The Use of Helium–Oxygen Mixtures in Chronic Obstructive Pulmonary Disease

a report by

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The use of helium in respiratory medicine was first described by Barach[1] in 1934. There was a resurgence of interest in helium in the 1980s for the treatment of acute asthma, as deaths from this disease begun to rise.[2] Helium has the lowest density of any gas except hydrogen, but it is about 1.1 times more viscous than air. Helium is expected to have a favorable impact in the presence of turbulent flow, when the resistive pressure drop is mainly density-dependent, but an adverse effect in the presence of laminar flow, when the resistive pressure drop is viscosity-dependent.[3] Being metabolically inert, helium must always be delivered in a mixture containing oxygen. Such mixtures are currently named heliox, most commonly 20% O_2 in He. Because of its physical properties, heliox may be useful in several conditions, such as upper airway obstruction, asthma attacks, exacerbation of chronic obstructive pulmonary disease (COPD), croup, and post-extubation stridor.[4] It has also been used during exercise in patients with airway obstruction, and in bronchoscopies performed during mechanical ventilation, high-frequency jet ventilation, decompression sickness, and magnetic resonance imaging (MRI) of the lung.[5]

Administration of Heliox

Heliox should be administered to patients in a safe and effective manner, given its relatively high cost. Less than 20% oxygen should be avoided because it will cause or worsen hypoxia, whereas if mixtures with more than 40% oxygen are required, helium would be unlikely to produce any relevant effect.[6] In spontaneously breathing subjects, heliox is administered via a face-mask connected to a reservoir bag, with sufficient inflow to keep it inflated. This flow amounts to 12–15l/min and requires 3–6 H-size cylinders per day. When using oxygen-calibrated flow meters, the actual flow of heliox is greater than that indicated by the pneumotachograph.[6] Heliox administration can be problematic during mechanical ventilation:[7–9] ventilators are designed for use with air or O_2–air mixtures, and their pneumotachographs are calibrated accordingly. This problem can be partially avoided by using pressure-controlled instead of volume-controlled ventilation, because pressure sensors are not affected by gas composition. The only ventilator approved by the US Food and Drug Administration (FDA) for heliox delivery is Viasys AVEA.[9] The Aptaér heliox delivery system (GE Healthcare, Madison, Wisconsin) recently became available for delivering heliox with non-invasive-pressure support ventilation.[10]

Heliox Breathing at Rest

Barach[11] suggested the use of heliox on the presumption that airway resistance should decrease if turbulent flow occurs in COPD patients. However, in these patients Grapé et al.[12] found a significant decrease in pulmonary resistance, whereas Wouters et al.[13] found no change in total respiratory resistance. The effect of heliox on dynamic hyperinflation is also controversial. Grapé et al.[12] found no significant reduction in functional residual capacity (FRC) with heliox, while Swida et al.[14] observed a substantial fall. This discrepancy may reflect subject-related differences in the evolution of the disease; indeed, Meadows et al.[15] found that only half of their COPD patients performing an expiratory forced vital capacity (FVC) maneuver exhibited an increase in maximal expiratory flows with heliox.

In a recent study, Pecchiari et al.[16] assessed the effect of heliox breathing on tidal expiratory flow limitation (EFL), dynamic hyperinflation, and breathing pattern. In addition, they studied the effects of salbutamol administration in order to compare the benefits of this bronchodilator with those of heliox in the same patients. Their main finding was that heliox had no effect on dynamic hyperinflation in all COPD patients who were flow-limited while breathing air at rest, regardless of posture. In contrast, salbutamol significantly increased inspiratory capacity (IC) in both seated and supine postures. Heliox also had no effect on IC and hence on hyperinflation in non-flow-limited patients, as hyperinflation is minimal or absent in these patients.[17] Accordingly, heliox administration does not appear to be useful for reducing dynamic hyperinflation in stable, flow-limited COPD patients at rest.

