, and in the alveoli, of normal subjects when inhaled in air or $He:O_2$ (80:20) (39). They studied 9 human subjects with and without bronchoconstriction. Bronchoconstriction was induced by administration of aerosolised methacholine bromide. The Teflon particles were delivered with a flow rate of 0.5 L s^{-1}. Deposition in the mouth and throat did not differ between air and $He:O_2$ delivery. The number of Teflon particles deposited in the alveoli was larger when the subjects were unconstricted and significantly greater in the constricted subjects when inhaled with $He:O_2$. As the sedimentation rate of particles is roughly identical in air and $He:O_2$ (80:20), the authors conclude that the increase in alveolar deposition seen with $He:O_2$, is due to a reduction in turbulence in the bronchial tree.

The same group investigated alveolar particle deposition in 10 stable asthmatic subjects (40). They used 3.6 μm particles labelled with In^{111}. These they delivered using either air or $He:O_2$ (80:20) at 0.5 and 1.2 L s^{-1}. Measurements were taken immediately following inhalation and at 24 h. The measurements taken at 24 h (Ret 24) were considered to represent alveolar deposition. For both flow rates, Ret 24 was significantly higher with $He:O_2$. The difference observed between air and $He:O_2$ inhalation was larger than that seen in the normal subjects in their previous study.

As bronchodilators are classically delivered by jet (i.e. updraft) nebulisation, Hess and colleagues evaluated the particle size and inhaled mass of albuterol nebulised with air and $He:O_2$ (80:20) at several flow rates using a lung model (41). 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 conclude that flow rates and/or drug concentration should be increased when $He:O_2$ is employed to drive nebulisers.

A further lung model study by Goode et al. (42) attempts to establish the optimal in vitro particle delivery technique during mechanically ventilation. First, these investigators examined the effect of decreasing gas density on the mass of preformed albuterol aerosol delivered to the main bronchi of their model. They found these two variables to be inversely proportional with $He:O_2$ (80:20) delivering 50% more drug than 100% O_2. They then repeated this experiment using heated humidified gas in place of the dry gas. This reduced the delivery of drug by ~50% for all gas densities. They concluded that the increase in the proportion of laminar flow caused by the reduction in gas density reduced the quantity of aerosol deposition within the ventilator circuit hence enhancing its delivery to the major airways. For their third experiment these investigators compared the mass of aerosol produced by updraft nebulisation with varying gas densities (an identical experiment to that performed by Hess et al. (41)). For the same flow rate, the higher the gas density the greater the mass of aerosol produced, as you would predict from the Bernoulli principle. To achieve equivalent nebulisation, the flow rate of $He:O_2$ 70:30 has to be ~2.5× the flow rate of 100% O_2. For their final experiment, these investigators examined the effect of carrier gas density on the mass of nebulised albuterol delivered to the main bronchi of their lung model with their varied nebulisation regimes. Unsurprisingly, the greatest delivery was achieved with low flow 100% O_2 nebulisation into $He:O_2$ 80–20. Though not discussed by the authors, they intimate that increased delivery of aerosolised drug to the major airways will inevitably result in increased delivery to the distal airways where the majority of drugs act, thus enhancing their efficacy. It is difficult to extrapolate from these in vivo experiments to the limited data from clinical studies with mechanically ventilated patients receiving bronchodilator therapy and reach any conclusions. What this paper does set out however is the optimal method which should be adopted in any future studies.

In the clinical setting in non-ventilated patients however, the issue appears less clear. Henderson and colleagues performed a randomised control trial in 205 asthmatics with mild to moderate acute exacerbations (43). The control group received 3 nebu-

lised doses of albuterol 5 mg delivered by O_2 at 10 L min^{-1}, at 15 minute intervals. The treatment group received identical therapy but delivered by $He:O_2$ (70:30) at 10 L min^{-1}. PEFR and FEV_1 were used at 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 (44). There are two major methodological differences between the two studies. DeBoisblanc et al. performed in vivo experiments to ensure that rate of respirable particle generation was identical in the control and treatment groups; Henderson et al. did not. Secondly, in the COPD study, spirometry was performed after 60 and 120 minutes as opposed to 45 minutes in the asthma study. The authors of the second paper 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 majority of the asthma trials, who enrolled mild to moderately affected patients. Whether severely affected patients would receive and benefit from enhanced bronchodilator delivery remains unknown.

