Monaldi Arch Chest Dis
2007; 67: 3, 159-164

Clinical use of Heliox in Asthma and COPD

G. Valli, P. Paoletti, D. Savi, D. Martolini, P. Palange

ABSTRACT: ***Clinical use of Heliox in Asthma and COPD. G. Valli, P. Paoletti, D. Savi, D. Martolini, P. Palange.***

Heliox is a low density gas mixture of helium and oxygen commonly used in deep diving (> 6 ATM). This mixture has been also used for clinical purposes, particularly in the critical care setting. Due to of its physical proprieties, Heliox breathing reduces air flow resistances within the bronchial tree; in patients with obstructive lung diseases Heliox may also reduce the work of breathing and improve pulmonary gas exchange efficiency. Beneficial effects have been documented in severe asthma attacks and in patients with chronic obstructive pulmonary disease. A reduction in WOB during mechanical ventilation and an increase in exercise endurance capacity have also been described in COPD. Heliox has been also used in the treatment of upper airways obstruction, bronchiolitis and bronchopulmonary dysplasia. Despite the encouraging results, Heliox use in routine practice remains controversial because of technical implications and high costs.

Monaldi Arch Chest Dis 2007; 67: 3, 159-164.

Keywords: Heliox, COPD, asthma, mechanical ventilation, work of breathing.

Dipartimento Medicina Clinica, Università "La Sapienza", Roma, Italy.

Correspondence: Paolo Palange, MD; Dipartimento di Medicina Clinica, Università "La Sapienza", V.le Università 37, 00185 Roma, Italy; e-mail paolo.palange@uniroma1.it

Introduction

Human airways are complex tubes through which air flows. Gas flow rate is a function of the pressure difference (ΔP) and resistance that the system opposes to the gas flow. The relationship between flow rate (Φ), resistance and ΔP strictly depends on the nature of the flow which could be laminar, turbulent or transitional [1]. To be precise, in normal humans, airflow is never completely laminar or turbulent, but is rather a combination of the two patterns. Nevertheless, it is useful to consider the two components separately in order to allow for a quantitative mathematical description.

When the flow is laminar the relationship between gas flow rate, pressure gradient along the airways (ΔP) and resistance of the system (R) is linear, as described by the formula (1):

(Eq. 1) $$\Phi = \Delta P / R$$

The Poiseuille-Hagen equation (2) describes the principal factors influencing airway resistance during laminar flow:

(Eq. 2) $$R = (8 \cdot l \cdot \eta) / (\pi \cdot r^4)$$

In this equation the fourth power of the radius (r) explains the critical importance of airway calibre. It should be recognised that, with constant tube dimension, viscosity (η) is the only property of gas which affects resistances when the flow is laminar. Under these conditions, breathing a low density (ρ) gas, such as helium, that has a η close to that of air, has little influence on the airways resistance and flow (table 1).

In healthy humans, even during quiet breathing, flow characteristics are also determined by complex interplays between other factors, including the bronchial branching patterns, the angles of branching and the degree of roughness of the walls that may change with inspiration and expiration [2, 3]. All these factors could affect the flow pattern by changing it from laminar into turbulent. When the flow becomes turbulent energy is dissipated in chaotic motions, resistance increases and, to maintain the same airflow, the driving pressure (ΔP) needs to be increased. When turbulence occurs, flow is mostly related to the ρ of the inspired mixture according to the following law:

(Eq. 3) $$\Phi \propto \Delta P / \rho$$

The nature of flow, in the case of long straight unbranched tubes, can be approximately predicted by the Reynold's number (R), which is derived from the ratio [3]:

(Eq. 4) $$R = (v \cdot 2r \cdot \rho) / \eta$$

where *v* is the mean linear velocity of the gas and 2r is the diameter of the tube. For $R > 4000$, flow is turbulent while for $R < 2100$, it is laminar; between these values, both type of flow coexist. Therefore the flow is more likely to be laminar if the cross-sectional area of the airways and the gas velocity decreases. Both the velocity of gas flow and airway diameter (and therefore Reinold's

