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Room air dilution of heliox given by facemask

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Abstract Objectives: To measure the extent of dilution of helium-oxygen (heliox) by room air when given via high concentration reservoir mask to spontaneously breathing subjects. Substantial dilution of heliox by room air under these circumstances might alter its physical properties sufficiently to negate any potential clinical benefit in obstructive respiratory failure. **Design:** Healthy volunteers breathing different concentrations of helium in oxygen via two different masks in a randomised crossover design. **Setting:** Operating theatre in a university hospital. **Participants and interventions:** Six healthy volunteers. The concentrations of helium, nitrogen and oxygen were measured in the trachea of each volunteer using a mass spectrometer during normal breathing, hyperventilation and hypoventilation. **Measurements and results:** During normal breathing of Heliox21 (79% helium) via a standard non-rebreathe reservoir mask, within subject median percentage tracheal helium was 37.2% (range

29.3–52.2%) and nitrogen was 41.7% (27.4–49.4%). Air entrainment was affected by changes in breathing pattern: tracheal nitrogen concentration was greater during hyperventilation (55.4%; range 49.4–63.5%) and less during hypoventilation (33.1%; range 24.6–39.6%, $p = 0.043$). Tracheal nitrogen could be almost completely abolished by administering heliox via a tightly fitting cushioned face-mask, even during hyperventilation (2.2%; range 0.6–6.1%, $p = 0.028$). **Conclusions:** Heliox administration via a standard high-concentration reservoir mask leads to significant dilution by room air. For the full potential benefits of heliox to be realised in spontaneously breathing patients, it should be administered via a system that achieves a gas tight seal, with no leaks between the delivery device and the surroundings.

Keywords Helium · Lung Diseases, Obstructive · Masks · Nitrogen · Oxygen

Introduction

Heliox (a mixture of helium and oxygen) has been used as a respiratory therapy since the mid 1930s [1]. Helium is seven times less dense than nitrogen and eight times less dense than oxygen [2]. Its low density alters the dynamics of gas flow, promoting laminar flow and reducing flow resistance where turbulence persists, thus reducing work of breathing, improving ventilation and the delivery of ne-

ulised drugs to narrowed airways [2, 3]. Heliox has been proposed as a treatment for obstructive respiratory diseases including acute upper airway obstruction, post-extubation stridor, croup, bronchiolitis, acute asthma and exacerbation of chronic obstructive pulmonary disease, but its efficacy has not been firmly established [4].

Dilution of heliox by room air during administration would increase the density of the gas mixture administered and might reduce its efficacy. This problem was

recognised many years ago: an early proponent advised administering heliox using closed circuit rebreathing apparatus, closed tents or hoods [5]. However, heliox is now generally administered to spontaneously breathing patients by a high-concentration reservoir mask. These are either partial-rebreathe masks (no valve between reservoir bag and mask) or non-rebreathe masks (valve present). During oxygen administration, these masks provide an inspired concentration of about 70% because of air entrainment [6], but higher values have been recorded with use of a tight-fitting three-valve non-rebreathe mask using a flow rate of 15 l/min [7]. We determined the extent of dilution of inhaled heliox gas mixtures by room air with a non-rebreathe reservoir mask compared with a closed delivery circuit providing a tight seal between the mask and face.

Materials and methods

The study was a randomised, blinded, crossover investigation of healthy adult volunteers. Statistical simulation suggested that six subjects would be sufficient to detect an effect size of 1.5 or more with 80% power, when a mask allowing a degree of room air entrainment was compared with a mask allowing minimal entrainment.

Subjects and breathing patterns

Institutional ethical approval was obtained (Cambridge 2 Research Ethics Committee, Cambridge, UK), and six volunteers gave written, informed consent to participate. They were trained to adopt two breathing patterns paced by a metronome: a normal breathing pattern of 12 breaths per minute, and a hyperventilation pattern in which they took deeper breaths 18 times per minute. The extent of chest expansion was gauged using a stethograph (Division of Anaesthesia, Cambridge, UK) – an air filled bladder strapped around the chest. The cyclical pressure changes generated in the stethograph during breathing were transduced and displayed on a monitor (S/5, Datex-Ohmeda, GE Healthcare, Helsinki, Finland) to give a visual indication of tidal volume. Once the subjects were familiar with the breathing patterns, a calibrated spirometer

(Vitalograph Compact, Vitalograph Ltd, Buckingham, UK) was employed to measure the tidal volumes and peak inspiratory flow rates of each subject in room air (Table 1).