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Heliox Breathing During Exercise

Since heliox does not increase mid-expiratory flow in flow-limited patients at rest,[16] it seems likely that there should also be little improvement when these patients breathe heliox during exercise. In contrast, heliox breathing in non-flow-limited patients is expected to improve exercise performance as a result of increased maximal flow and decreased airway resistance. Indeed, studies conducted in healthy volunteers during physical exercise documented that the effects of breathing low-gas-density mixtures are evident at high workloads, when tidal breathing achieves maximum flow and FRC tends to increase. The effect of breathing heliox during exercise should be different in flow-limited and non-flow-limited COPD patients,[18] thus explaining the controversial results reported in the literature. Two studies[19,20] have shown a small, though significant, increase in peak exercise ventilation and oxygen uptake. Palange et al.[21] reported a two-fold increase in exercise endurance capacity with heliox, which was attributed to increased maximal ventilation and tidal volume at peak exercise and a reduction in lung hyperinflation and dyspnea at iso-time, indicating that resistive unloading with low-density-gas mixtures could be beneficial in COPD patients in terms of symptoms and exercise capacity. Two studies[22,23] have confirmed the beneficial effects of heliox reported by Palange et al.[21] Moreover, it has been shown that reducing inspired gas density improves exercise performance to the same extent as increasing inspired oxygen, these effects being more evident in patients with severe airflow obstruction.[24,25] In fact, the increase in endurance time with heliox found by Palange et al.[21] appears to be greater than that reported in studies using oxygen supplementation[26] or pharmacological bronchodilation.[25,27]

In contrast, according to other studies in COPD patients[28–30] none of the exercise variables mentioned above changed with heliox, indicating that it has no immediate advantage. In view of the results of Pecchiari et al.,[16] this could reflect differences in the preponderance of flow-limited COPD patients in the various studies. Further exercise studies should therefore be performed in COPD patients who are classified as flow-limited and non-flow-limited at rest based on the use of the negative expiratory pressure technique.[17,18] Differences in methodology might also have contributed: flow and volumes are usually measured with a pneumotachograph calibrated using the inspired gas mixture, and the expiratory flow would therefore be underestimated because the viscosity of the expired gas mixtures is lower than that of the inspired mixture.[31] Although heliox does not reduce dynamic hyperinflation at rest in non-flow-limited COPD patients, it may improve exercise performance by increasing both maximal inspiratory and maximal expiratory flow, while in flow-limited patients heliox could improve exercise performance by decreasing the inspiratory work of breathing, independent of an increase in maximal expiratory flow and a reduction of dynamic hyperinflation. Model studies have shown that inspiratory dynamic work should be reduced with heliox by up to 50–60%, depending on the extent of turbulent flow and airway resistance while breathing air.[32,33] Moreover, in patients who are not flow-limited, this gain would involve the total dynamic work. It is therefore not surprising that COPD patients invariably report a sensation of relief when breathing heliox instead of air, especially during physical exercise.

Heliox for Treatment of Exacerbations

Due to its low density, heliox has the potential to decrease the dynamic work of breathing and possibly avoid the need for intubation and mechanical ventilation in severe COPD patients. However, as yet only very few randomized, controlled trials have been reported.[10] Heliox has been shown to decrease arterial partial pressure of carbon dioxide (pCO_2) and CO_2 production, increase expiratory airflow, and decrease work of breathing in stable COPD patients, but not in patients with acute exacerbation. In most severe cases, intubation and mechanical ventilation become mandatory to treat the acute respiratory failure. However, mechanical ventilation is associated with several complications, such as pneumonia and ventilator-induced lung injury. Therefore, strategies that avoid intubation are currently under investigation, such as non-invasive ventilation in combination with heliox. However, the conclusions of a rigorous systematic review performed by the Cochrane group[34] do not support the use of heliox in COPD treatment. Additional evidence in this area has been provided by a recent meta-analysis that includes only controlled studies.[35] It seems, therefore, that definitive evidence of a beneficial role of heliox in the treatment of severe COPD is lacking and its generalized use cannot be recommended. On the other hand, in cases of severe COPD in which intubation should be avoided, non-invasive ventilation in combination with heliox administration is an intervention worth considering.[36–38] Tassaux et al.[39] first reported on the acute effects of breathing heliox during non-invasive ventilation. In this prospective randomized study, it was found that compared with air–oxygen mixtures heliox improved patient comfort, reduced dyspnea, increased the time available for expiration, and favored CO_2 elimination, but there was no decrease in intubation and mortality rate. Using the esophageal balloon technique, Jaber et al.[36] observed a significant decrease in respiratory pressure–time index and work of breathing with combined heliox breathing and non-invasive ventilatory support. In another multicenter study[40] on the effects of non-invasive ventilation with heliox or with air–oxygen mixtures, no difference occurred in the intubation rate nor in the length of stay in the intensive care unit (ICU), but hospital stays were shorter and total costs were lower in the group of patients treated with heliox. Gerbeaux et al.[41] also found a significant decrease in ICU and in-hospital stays, as well as a decrease in intubation and mortality rates with heliox administration.