Table 1. - Physical properties of clinically used gas mixtures relating to gas flow (AIR: $N_2$0.79-$O_2$0.21)

	VISCOSITY RELATIVE TO AIR	VAPOUR DENSITY RELATIVE TO AIR	VAPOUR DENSITY / VISCOSITY
Hyperoxia (FiO_2 1.00**)**	1.11	1.11	1.00
Hyperoxia (FiO_2 0.30)	0.89	1.41	1.59
Heliox	1.08	0.33	0.31

number) decrease in successive airway generations from a maximum in the trachea to almost zero at the beginning of the pulmonary acinus. At the level of the acinus, the gas exchange depends on the differential pressure and on the diffusing capacity of the gas, rather than on the air flow generated. A predominantly laminar flow at this level in the conducting airways has some practical implications. First, in healthy subjects the small airways make only a small contribution to total airway resistances, and the resistance of the larger airways dominates the overall pulmonary resistance. Second, as described by the *Eq. 2*, the small airways respiratory resistance is mainly controlled by changes in airway diameter [4]. Finally, the physical characteristics of the airway lining fluid will influence frictional resistance more with turbulence than with laminar flow.

Reynold's number also affects the distance required for laminar flow to become establish after the turbulence (EL, entrance length):

(Eq. 5) $EL \approx 0.03 \cdot 2r \cdot R$

Thus for gases with a low ρ/η as Heliox, not only will the resistance be less during turbulent flow but also laminar flow will become established more quickly after bifurcations, corners and obstructions.

In patients with airways obstruction, turbulent flow occurs very frequently even at low breathing rates and during quiet breathing [5]. In these patients the total airways resistance (RAW) is very high (see table 2) and leads to isovolume air flow reduction and increased work of breathing. The high RAW is due to the increased resistance in peripheral airways (< 3 mm diameter), although a significant increase in RAW could be observed also in the major intra-thoracic conducting airways [6]. In chronic obstructive pulmonary disease (COPD), the increased resistance is also due to the following mechanisms: 1) the increased secretions in bronchial lumen; 2) inflammatory infiltration of the airway wall; 3) the narrowing of the airways due to reduced lung elastic recoil [7]. All these mechanisms contribute to an increase in turbulent airflow that occurs even at low level of ventilation.

Breathing mixtures which contain Helium are used in deep diving. The high environmental pressures reached during deep diving (> 6ATM) induce airflow limitation and increases the work of breathing (WOB) [8]. The mixture in which helium completely substitutes nitrogen as complement gas for oxygen, named Heliox (0.79 He-0.21 O_2) has a 1/3 density than atmospherically air [9, 10]. In deep diving, Heliox acts by diminishing the airflow resistance and by decreasing turbulences.

The physical proprieties of helium could have important clinical applications in respiratory diseases. Heliox is increasingly used in clinical setting to reduce airways resistances and to increase airflow rate. By using a fluid mechanical model of the human lung, Papamoschou described a theoretical analysis comparing flow rates of Heliox and air-oxygen mixtures [11]. The author found a 50% improvement in flow rates when nitrogen was substituted with helium in normal environmental conditions. Beneficial effects of Heliox have been observed in patients with asthma, chronic obstructive pulmonary disease (COPD), bronchiolitis [12], bronchopulmonary dysplasia [13] and pneumothorax [14]. In animal models of lung injury, Kats and co-workers described an enhanced and more uniform distribution of ventilation during Heliox breathing that allowed the lowering in $PaCO_2$ together with the increasing in PaO_2 [15]. The potential beneficial effect of Heliox has been tested in the settings of both invasive [16] and non-inva-

Table 2. - Distribution of total lung resistance (RL)