During data collection, subjects maintained each breathing pattern for 2 min. Data were collected during normal breathing, hyperventilation and the period of hypoventilation that followed whilst arterial carbon dioxide tension normalised.

Gas sampling from distal trachea

Gases were sampled continuously through a tracheal suction catheter (14Ch Caretip, Meddis Ltd, Wallingford, UK) placed 2 cm proximal to the carina. The percentages of tracheal helium, nitrogen and oxygen were measured every 700–800 ms using a quadrupole mass spectrometer with a 95% response time of 300 ms (HPR-20 Gas Analysis System, Hiden Analytical, Warrington, UK) calibrated against two alpha-gravimetric gas mixtures (British Oxygen Company Medical, Guildford, UK). The catheter had been positioned under direct vision using a paediatric intubating fibroscope in the anaesthetised airway of the alert subject. Intubating conditions were achieved with 200 µg glycopyrronium intravenously as an antisialogue and topical application of 5% lidocaine and 0.5% phenylephrine to the nasopharynx, after which the oropharynx, larynx, vocal cords and trachea were sprayed with 4% lidocaine. To ensure the gas sampling system was free from external to internal leaks, Heliox21 (21% O₂, 79% He) was sprayed onto the gas sampling system (especially around any joints) as helium free gas was aspirated into the mass spectrometer, while scanning for helium. The values of all measured gases demonstrated drift of < 1 (%) per hour.

Delivery of heliox and oxygen via different facemasks

Subjects were randomised to receive gas mixtures containing either decreasing or increasing concentrations of helium. The subject was blinded to their group. Three minutes were allowed between each test gas to allow equilibration with the lungs prior to the subject fixing their

Table 1 Physiological profiles of subjects. *BMI*, body mass index; *PIFR*, peak inspiratory flow rate; *Hyper*, hyperventilation breathing pattern; *Norm*, normal breathing pattern

Subject no. and gender	Age (years)	Weight (kg)	Height (m)	BMI	Tidal volume (l)		PIFR (l/min)	
					Hyper	Norm	Hyper	Norm
1: M	33	74	1.81	22.6	2.12	0.90	2.73	0.94
2: F	37	54	1.51	23.7	1.62	0.56	1.84	0.94
3: F	29	90	1.7	31.1	1.88	0.62	2.92	0.56
4: M	36	70	1.66	25.4	1.97	0.85	2.31	0.70
5: M	35	67	1.76	21.6	2.48	1.02	3.61	1.06
6: F	29	96	1.72	32.4	2.85	1.68	3.98	1.31

breathing pattern. The performance of a three-valve non-rebreathe mask with a 1.2-l reservoir bag, fitted using the elastic strap (single pull on each side) and metal strip over the nose (single squeeze; Fig. 1; Intersurgical Ltd, Wokingham, UK), was compared with an air-cushioned anaesthetic mask (Intersurgical Ltd, Wokingham, UK) fitted using a four-point fixation harness and connected to a disposable anaesthetic breathing circuit incorporating a 2-l reservoir bag and a one-way expiratory valve (Fig. 2; Intersurgical Ltd, Wokingham, UK). Subjects were allowed to adjust the masks to achieve a comfortable fit. The fresh gas flow rate into each mask for all subjects and for all test gases was 15 l/min. Heliox21, Heliox28 (28% O₂, 72% He), Heliox40 (40% O₂, 60% He) and 100% oxygen were delivered from a Heliox Mixing Station (Gas Control Equipment, Warrington, UK / BOC Medical, Guildford, UK) using a flowmeter with industry-calibrated (British Standard EN ISO 9001:2000), density-adjusted scales for each gas (Gas Control Equipment, Warrington, UK /

Instruments to Industry, Liverpool, UK). Normal ventilation and Heliox28 / Heliox40 data were not recorded for the anaesthetic mask and breathing circuit due to time constraints.