> Widespread use of heliox cannot be recommended in general clinical practice, but only in very carefully selected cases.

Heliox During Mechanical Ventilation

Tassaux et al.[42] reported that the use of heliox could markedly reduce trapped lung volume, intrinsic positive end expiratory pressure (PEEPi), and peak mean airway pressure in mechanically ventilated COPD patients. They noted no effect on hemodynamics or arterial blood gases. In contrast, Lee et al.[43] found positive effects of heliox on hemodynamics, such as decreased mean pulmonary arterial, wedge, and right atrial pressure and increased cardiac index, but only trivial changes in PEEPi and end expiratory lung volume. However, changes in hemodynamics occur only for as long as the patients breathe heliox, because there is no direct influence on the cause of airway obstruction.[44] Finally, two recent studies suggest that, by reducing the work of breathing and PEEPi, heliox administration could be useful during the weaning process.[45,46] In view of the contrasting results obtained with heliox administration in mechanically ventilated COPD patients, the systematic use of heliox in these patients cannot be recommended at present.[47]

Heliox and Expiratory Flow Limitation

Tidal EFL is the condition in which augmentation of the expiratory driving pressure over the same volume range does not result in an increased airflow—i.e. maximal flow is reached with submaximal efforts. Normal subjects do not exhibit tidal EFL even during maximal exercise, whereas EFL is often observed in COPD patients even during breathing at rest.[16,17,48–50] EFL can promote dynamic hyperinflation and PEEPi, leading to increased inspiratory work, impairment of respiratory muscle function, and alterations of hemodynamics.[51] In the absence of EFL, dynamic hyperinflation can ensue only because of excessive shortening of expiratory duration relative to the expiratory effort. If turbulent flow occurs during tidal breathing, heliox administration would result in a decrease of dynamic hyperinflation at fixed expiratory duration and effort to an extent predictable from the value of airway resistance measured during inspiration, which in turn would also be reduced, leading to decreased respiratory work. In the presence of EFL, no prediction can be made regarding the expiratory effects of heliox administration from the concomitant changes in inspiratory airway resistance, but these effects can be understood through the analysis of airway resistance during expiration, as it determines expiratory flow at fixed driving pressure.[52,53] Thus, heliox administration in COPD patients with EFL can exert beneficial mechanical effects during expiration and, indirectly, inspiration, mainly insofar it causes reduction of dynamic hyperinflation and PEEPi. There is only a limited number of studies in COPD patients, either mechanically ventilated or spontaneously breathing at rest, in which the effects of heliox administration on dynamic hyperinflation have been assessed. Some studies have reported a reduction of the end expiratory volume or PEEPi with heliox relative to air breathing,[14,43,54,55] while others have failed to observe any appreciable change.[12,16,21,36,45] These contrasting observations could be explained on the basis of differences among the various groups of COPD patients in the prevalence and nature of EFL, as indicated below. However, with the exception of one study,[16] EFL was not assessed in the reports mentioned above. Brighenti et al.[33] have recently developed a dynamic, non-linear mathematical model that derives the normal morphometry of the tracheobronchial tree from Weibel[56] and the mechanical properties of airway generations from Lambert,[57] and includes both mechanisms—wave speed and viscosity—that cause EFL.[58] The model, which proved capable of accurately reproducing the values of airway resistance as directly assessed at end inflation in intubated, mechanically ventilated normal subjects and COPD patients, was used to simulate the response to air and heliox ventilation when tidal EFL was caused by mechanical alterations affecting to various extents the central and/or the peripheral regions of the bronchial tree. A significant improvement in dynamic hyperinflation occurred only with alterations limited to the central airways (fourth and fifth generation), when EFL is due to the wave-speed mechanism, and the contribution of peripheral to total apparent airway resistance is marginal. Hence, due to the extent to which COPD affects primarily the peripheral airways, and to the fact that the same mechanisms operate in both model and COPD patients, heliox administration should not be expected to appreciably reduce dynamic hyperinflation in the majority of COPD patients who exhibit EFL at rest. Conversely, the favorable outcome of heliox administration in COPD patients would depend on the prevalence of expiratory-flow-limited subjects and the incidence of types of mechanical alterations that cause EFL.

Conclusions

Definitive evidence of a beneficial role of heliox in the treatment of severe COPD is lacking. Furthermore, there is not enough evidence to support the systematic use of heliox to treat acute exacerbations of COPD in either ventilated or non-ventilated patients. Therefore, widespread use of heliox cannot be recommended in general clinical practice, but only in very carefully selected cases. ■

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