Medicinal helium/oxygen mixtures
Summary of scientific data

Contents:

History	1
Mechanism of action	3
Gas flow physics	4
Medicinal helium/oxygen mixtures in asthma and asthma therapy in combination with aerosol delivery (nebulization)	7
Medicinal helium/oxygen mixtures in chronic obstructive pulmonary disease	13
Medicinal helium/oxygen mixtures in bronchiolitis	19
Medicinal helium/oxygen mixtures in pediatric respiratory disorders	20
Medicinal helium/oxygen mixtures in airway obstruction (accident, croup, post-extubation stridor, pneumothorax, cancer)	23
Medicinal helium/oxygen mixtures and mechanical ventilation	25
Summary of articles	28

Medicinal helium/oxygen mixtures Summary of scientific data

1. History

In 1923, Cook registered a medicinal helium/oxygen mixture called Heliox with the US Patent Office. Therapeutic use of helium/oxygen mixtures was first reported in 1934. The rationale is that gas of a lesser density can more easily bypass an obstruction and therefore be inspired further with less effort and resistance.

Alvan Barach first used the mixture for medical purposes in 1934 and confirmed the biological inertness of helium by exposing mice to 79% helium and 21% oxygen for two months without deleterious effects. He reported the successful use of helium/oxygen mixtures in four cases of asthma in adults and two cases of upper airway obstruction in infants. Interestingly, the patients were relieved of their dyspnea in 6 to 10 breaths. When the helium was removed, the dyspnea came back in 3 to 4 breaths.

Barach was the first to use helium to improve airflow in patients with airway obstruction, but it was soon replaced by other treatment modalities. Congress regulated the sale of helium after the explosion of the airship Hindenburg in 1937, and its availability was further reduced during World War II.

Since then, use of helium has been relegated mainly to use in upper airway obstruction and diagnostic studies. It has been described as safe and effective for both spontaneously breathing patients and intubated patients receiving mechanical ventilation, but its therapeutic potential has not been fully explored.

After the war, with the advent of pharmacological bronchodilators with improving side-effect profiles, helium was discarded as a treatment for asthma. There were a few reports of its respiratory use showing no significant improvement in asthmatic patients and in patients with emphysema. Helium/oxygen was described to be an effective treatment for upper airway obstruction in 1976, and a few studies reported this usage over the next 10 years.

In the 1980s medicinal helium/oxygen mixtures resurfaced due to increased incidence of death by asthma. Evidence of beneficial action is conflicting, but clinical trials and case reports have shown benefit in selected patients. In 1987, the use of helium/oxygen in the treatment of patients with asthma resurfaced in the US and France. Within a few years, its use spread to many other sites.

Linde Gas Therapeutics holds a marketing authorization for a helium/oxygen mixture in the United Kingdom with the indication: “To prevent atelectasis and to assist oxygen flow into lung alveoli in cases of respiratory obstruction. Also for use in respiratory function tests.”

References:

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.

Rodrigo G et al. Use of helium/oxygen mixtures in the treatment of acute asthma - a systematic review. Chest 2003;123(3):891-6

Kass JE. Heliox Redux. Chest 2003; 123(3):673–6.

Fink JB. Helium-oxygen: An old therapy creates new interest. J Resp Care Pract 1999; 12:71–6.

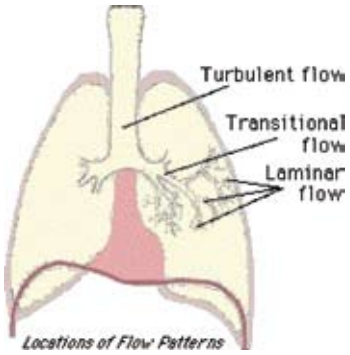
2. Mechanism of action

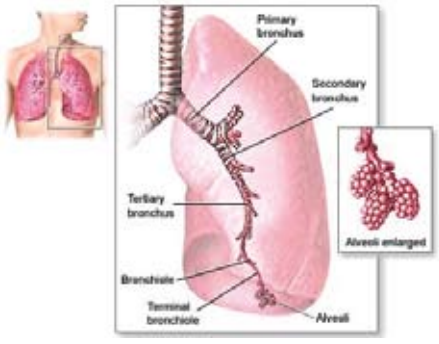
Helium is a colorless, tasteless, non-combustible, non-explosive gas that is seven times lighter than air. One of its most important properties is that it is biologically inert and insoluble in human tissues, having no bronchodilator anti-inflammatory effect. Its key benefit seems to be as a temporizing agent working while conventional treatments have time to act. Helium has the lowest specific gravity of any gas, with the exception of hydrogen, which is highly combustible.