	NORMAL (cm H_2O, l-1 s) (% of total)	SEVERE COPD (cm H_2O l-1 s) (% of total)
Extra-thoracic airway	0.5 (33)	0.5 (8)
Major intra-thoracic conducting airways	0.5 (33)	1.0 (17)
Peripheral airways (L3mm diameter) and lung tissue	0.5 (33)	4.5 (75)
Total	1.5 (100)	6.0 (100)

sive mechanical ventilation [17, 18]. It has been shown that Heliox, because of its low density and because it does not combine with active membranes, promotes a greater diffusion of oxygen through the airways, resulting in clinical and laboratory improvements in lung gas exchange within a short period of time. Some investigators have reported a substantial increase in gas exchange efficiency with Heliox breathing during high frequency oscillatory ventilation [19].

Heliox in clinical practice

1. Asthma

In asthmatic patients Heliox decreases dyspnea and WOB and it is now considered a rescue treatment for severe acute asthma attack [20]. The earliest use of Heliox was in 1935 for the treatment for upper and lower respiratory tract obstruction [21]. Heliox has been thought to have beneficial effects in patient with severe asthma both in the setting of mechanical ventilation and spontaneous ventilation. The interest in Heliox for treatment of asthma became prominent in the 1980 when deaths from asthma began to rise. For those patients under mechanical ventilation as a result of severe asthma attacks, Heliox administration allows the reduction of lung inflation pressure and improves blood gases [22]. It has also been shown that, in spontaneously breathing patients, Heliox reduces airway resistance when pharmacological therapy (i.e. bronchodilators) has failed [23]. In a systematic review, Ho and co-worker [24] reported that Heliox may improve lung mechanics and symptoms in acute asthma attacks within the first hour of use, while it becomes less advantageous after that first hour. From a practical viewpoint, the use of Heliox was restricted to patients who were difficult to ventilate, with high inflation pressures and haemodynamic instability [23]. Less is known about the usefulness of Heliox in asthmatic patients during spontaneous breathing: controlled studies are lacking and the effect of Heliox in the individual patient is difficult to predict; the duration of administration and optimal helium/oxygen mixture remain undetermined; the cost of treatment remains relatively high [25].

In addition to the benefit derived from breathing Heliox on lung mechanics, there is evidence that Heliox may be effective in better delivering inhaled particles to the distal airways of asthmatics. Heliox seems to promote an effective deposition of radiolabeled particles in the lung [26]. Kress *et al* have shown that jet nebulisation of albuterol with Heliox improves spirometric measurements in patient with acute asthma more than standard oxygen-driven albuterol nebulisation [27]. Thus, Heliox should be considered as a useful vehicle for β-agonists nebulisation in patients presenting with acute asthma exacerbations. Based on these finding, Kress and coworkers recommend to consider the use of Heliox for severe asthma exacerbations refractory to standard therapy. From a practical standpoint, to nebulize albuterol with Heliox in the acute asthma attack could serve two purposes: 1) to improve airflow thanks to physical properties of the gas, and 2) to improve expiratory flows and volumes, presumably by improving the β-agonist delivery to its site of action in the lungs.

Despite some encouraging results, the clinical use of Heliox to treat acute asthma attack it is not accepted worldwide. In a recent review, for example, Rodrigo and co-worker [23] concluded that existing evidence does not support emergency-department use of Heliox in patients suffering moderate-to-severe acute asthma. Further studies are needed to determine whether Heliox affects duration of stay or intubation rate and to better characterised the population that could benefit from it.

2. Chronic Obstructive Pulmonary Disease (COPD)

2.1 Acute exacerbation

Acute exacerbation of chronic obstructive pulmonary disease (COPD) is often associated with a severe worsening in dyspnea and with the development of respiratory and ventilatory failure. In the critical care setting the treatment is directed at decreasing the work of breathing and improving gas exchange. In the most severe cases this can only be achieved by intubation and mechanical ventilation. However this approach is associated with several complications including ventilator associated pneumonia, ventilator induced lung injury, and weakness of respiratory muscles leading to ventilator dependence. Possible alternative strategies to avoid intubation are: 1) non-invasive ventilation (NIV); 2) the use of low density gas mixture such Heliox with or without NIV.