Data analysis

Randomisation was performed on-line (<http://www.randomizer.org>). Data from the mass spectrometer were recorded on a personal computer using MASsoft software (Hidden Analytical, Warrington, UK) and analysed using Statview (SAS Institute, Cary, NC, USA). All subjects completed the study, with the exception that hypoventilation and some oxygen data were not recorded for subject 4 and no data were recorded with Heliox40 for subject 2, due to discomfort. Up to 160 measurements were recorded during inspiration and expiration once the subject had achieved a steady state at each breathing



Fig. 1 A three-valve non-rebreathe reservoir mask (Intersurgical Ltd, Wokingham, UK)



Fig. 2 Air-cushioned anaesthetic facemask connected to a disposable anaesthetic breathing circuit (Intersurgical Ltd, Wokingham, UK)

pattern. As these were not fully independent measures, we calculated summary measures for each subject at each phase of the experiment. Inspection of the data showed that within-subject and within-experiment variations of measured percentage of mixed tracheal nitrogen ($\%N_{2trach}$) were small, and median values of $\%N_{2trach}$ from each subject ($m\%N_{2trach}$) provided good summary measures for statistical analysis without making any assumptions of normality of distribution. Within-subject comparisons for different experimental conditions were undertaken using the Wilcoxon signed-rank test. The influence of breathing pattern on room air entrainment was examined by comparing subject's $m\%N_{2trach}$ while breathing Heliox21 via the non-rebreathe reservoir mask when hyperventilating, hypoventilating and with normal breathing. To examine the influence of mask seal, subject's $m\%N_{2trach}$ values with each mask were compared while hyperventilating and hypoventilating with both Heliox21 and 100% oxygen. In order to determine whether there was a diffusive element to the nitrogen entrainment, we compared $m\%N_{2trach}$ values recorded with the different test gases during normal breathing with the non-rebreathe reservoir mask only.

Effect of breathing pattern on room air entrainment

For all gas mixtures delivered by non-rebreathe reservoir mask, room air dilution was greatest during hyperventilation and lowest during hypoventilation. For example, using $m\%N_{2trach}$ as an indicator of air entrainment, the median and range of $m\%N_{2trach}$ in our subjects was 55.4% (49.4–63.5%) during hyperventilation, 41.7% (27.4–49.4%) during normal ventilation and 33.1% (24.6–39.6%) during hypoventilation, when breathing 79% helium in Heliox21 – differences which gave p -values of 0.028 ($n=6$)–0.043 ($n=5$) with paired Wilcoxon signed-rank comparisons (Fig. 3; Table 2). As $m\%He_{trach}$ changed in inverse proportion to $m\%N_{2trach}$ (Fig. 3), this resulted in medians and ranges of $m\%He_{trach}$ of 22.4% (14.1–28.4%) during hyperventilation, 37.2% (29.3–52.2%) during normal ventilation and 48.0% (40.3–56.0%) during hypoventilation. Similar relationships were seen with Heliox28 and Heliox40 with the non-rebreathe reservoir mask. There was minimal variability in the performance of the tightly fitting anaesthetic mask between hyperventilation and hypoventilation (Fig. 3; Table 2).

Results

There was substantial dilution of heliox (and oxygen under control conditions) by room air for all breathing patterns and gases when the non-rebreathe reservoir mask was used (Table 2).

Effect of mask type on room air entrainment

Room air entrainment was almost abolished when Heliox21 (Fig. 3) and 100% oxygen were delivered via the tightly fitting anaesthetic facemask. For example, when nitrogen entrainment was maximal during hyperventila-

Table 2 Median and range of within-subject median percentage gas values in mixed tracheal gas ($m\%He_{trach}$, $m\%N_{2trach}$ and $m\%O_{2trach}$) by breathing pattern, gas and mask type. Oxygen consumption and re-breathing of dead-space gases (physiological and/or device) gives

lower $m\%O_{2trach}$ values to what would be present in inspired gas alone. *NRM*, non-rebreathe reservoir mask; *ABC*, anaesthetic breathing circuit