Low specific gravity is usually associated with low density. This is proportional to the flow rate of the gas – the lower the density, the higher the rate of flow. Combining helium and oxygen results in a gas with a similar viscosity to air, but substantially lower density. To understand how medicinal helium/oxygen mixtures may be of benefit in various disorders of the airways, it is necessary to be familiar with a few concepts of physics.

Gas flow in airways may be laminar, turbulent, or a combination of the two (transitional). Due to flow rate and airway resistance in obstructions, it is turbulent in most cases.

Setting in healthy adults:





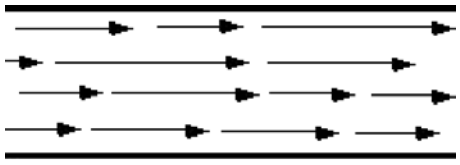
3. Gas flow physics

A relatively large driving pressure is required to sustain turbulent flow. Driving pressure during turbulent flow is proportional to the square of the flow rate, such that to double the flow rate one must quadruple the driving pressure.

Turbulent Flow

$\triangle P = K \dot{V}^2$ where $\triangle P$=driving force, K=constant, $\dot{V}$=air flow

When flow has low velocity and goes through narrow tubes, it tends to be more orderly and streamlined, and to flow in a straight line. This type of flow is called laminar flow. Unlike turbulent flow, laminar flow is directly proportional to the driving pressure, such that to double the flow rate, one needs only double the driving pressure.

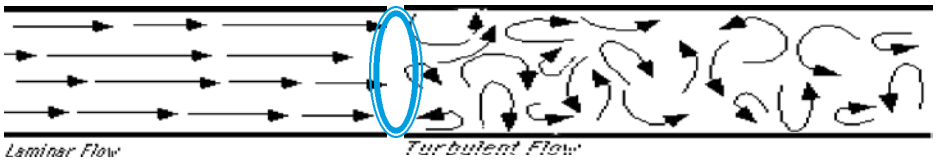


Laminar Flow

Poiseuille's Law: $\triangle P = \dot{V}(8\eta l/\pi r^4)$

Where $\triangle P$=the difference in pressure between the two points, $\dot{V}$=air flow, r=the radius of the tube, η=gas viscosity, and l=length of the tube.

An obstruction turns laminar flow into turbulent flow:

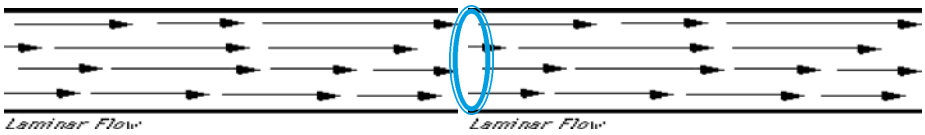


Laminar Flow *Turbulent Flow*

Laminar flow is the most efficient way in which oxygen is delivered to the more distal parts of the bronchial tree. The type of flow occurring at any given point is determined by the Reynolds number of the gas. This is a unitless quantity proportional to the product of the airway diameter and the velocity and density of the gas, divided by its viscosity. When the Reynolds number is high (greater than 3,790), flow is predominantly turbulent.

The effective cross-sectional area of the airways increases with each division from the trachea to bronchi. As this happens, the flow rate of inspired gas falls.

As the flow rate drops, the Reynolds number falls and flow becomes more laminar than turbulent. There will be a transitional region within the substance of the lungs where turbulent flow becomes laminar. Exercise, or any disease that increases ventilatory requirements, will shift this transitional area distally, causing a greater predominance of turbulent flow.