COPD

In 1985 Swidwa and colleagues investigated the effects of $He:O_2$ in 15 severe (FEV_1 <1 L) but stable COPD patients (45). 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 (iPEEP).

Jolliet and colleagues investigated the effects of $He:O_2$ in a group of 19 acutely decompensated COPD patients (46). Hypoxic patients were excluded. Each patient was stabilised on non-invasive pressure support ventilation (NIPSV), a process that took a mean of 17 h. 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 (Vt) 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 (Ti) and $PaCO_2$ with both gas mixtures, but for these variables the effects of $He:O_2$ were significantly greater. Notably the reduction in $PaCO_2$ was proportional to the baseline value. The authors suggest that the reduction in Ti, is the crucial factor and explains the decrease in $PaCO_2$. They argue that a shorter Ti coupled with an increase in Vt, 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 (47). 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 was set on the ventilator. As in the previous study, PaO_2, Vt and Vmin increased with NIPSV whilst RR, Ti and $PaCO_2$ fell. $He:O_2$ alone reduced iPEEP, $PaCO_2$ 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 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 (48). Yet again, hypoxic patients were excluded. The patients were ventilated in a mandatory volume control mode with zero PEEP. Patients' haemodynamic 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, Vt or respiratory system compliance were seen. $He:O_2$ did however produce significant reductions in peak and plateau airway pressures, iPEEP 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 (49). 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^{-1} day^{-1}. This significant savings could theoretically result in improved growth for such infants at this vital stage in their development.

Neonatal respiratory distress syndrome (RDS)

Elleau and colleagues performed a randomised control trial of $He:O_2$ versus $N_2:O_2$ in 27 premature neonates with RDS (50). Of note, none of these neonates received surfactant. The maximum 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 RSV bronchiolitis. Hollman and colleagues administered $He:O_2$ to 18 spontaneously breathing infants and assessed their response using a clinical asthma score (51). Thirteen of the patients had mild to moderate disease, 5 of whom, showed improvement after 20 minutes of $He:O_2$. Five patients with severe disease all showed significant improvement after 20 minutes therapy; 2 of these patients were re-scored after 40 minutes and both showed a further significant improvement. The reduction in clinical asthma score correlated well with the 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; 6 of these children required face mask CPAP but only one of the 6, required intubation.

In contrast Gross and colleagues, who studied ten mechanically ventilated infants with RSV bronchiolitis, found no statistically significant improvement with $He:O_2$ (52). 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 $PaCO_2$. Of the infants 6 showed a significant improvement in PaO_2/FiO_2 (increase by >40 mmHg). Of the remaining 4, 3 were very hyperoxic at the beginning of the trial with PaO_2's 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 MV following corrective cardiac surgery were given a trial of $He:O_2$ (60:40) CPAP via endotracheal tube (53). In 9 of the patients there was an improvement in PaO_2 during the first 24 hours, which returned towards baseline over successive days. $PaCO_2$ gradually increased over the weaning period as respiratory rate fell. Respiratory rate was initially elevated on starting $He:O_2$ CPAP but within 1–2 hours settled with the authors commenting that respiratory distress lessened day by day. All 11 patients were successfully weaned to extubation without requiring re-initiation of MV. 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 (iNO) (54). Nine infants were entered into this study. Six received NO in N_2 for 30 minutes, followed by NO in He for 30 minutes and then returned to NO in N_2. The remaining 3 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 Vt (pressure controlled ventilation, settings maintained, average increase 0.7 ml kg^{-1}) and a consequent significant decrease in $PaCO_2$.

A non-comparable study in adult post-cardiac surgery patients was performed by Yahagi and colleagues (55). 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/cm H_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 cm H_2O, cardiovascular compromise can result, and $He:O_2$ could effectively be used intra-operatively to prevent at least a proportion of such cases.