Breathing pattern	Mask	Gas	Number	($m\%He_{trach}$)	Median ($m\%N_{2trach}$)	($m\%O_{2trach}$)
Hyperventilation	NRM	Heliox21	6	22.4 (14.1–28.4)	55.4 (49.4–63.5)	19.9 (19.6–20.2)
		Heliox28	6	20.6 (15.0–44.0)	55.3 (30.6–61.1)	21.8 (21.4–23.0)
		Heliox40	5	16.9 (14.1–41.0)	55.6 (25.9–59.0)	24.9 (24.4–31.0)
		Oxygen	6	0	55.9 (23.0–60.7)	41.8 (36.9–74.3)
	ABC	Heliox21	6	79.4 (74.8–80.1)	2.2 (0.6–6.1)	16.1 (15.6–17.4)
		Oxygen	5	0	2.0 (0.8–7.5)	93.9 (89.1–95.3)
Normal	NRM	Heliox21	6	37.2 (29.3–52.2)	41.7 (27.4–49.4)	18.5 (17.1–19.0)
		Heliox28	6	34.3 (22.7–50.4)	41.7 (25.7–53.2)	21.3 (20.7–21.6)
		Heliox40	5	30.3 (22.8–51.7)	39.7 (14.7–48.4)	27.5 (25.4–30.4)
		Oxygen	6	0	41.8 (13.5–45.8)	55.2 (50.8–82.3)
Hypoventilation	NRM	Heliox21	5	48.0 (40.3–56.0)	33.1 (24.6–39.6)	17.7 (16.0–18.2)
		Heliox28	5	42.3 (33.9–49.2)	32.7 (26.7–41.9)	21.3 (20.4–21.8)
		Heliox40	4	35.5 (28.5–57.9)	33.4 (9.5–42.4)	28.3 (27.1–30.1)
		Oxygen	5	0	31.0 (8.4–45.1)	66.1 (52.3–87.4)
	ABC	Heliox21	5	81.5 (79.8–82.4)	1.1 (0.2–1.9)	14.2 (13.8–15.8)
		Oxygen	5	0	1.1 (0.3–3.3)	95.4 (92.6–95.8)

Ranges are in parentheses

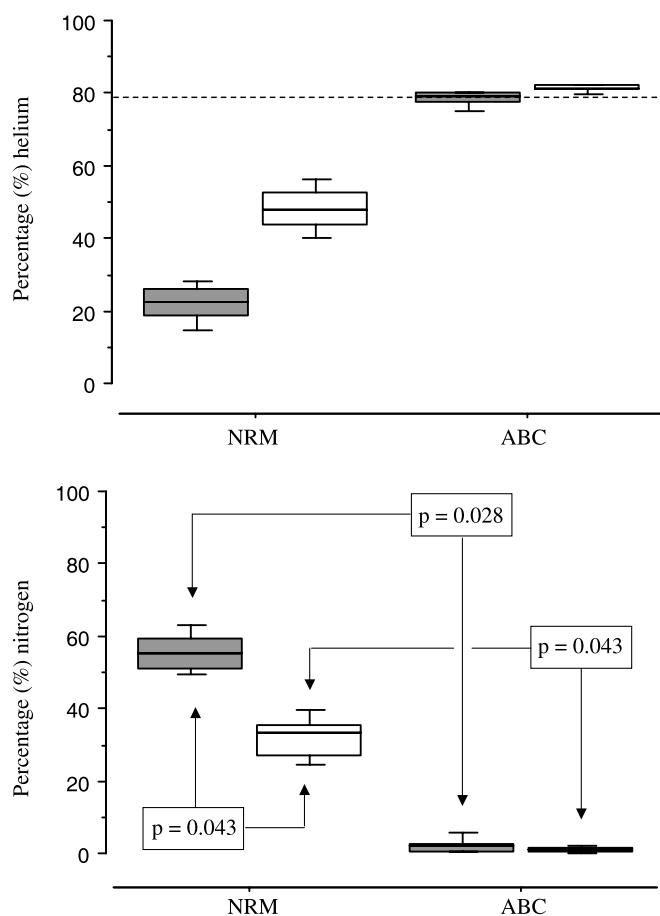


Fig. 3 Box and whisker plots (median, interquartile range, 10th to 90th percentiles) of subject medians for percentage helium and nitrogen in mixed tracheal gas by mask type and breathing pattern (*grey boxes*: hyperventilation; *white boxes*: hypoventilation) while breathing Heliox21. The percentage helium in Heliox21 (79%) is indicated by a *dashed line*. Wilcoxon signed-rank *p*-values on paired nitrogen values referred to in the text are shown. *NRM*, non-rebreathe reservoir mask; *ABC*, anaesthetic breathing circuit