Medicinal helium/oxygen mixtures act by lowering the resistance to gas flow within the airways and permitting an increase in ventilation. This happens for two main reasons. First, and most importantly, breathing medicinal helium/oxygen mixtures leads to a reduction in the Reynolds number, converting turbulent flow to efficient laminar flow. Second, because of their low density, medicinal helium/oxygen mixtures decrease the pressure gradient needed to achieve a given level of turbulent flow, which in theory reduces the work of breathing. The use of medicinal helium/oxygen mixtures in asthma and upper airway obstruction has not been to treat the underlying disease, but to reduce airway resistance and respiratory muscle work until definitive treatments act.

Anecdotal evidence suggests that in order to significantly reduce airway resistance, concentration of helium must be high – ideally greater than 70% of the inhaled gas mixture. This will limit the amount of oxygen that can be delivered simultaneously. However, the hypoxemia associated with airway disease is usually modest, and is usually responsive to small amounts of oxygen because the underlying mechanism of gas exchange impairment is a ventilation perfusion mismatch.

References:

Reuben AD, Harris AR. Heliox for asthma in the emergency department: a review of literature. Emerg Med J 2004; 21:131–135.

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Ho A et al. Heliox vs. air-oxygen mixtures for the treatment of patients with acute asthma. Chest 2003; 123:882–90.

Piva J et al. The use of helium-oxygen mixture in the ventilation study of children with chronic obstructive lung disease. Journal de Pediatria 2000; 76(1):17–26.

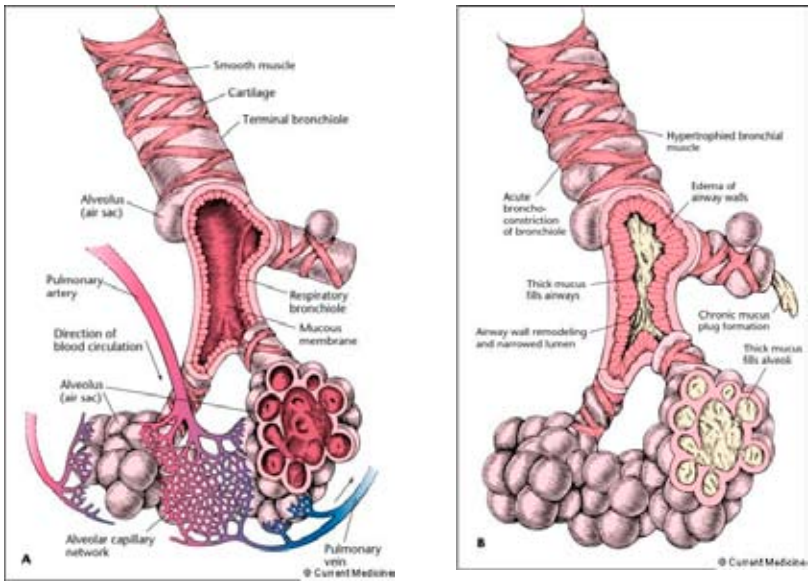
Rose JS et al. Prospective randomized trial of Heliox-driven continuous nebulizers in the treatment of asthma in the emergency department. J Emerg Med 2002; 22(2):133–7.

Fink JB. Helium-oxygen: An old therapy creates new interest. J Resp Care Pract 1999; 12:71–6.

4. Medicinal helium/oxygen mixtures in asthma and asthma therapy in combination with aerosol delivery (nebulization)

Asthma:

Asthma is a chronic inflammatory disorder of the airways. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. The inflammation also causes an associated increase in existing bronchial hyper-responsiveness to a variety of stimuli. Episodes are usually associated with airflow obstruction, which is often reversible, either spontaneously or with treatment.



A: Normal anatomy of lung near the terminal bronchiole, demonstrating the efficiency with which normal gas exchange occurs.