During COPD exacerbation elastic and resistive components of the WOB are markedly increased [28-30] leading to respiratory muscle fatigue. Respiratory muscle fatigue is a key factor determining weaning trial failure [31, 32], and prolonged ventilator dependence [30] in intubated patients. Severe COPD patients, in fact, frequently develop dynamic hyperinflation that leads to intrinsic positive end expiratory pressure (PEEPi), especially during positive pressure ventilation [33]. The presence of PEEPi adversely affects lung mechanics, by increasing WOB, and by worsening gas exchange and hemodynamics [34, 35]. PEEPi may be reduced by broncodilatation, by lengthening expiratory time, and by lowering tidal volume. During the acute stage, however, these strategies may not be effective because patient's respiratory drive is strong and respiratory rate is high [17, 18, 36].

In intubated COPD, Heliox has been shown to enhance lung emptying, to induce a rapid decrease in PEEPi [16], especially during controlled mechanical ventilation [37] and T-piece breathing [36], and to improve cardiac performance by reducing the PEEPi's hemodynamics effects [38]. Besides, Heliox improves patient comfort and gas exchange also during NIV [17,18]. Jabber and coworkers found that Heliox administration during NIV induces an increase in pH, a decrease in $PaCO_2$, and a reduction in patient inspiratory effort

(figure 1). This data suggests that the use of Heliox may allow a larger population of patients to benefit from NIV. Andrews and Lynch have recently performed a meta-analysis of the literature to determine if breathing helium-oxygen mixture, in addiction to conventional therapy or NIV, may improve lung gas exchange and may reduce the odds of intubation in the acute setting [39]. The authors considered 8 controlled studies performed on patients treated for acute exacerbation in the setting of emergency department, intensive care units or respiratory ward. Two of the studies compared Heliox vs air breathing during NIV, while the others considered an Heliox mixture, the oxygen composition of which did not exceed 0.40, during self ventilation. The authors concluded that, despite a beneficial effect of Heliox breathing was reported in all trials, definitive evidence is lacking because of the low methodological quality of the studies.

2.2 Exercise tolerance

The chief complaint of many patients with COPD is that they are no longer able to sustain a physical effort that normal subjects would find tolerable [40, 41]. Exercise limitation is felt to be multifactorial and related to pulmonary abnormalities as well as to peripheral muscle dysfunction. A key concept is that in COPD exertional dyspnea is mostly due to the development of lung dynamic hyperinflation (DH) during exercise. Heliox breathing reduces the airflow resistance increased by the turbulent flow regimen at high rates of ventilation [42] and, thereby, may improve exercise tolerance by increasing the maximal attainable ventilation. In a recent published study in severe COPD patients (figure 2), breathing Heliox doubled the endurance time during a high intensity constant work-rate cycle ergometer test, from a