tion, $m\%N_{2trach}$ was 55.4% (49.4–63.5%) when subjects breathed Heliox21 via the non-rebreathe facemask, but this fell to 2.2% (0.6–6.1%) with the tightly fitting mask ($p = 0.028$; Fig. 3). The reduction in entrainment with the tightly fitting mask was also statistically significant when subjects breathed 100% oxygen ($p = 0.043$).

Effect of helium concentration administered on room air entrainment

Helium was delivered at concentrations of 79% (Heliox21), 72% (Heliox 28) and 60% (Heliox40). There was no relationship between $m\%N_{2trach}$ measured with the non-rebreathe reservoir mask during normal breathing and the amount of helium in the administered gas mixture. (Wilcoxon signed-rank tests for all six

possible comparisons yielded *p* values between 0.116 and 0.893.)

Discussion

The extent of room air dilution during heliox administration via a standard high-concentration non-rebreathe reservoir mask was surprising. Room air entrainment would be expected to be maximal during hyperventilation, when the peak inspiratory flow rate is highest. During hyperventilation, while breathing Heliox21 via the non-rebreathe reservoir mask, the median $m\%N_{2trach}$ was 55.4%. The corresponding hypoventilation value, when entrainment should be minimal, was 33.1%. Increasing the concentration of helium delivered did not reduce the amount of nitrogen present. The only way of eliminating nitrogen from the administered gas was to apply a tightly fitting anaesthetic-type facemask held in place by a harness. Under these conditions, the median $m\%N_{2trach}$ was 2.2% even during hyperventilation. Low inspired oxygen concentrations were measured in the closed anaesthetic breathing system during delivery of Heliox21, which may necessitate the giving of supplemental oxygen (or Heliox28) in clinical practice.

The extent of room air dilution we measured under control conditions when delivering 100% oxygen as a control is in keeping with other recently published literature [8], suggesting that our protocol is robust, but it still has some limitations. Firstly, the sample size is small and the data are incomplete; however, using volunteers as their own controls in a crossover design increases the power of the study. Data collection was limited by the duration of anaesthesia to the upper airway, which lasted 90–120 min. Some subjects found that the sampling catheter became uncomfortable, in which case some recordings were omitted in favour of those thought to be most clinically relevant. Our subjects' 'resting normal' ventilation patterns may have been somewhat vigorous: it is difficult to relax when great attention is being paid to one's breathing, and the effects of airway anaesthesia may have increased tidal volumes [9]. Finally, the airway anatomy and breathing patterns of healthy volunteers might not accurately reflect those of patients. The measurement techniques were invasive and would not be tolerated by a patient in respiratory distress. We do not believe that the use of healthy volunteers overestimates the extent of room air dilution of heliox; arguably, the problem may be even worse. We applied the facemask with perhaps more care than would be seen in clinical practice, and in elderly patients with no teeth or concave cheeks mask fit might be even less satisfactory.

Heliox is meant to exert its beneficial therapeutic effects by virtue of the low density of helium. If helium is replaced by nitrogen (and to a lesser extent oxygen) entrained from the surroundings, these clinical effects are

likely to be diminished. This study cannot predict what the clinical consequences of such extensive dilution of helium might be, but it is perhaps helpful to consider the theoretical basis for heliox therapy. It is thought that the low density of helium reduces turbulent gas flow in narrowed airways in favour of laminar flow and allows a reduction in differential pressure where turbulence persists, which reduces the work of breathing and improves nebulised drug delivery to the lung periphery [2, 3]. The Reynolds number predicts whether fluid flow through a smooth tube is laminar, turbulent or transitional [2], by using the product of density, linear velocity and radius divided by viscosity. Our data suggest at least a 1.6-fold increase in the Reynolds number when heliox is delivered via the non-rebreathe reservoir mask compared with the anaesthetic mask, so laminar flow conditions are certainly less likely to be achieved; however, reality is more complex. The bronchial tree is not smooth and branches extensively promoting transitional or turbulent flow, and the fact that helium is more viscous than nitrogen may subtly increase work of breathing under laminar conditions [10].