B: Same region during acute asthmatic episode, demonstrating airflow obstruction in asthma. Smooth muscle along airway walls is constricted and hypertrophied. Along with extensive plugging of the airways by mucus, airway walls are thickened and edematous as a result of inflammatory changes. Eventually, airway walls may be remodeled, leading to fixed obstruction in some patients. Unchecked airway inflammation resulting in such extensive pathologic changes may cause severe hypoxemia from ventilation-perfusion mismatches and even intrapulmonary shunting.

Status asthmaticus is defined by Bechler Karsch (1994) as an asthma attack that is refractory to conventional treatment and can lead to respiratory failure and death if not properly managed. The vast majority of patients with acute exacerbations of asthma are successfully treated with routine therapy. A small subset of patients will however fail to respond to conventional therapy and may require urgent intubation and mechanical ventilation. The initiation of mechanical ventilation in patients with severe asthma may save lives, but is associated with increased morbidity.

Anecdotal case studies have suggested that there is a subgroup of patients with status asthmaticus who are unresponsive to conventional therapies, and who may benefit from breathing medicinal helium/oxygen mixtures until definitive therapies take hold. As previously noted, helium is an inert agent and medicinal helium/oxygen mixtures have no bronchodilator or anti-inflammatory effect. Its main action seems to be in acting as a temporizing agent allowing the usual forms of therapy to reach their peak activity.

Under most breathing conditions, airflow in humans is laminar; at high gas velocities and with severe airway narrowing, increasingly turbulent airflow may occur. In the context of asthma, turbulence has two major consequences: (1) the airway resistance for any given degree of anatomic obstruction will be greater, leading to a greater work of breathing and the potential for more dynamic hyperinflation; (2) turbulence makes the delivery of aerosolized particles to the lower airway more difficult, since gas streams impacting on airway walls can result in droplet deposition above the intended site of delivery.

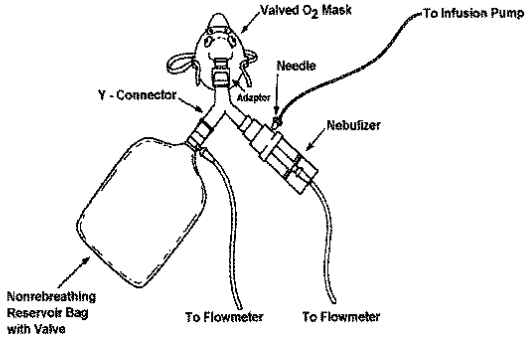
Medicinal helium/oxygen mixtures have been described as improving breathing in patients with critical upper airway obstruction, mainly by increasing ventilation and decreasing work of breathing. When compared with air, medicinal helium/oxygen mixtures have been found to deposit aerosolized particles more peripherally in the lungs in asthmatic subjects.

Little is known regarding the use of medicinal helium/oxygen mixtures in acute asthma. First, their effect is difficult to assess without controlled studies. Second, the duration of administration and optimal helium/oxygen mixture remain undetermined. Finally, the cost of treatment is relatively high. To date, no systematic reviews on this topic have been published, so it is not surprising that the use of medicinal helium/oxygen mixtures is variable and institution specific. Over 70 years after its use was first proposed, the role of medicinal helium/oxygen in asthma patients is still not clear defined.

However, the majority of publications are in favor of medicinal helium/oxygen mixtures in asthma, and describe positive effects at least on quality of life.

The pulmonary deposition of particles within an aerosol is influenced by the density of the gas being administered to the patient. Accordingly, medicinal helium/oxygen mixtures are likely to influence pulmonary deposition of aerosol bronchodilators, yet few investigators have studied this interaction.

Principle of nebulization:



Hess et al. found that compared with air, operating a nebulizer with medicinal helium/oxygen mixtures decreased both the fraction of the nominal dose, collected on a filter placed at the end of the T connector, and the aerosol's respirable mass in an in vitro model. Conversely, patients with asthma who breathed medicinal helium/oxygen mixtures 80/20 displayed greater pulmonary deposition of monodisperse Teflon particles than when breathing air. However, the influence of medicinal helium/oxygen mixtures on aerosol delivery during mechanical ventilation is not known.