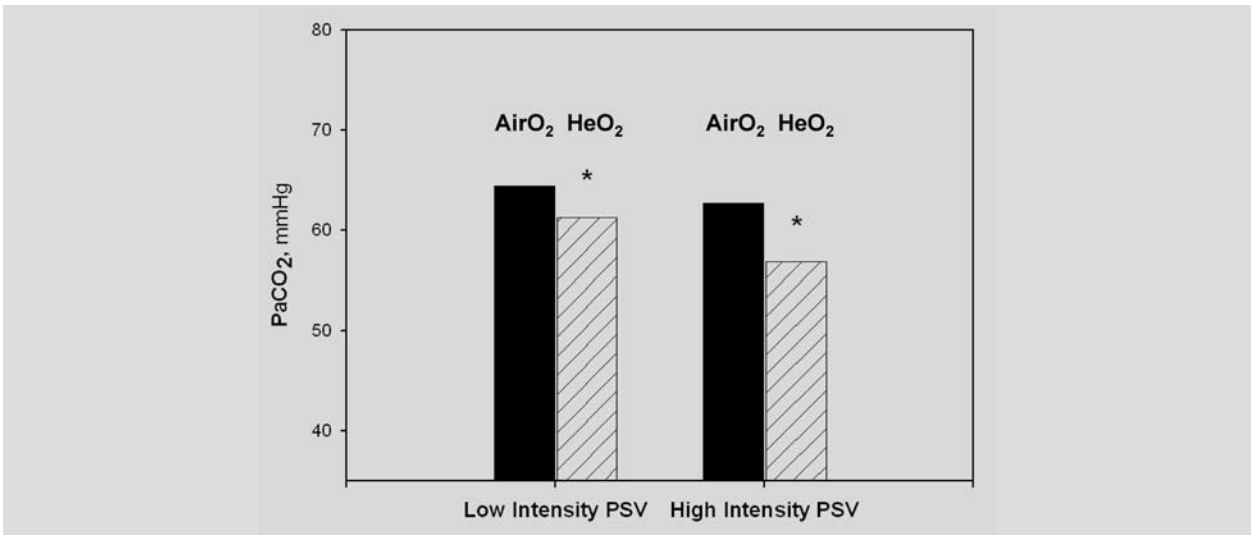


Fig. 1 - Markedly improve in lung gas exchange induced by Heliox (HeO_2) during non-invasive pressure support ventilation (PSV) at low pressure (~spontaneous breathing) and at high pressure (18±3 cmH_2O). Substituting Heliox for Air enhanced the efficacy of the PSV, providing a significant decrease in $PaCO_2$. *Modified from Jaber S, et al. Noninvasive ventilation with helium-oxygen in acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000, 161: 1191-2000.*