This study did not aim to explain how heliox might work, but the findings of substantial dilution by entrained room air might explain why it has failed to impress in clinical trials, a view borne out by several systematic reviews [2, 11–19]. It is difficult to reconcile how a treatment that is said to be capable of reversing life-threatening pathology within ten breaths [20, 21] seems not to confer any additional benefit above standard treatments in randomised trials. We believe that the results of many clinical trials of heliox may have been influenced by air entrainment, and that using a variable performance mask to deliver heliox is like conducting a trial of a drug without knowing the dose.

Of the 19 studies included in the two meta-analyses of heliox use in acute asthma by the Cochrane reviewers [11] and Ho and colleagues [13], 17 investigated heliox use in non-intubated patients; of these, 13 used partial- or non-rebreathing (reservoir) masks. The same Cochrane reviewers state that in three other trials room air entrainment would have been likely [12]. The variable performance of a standard non-rebreathe reservoir mask as demonstrated in our study adds real conviction to the concerns about room air entrainment voiced by these authors [12, 13]. While tidal volume may fall in asthma, the presence of expiratory air-flow obstruction leads to a prolonged expiratory time and a shortened inspiratory time, usually on a background of tachypnoea. Such a ventilation pattern with a variable performance facemask would tend to increase room air entrainment and reduce helium concentration, a point illustrated by the *in vitro* work of Dhuper and colleagues [22]. To date, when heliox has been administered by partial- or non-rebreathe reservoir masks for asthma, it only seems to benefit patients with severe symptoms [11, 23–25]. Acute exacerbations of both chronic obstructive pulmonary disease and asthma are

associated with inspiratory air-flow limitation [26], and the presence of inspiratory wheeze in asthma is associated with lower peak expiratory flow rate [27]. Our data suggest that the amount of air entrained would be least under these circumstances.

It may be no coincidence that the trials that have reported the most impressive results with heliox have been conducted in patients who are non-invasively or invasively ventilated, and therefore have a tight seal between the airway and delivery device [28–31]. Furthermore, there are now a number of studies which demonstrate reductions in dynamic hyperinflation and/or improvements in exercise performance in stable chronic obstructive pulmonary disease where the method of heliox administration is more appropriate and would have led to no or reduced room air entrainment compared with the non-rebreathe reservoir mask we have studied. These studies used a mouth-piece [32–34], a non-rebreathe mask with an inspiratory demand valve system [35] or a new non-rebreathe mask of improved design, which incorporates features to limit room air entrainment [36]. A similar study using “a non-rebreather mask” to administer Heliox21 at 10 l/min did not demonstrate improved exercise ability [37].

It now seems generally accepted that heliox should be delivered via a non-rebreathe reservoir mask [15, 21]. Although this recommendation is practical it is not evidence-based. Given the extent of room air entrainment into a standard non-rebreathe reservoir mask demonstrated here, and its virtual elimination when a mask that is designed to give a good seal against the face is used in combination with a closed rebreathing circuit, we are concerned that inadequate concentrations of helium are routinely given to patients and the subjects in many clinical trials. The amount of leak between facemasks of fixed shape and vastly differing human facial contours will be variable even before inconsistencies in mask application are taken into account. Maintaining a tight fit with modern high-concentration reservoir masks is difficult to achieve. Simply increasing the fresh gas-flow rate to compensate for any leaks may not be enough to eliminate all variability in the performance of devices where the mask-to-patient interface is suboptimal. This approach would also increase the cost of the therapy.

To date, meta-analyses of heliox studies and consensus papers invariably state that there is no firm evidence for its use in obstructive airways disease [4, 11–19]. Heliox may have an important role to play, particularly in patients who are breathing spontaneously, as long as it is delivered properly. We recommend that further randomised trials be conducted in spontaneously breathing subjects using a leak-free delivery system to eliminate room air entrainment. Only then can the true place of heliox in the respiratory care of spontaneously breathing patients be determined.

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