The hypoxia controversy

In 1985, Butt and colleagues published a cross-over study in infants (56). They administered $He:O_2$ to 3 groups, 6 premature infants with BPD and subglottic stenosis, 5 normal term infants and 6 infants with respiratory failure receiving CPAP. They observed a marked fall in oxygenation in groups 1 and 2 but not in 3, which they claimed resulted from the reduction in gas density. They also noted a reduction in respiratory rate but no change in $tcPCO_2$. The explanation for the observed hypoxia was found by Stillwell and colleagues (57), who proved that the oxygen hoods used by Butt et al. delivered hypoxic mixtures. As for the lack of change in $tcPCO_2$, as all of these infants were spontaneously breathing, it is reasonable to assume that as their respiratory rate fell, so did their Vmin, hence the administration of $He:O_2$ led to an improvement in CO_2 excretion. Also of note is that no other study of the effects of $He:O_2$ has demonstrated that lowering the density of inspired gas provokes hypoxaemia. This study emphasises the importance of thoroughly testing the effects of He on clinical equipment.

High frequency ventilation

Surgery on the larynx and/or trachea can be facilitated by $He:O_2$ (58, 59). In the second of these two papers, the authors report the beneficial effects of substituting $He:O_2$ (60:40) for $N_2:O_2$ (60:40) when employing high frequency jet ventilation. They report 10 cases in which they conducted a cross-over trial. None of the subjects were hypoxic and no improvement in PaO_2 was seen. They did however observe a significant decrease in $PaCO_2$ and a significant increase in gas flow for the same driving pressure.

A similar result is reported by Winters et al. (60), who published a case series of 5 paediatric patients with severe hypoxaemic respiratory failure. Each patient received $He:O_2$ as an adjunct to high frequency oscillatory ventilation. The predominant effect of $He:O_2$ was a dramatic reduction in $PaCO_2$ by an average of 24% within 45 minutes.

Technical problems encountered with $He:O_2$ administration

The issue of nebulisation therapy is discussed above. There are 3 studies that have examined the effects of He on the performance of mechanical ventilators (61–63). As might be predicted, some ventilators are largely unaffected by He whilst others fail to function at all. In addition to these findings, monitoring of respiratory variables, in particular, flow and volume measurements (64–66) as well as capnography (67, 68) are adversely affected by He. To ensure safety, any delivery or monitoring equipment must be tested for reliability prior to clinical use with He.

Summary

It is evident that drawing any broad conclusions from this body of work is hampered by its heterogeneity. However, we would argue that there is reasonable evidence to suggest that the administration of $He:O_2$ improves both oxygenation and ventilation above and beyond current standard therapies in patients with the severest disease. Hence further research should concentrate on $He:O_2$ administration to either prevent mechanical ventilation or as an adjunct to mechanical ventilation.

There appears to be broad agreement that ventilatory failure, with resultant hypercarbia, will benefit from heliox therapy by reducing the work of breathing and enhancing CO_2 excretion. However, numerous authors have stated that, in order to be of benefit, $He:O_2$ mixtures must be administered in ratios where the $FiHe \geq 0.6$, thus they have excluded hypoxic patients. Yet, in the few studies that have investigated such patients, namely those of Petros (54), Yahagi (55), Schaeffer (33), Elleau (50) and the hypoxic patients in the study by Gross et al. (52) this conjecture is refuted. They demonstrate that benefits can be seen with a FiHe as low as 0.20 and that oxygenation is significantly improved by substitution of $He:O_2$ for $N_2:O_2$. Thus hypoxic respiratory failure should not be considered a contra-indication to $He:O_2$.

With regard to mechanical ventilation, there is now a consensus that this intervention frequently causes substantial lung injury and, some argue, results in the multi-organ failure that so many respiratory failure patients develop (69). In light of the recent evidence that minimizing this injury in patients with acute respiratory distress syndrome (ARDS) has a major impact on morbidity and mortality (70, 71) there is a compelling argument to consider $He:O_2$ in the treatment of these patients. Its use should facilitate an improvement in gas exchange for any given ventilatory strategy, or perhaps more usefully, allow a kinder ventilatory strategy to be adopted to maintain an acceptable level of gas exchange.

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