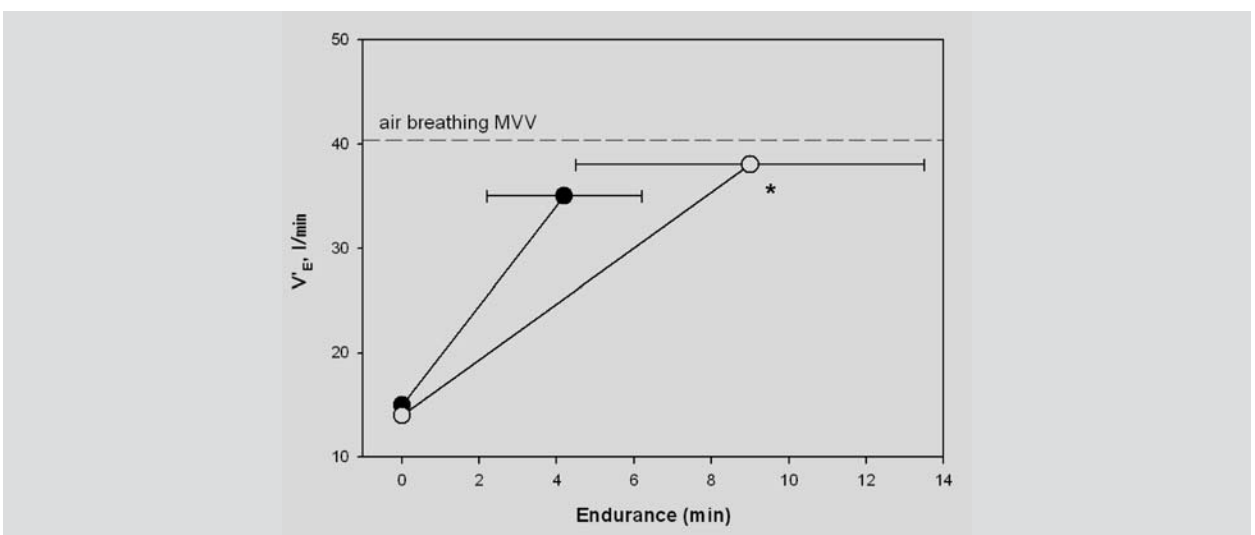


Fig. 2 - Great increase in endurance capacity (9.0±4.5 vs 4.2±2.0) induced by Heliox (○) compared to air breathing (●) in a group of COPD patients exercising at 80% of their maximal power output. Heliox improves maximal expiratory flow and maximal ventilatory capacity, as reflected by the increase in ventilation (V'E) at peak exercise. *Modified from Palange P, et al. Effect of Heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. J Appl Physiol 2004, 97: 1637-1642.*

mean of 4.2 min during room air to a mean of 9.0 min during Heliox [43]. The improvement in exercise tolerance could be attributed to both an increase in maximal ventilation and to a reduction in DH during exercise with Heliox: the latter was testified by the increase in inspiratory capacity (IC) at isotime (i.e., when the patient stopped exercising on room air) and even at peak exercise. Heliox breathing, therefore, acts in similar way to bronchodilators, in that it decreases airflow resistance, albeit via a different mechanism. The results of Palange and coworkers were recently confirmed by Laude and coworkers in a randomised crossover trial, finding that reducing inspired gas density can improve exercise performance in COPD as much as increasing inspired oxygen. These effects are most evident in patients with more severe airflow obstruction [44]. Furthermore Eves and coworkers, in addition to confirming the results of Palange and Laude, have demonstrated a reduction a WOB measured by oesophageal balloon. Based on the aforementioned papers, Heliox administration during exercise appears to be the most promising clinical indication [45].

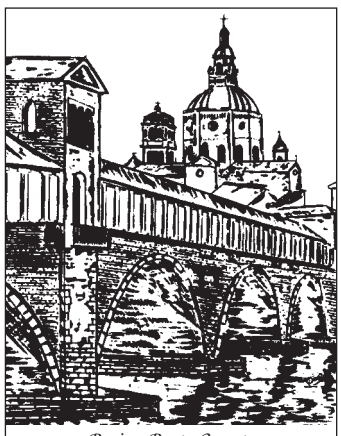
Conclusions

During the last few years Heliox has been increasingly used in clinical studies of patients with severe obstructive lung diseases. Based on the results of these studies Heliox seems particularly useful during acute exacerbation of asthma attacks requiring mechanical ventilation and in the aereosol delivery of bronchodilators in patients with severe asthma and under mechanical ventilation. In patients with severe COPD Heliox has been regarded favourably with respect to DH, dyspnea and exercise tolerance; this beneficial effect may in the future justify its use in rehabilitation exercise programmes. Longitudinal perspective studies in asthma and COPD are needed to encourage the routine use of Heliox in clinical practice.

References

1. O'Grady K, Doyle DJ, Irish J, Gullane P. Biophysics of airflow within the airway: a review. *J Otorinolaringol* 1997; 26: 123-8.
2. Olson D, Dart G, Filley G. Pressure drop and fluid flow regime of air inspired into the human lung. *J Appl Physiol* 1970, 28: 482-94.
3. Pedley TJ. Aerodynamic theory. In P.T. Macklem and J Mead, editors. Handbook of Physiology: The Respiratory Sistem III. American Physiological Society, Bethesda, MD, 1986: 41-54.
4. Kimmel E, Seri M, Fredberg JJ. Lung tissue resistance and hysteretic modelling of lung parenchyma. *J Appl Physiol* 1995; 79: 461-6.
5. Otis A, Bembower W. Effect of gas density on resistance to respiratory gas flow in man. *J Appl Physiol* 1949; 2: 300-6.
6. Yanai M, Sekizawa K, Ohrui T, *et al*. Site of airway obstruction in pulmonary disease: direct measurement of intrabronchial pressure. *J Appl Physiol* 1992; 72: 1016-23.
7. Tiddens HAWM, Paré PD, Hogg JC, *et al*. Cartilaginous airway dimensions and airflow obstruction in human lungs. *Am J Respir Crit Care Med* 1995; 152: 260-6.
8. Van Liew HD. Mechanical and physical factors in lung function during work in dense environments. *Undersea Biomed Res* 1983;10: 255-64.
9. Radford E. The physic of gases. In: Handbook of Physiology Edited by Macklem PT, Mead J. Bethesda: American Society of Physiology, 1964: 125-51.
10. Dubois A. Resistance to breathing. In: Handbook of Physiology. Edited by Macklem PT, Mead J. Bethesda: American Society of Physiology, 1986: 451-61.
11. Papamoschou D. Theoretical validation of the respiratory benefits of helium-oxigen mixtures. *Respir Physiol* 1995; 99: 183-90.
12. HollmanG, Shen G, Zeng L, *et al*. Helium-oxygen improves clinical asthma scores in children with acute bronchiolitis. *Crit Care Med* 1998; 26: 1633-35.
13. Wolfson MR, Bhutani VK, Shaffer TH, *et al.* Mechanics and energetics of breathing helium infants with bronchopulmonary dysplasia. *J Pediatr* 1984; 104: 752-7.
14. Barr J, Lushkov G, Starynsky R, *et al*. Heliox therapy for pneumothorax: new indication for an old remedy. *Ann Emerg Med* 1997; 30: 159-62.
15. Kats A, Gentile MA, Craig DM, *et al*. Heliox improves gas exchange during high-frequency ventilation in a pediatric model of acute lung injury. *Am J Respir Crit Care Med* 2001; 164: 260-64.
16. Tassaux D, Jolliet P, Roesler J, Chevrolet JC. Effect of helium-oxygen on intrinsic positive end-expiratory pressure in intubated and mechanically ventilated patients with severe chronic obstructive pulmonary disease. *Crit Care Med* 2000; 28: 2721-28.
17. Jolliet P, Tassaux D, Thouret JM, Chevrolet JC. Beneficial effects of helium-oxygen versus air-oxygen noninvasive pressure support in patients with decompensated chronic obstructive pulmonary disease. *Crit Care Med* 1999, 27: 2422-29.
18. Jaber S, Fodil R, Carlucci A, *et al.* Noninvasive ventilation with helium-oxygen in acute exacerbations chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 1191-2000.
19. Winters JW, Willing MA, Sanfilippo D. Heliox improves ventilation during high frequency oscillatory ventilation in pediatric patients. *Pediatr Crit Care Med* 2000; 1: 33-37.
20. Ho AMH, Dion PW, Karmakar MK, *et al*. Use of Heliox critical upper airway obstruction: physical and physiologic considerations in choosing the optimal helium: oxygen mix. *Resuscitation* 2002; 52: 297-300.
21. Barach AL. The use of helium in the treatment of asthma and obstructive lesions in the larynx and trachea. *Ann Intern Med* 1935; 9: 739-65.
22. Kass JE, Castriotta RJ. Heliox therapy in acute severe asthma. *Chest* 1995; 107: 757-760.
23. Rodrigo RJ, Rodrigo C, Pollak CV, Rowe B. Use of helium-oxygen mixtures in the treatment of acute asthma. *Chest* 2003; 123: 891-6.
24. Ho AMH, Lee A, Karmakar MK, *et al.* Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma: a systematic overview. *Chest* 2003; 123: 882-90.
25. Manthous CA, Hall JB, Melmed A, *et al*. Heliox improves pulsus paradodoxus and peak expiratory flow in nonintubated patients with severe asthma. *Am J Respir Crit Care Med* 1995; 151: 310-4.
26. Anderson M, Svantergren M, Bylin G, *et al*. Deposition in asthmatics of particles inhaled in air or in helium-oxygen. *Am Rev Respir Dis* 1993; 147: 524-8.
27. Kress JP, Noth I, Birman N, *et al*. The utility of albuterol nebulized with Heliox during acute asthma exacerbations. *Am J Respir Crit Care Med* 2002; 165: 1317-1321.

28. Fleury B, Murciano D, Talamo C, *et al*. Work of breathing in patients with chronic obstructive pulmonary disease in acute respiratory failure. *Am Rev Respir Dis* 1985; 131: 822-7.
29. Jounieaux V, Mayeux I. Oxygen cost of breathing in patients with emphysema or chronic bronchitis in acute respiratory failure. *Am J Respir Crit Care Med* 1995; 152: 2181-4.
30. Appendini L, Purro A, Patessio A, *et al*. Partitioning of inspiratory muscle workload and pressure assistance in ventilator- dependent COPD patients. *Am J Respir Crit Care Med* 1996; 154: 1301-9.
31. Zakynyhinos S, Vassilakopoulos T, Roussos C. The load of inspiratory muscles in patients needing mechanical ventilation. *Am J Respir Crit Care Med* 1995; 152: 1248-55.
32. Roussos C, Zakynyhinos S. Fatigue of the respiratory muscles. *Intensive Care Med* 1996; 22: 134-55.
33. Rossi A, Ganassini A, Polese G, *et al*. Pulmonary hyperinflation and ventilator-dependent patients. *Eur Respir J* 1997; 10:1663-74.
34. Romand JA, Suter PM. Dynamic hyperinflation and intrinsic PEEP during mechanical ventilation. *Eur J Anaesthesiol* 1994;11:25-28.
35. Ranieri VM, Dambrosio M, Brienza N. Intrinsic PEEP and cardiopulmonary interaction in patients with COPD and acute ventilatory failure. *Eur Respir J* 1996; 9: 1283-92.
36. Diehl JL, Mercat A, Guerot E, *et al.* Helium/oxygen mixture reduces the work of breathing at the end of the weaninig process in patients with severe chronic obstructive pulmonary disease. *Crit Care Med* 2003; 31: 1415-20.
37. Gainnier M, Arnal JM, Gerbeaux P, *et al*. Helium-oxygen reduces work of breathing in mechanically ventilated patients with chronic obstructive pulmonary disease. *Intensive Care Med* 2003; 29:1666-70.
38. Lee DL, Lee H, Chang HW, *et al*. Heliox improves hemodynamics in mechanically ventilated patients with chronic obstructive pulmonary disease with systolic pressure variations. *Crit Care Med* 2005; 33: 968-73.
39. Andrews R and Lynch M. Heliox in the treatment of chronic obstructive pulmonary disease. *Emerg Med J* 2004; 21: 670-5.
40. Rennard S, Decramer M, Carverley PMA, *et al*. Impact of COPD in North America and Europe in 2000: subjects' perspective of confronting COPD international survey. *Eur Respir J* 2002; 20: 799-805.
41. Katula JA, Rejeski WI, Wickley KL, Berry MJ. Perceived difficulty, importance, and satisfaction with physical function in COPD patients. *Health Qual Life Outcomes* 2004; 2: 18.
42. Pride NB, Milic-Emil J. Lung mechanics. In: Calverley P, Pride N, editors. Chronic obstructive pulmonary disease, 1st ed. London: Champman and Hall 1995; 135-160.
43. Palange P, Valli G, Onorati P, *et al*. Effect of Heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. *J Appl Physiol* 2004; 97: 1637-42.
44. Laude EA, Duffy NC, Baveystock C, *et al*. The effect of helium and oxygen on exercise performance in chronic obstructive pulmonary disease: a randomised crossover trial. *Am J Respir Crit Care Med* 2006; 173: 865-70.
45. Eves ND, Petersen SR, Haykowsky MJ, *et al*. Helium-hyperoxia, exercise, and respiratory mechanics in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 174: 763-71.



Pavia - Ponte Coperto