In-line nebulizers and metered-dose inhalers (MDIs) are used for bronchodilator therapy in mechanically ventilated patients. The efficiency of these devices in delivering aerosols to the lower respiratory tract is less in mechanically ventilated patients than in ambulatory patients. Methods for enhancing aerosol delivery in such patients could have clinical benefits and reduce costs. In a pediatric model of mechanical ventilation, albuterol delivery from an MDI was increased when the device was operated with a medicinal helium/oxygen 70/30 mixture versus the same balance of nitrogen and oxygen.

It is not known, however, how differing concentrations of helium might influence the generation of aerosols from Midis and nebulizers, and their delivery to the lower respiratory tract of mechanically ventilated patients.

4a. Clinical studies in favor of medicinal helium/oxygen mixtures – references to chapter 4

Source/Year/Title	Patients	Disease	Intervention	Results
Lee et al./2005/Acad Emerg Med Beneficial effects of Albuterol therapy driven by Heliox versus by Oxygen in severe asthma exacerbation	80	Acute asthma Exacerbation	Albuterol nebulized with oxygen vs. Heliox	Improvement in peak expiratory flow rate and dyspnea score
Sattonnet et al./2005/Poster The efficacy of Helium-oxygen mixtures "65% versus 35%" in acute asthma exacerbation	204	Acute asthma	Conventional treatment vs. Heliox therapy	Improvement in spirometry, avoids intubation, facilitates fast recovery
Gupta et al./2005/ Pediatr Crit Care Med Heliox administration in the pediatric intensive care unit: An evidence-based review	Review	Asthma	Heliox therapy	Heliox has positive effects with no adverse effects; more studies are needed to define the potential benefits
		Aerosol delivery		Heliox improved delivery of inhaled bronchodilators to the lower airway and improved gas movement as measured by spirometry
		Upper airway obstruction		Heliox relieves respiratory distress, decreases the work of breathing, improves gas exchange, and may alleviate the need of reduce the need for re-intubation in the post-op period
		Croup		Heliox improves the work of breathing as evidenced by croup score, but not to a greater degree than seen with conventional therapy
		High-frequency ventilation		Heliox cannot be recommended
Donina et al./2004/Eur Respir J The experimental study of Heliox	Animal study	Asthma	Ventilation and Heliox	Heliox can ameliorate oxygen diffusion and carbon dioxide elimination

Source/Year/Title	Patients	Disease	Intervention	Results
Ho et al./2003/Chest Heliox vs. air-oxygen mixtures for the treatment of patients with acute asthma	278	Acute asthma	Conventional treatment vs. Heliox	Mild to moderate benefits within the first hour of use, more pronounced in severe cases
Rose et al./2002/J Emerg Med Randomized trial of Heliox-driven continuous nebulizers in the treatment of asthma in the emergency department	36	Acute asthma	Albuterol nebulized	Superior patient prospective dyspnea score in Heliox group at 1h
Kress et al./2002/Am J Respir Crit Care The utility of albuterol nebulized with heliox during acute asthma exacerbations	45	Acute asthma	Albuterol nebulized with test gas	Mean FEV improved 14.6% (air); 32.4% (Heliox) treatment I; 22.7% vs. 51.2% after treatment II; 26.6% vs. 65.1% after treatment III
Goode et al./2001/ Am J Respir Crit Care Med Improvement in aerosol delivery with helium-oxygen mixtures during mechanical ventilation	-	-	Influence of Heliox in different mixtures and flow rates	Improvement of aerosol delivery with Heliox
Kass et al./1999/Chest The effect of heliox in acute severe asthma: a randomized controlled trial	23	Refractory asthma	Nebulized albuterol vs. steroid	Heliox improved parameters
Hendersson et al./1999/Ann Emerg Med Use of Heliox-driven nebulizer therapy in the treatment of acute asthma	205	Mild to moderate asthma attack	Nebulized albuterol vs. steroid	After 30 min Heliox parameters more than air
Schaeffler et al./1999/Crit Care Med Oxygenation in status asthmaticus improves during ventilation with helium-oxygen	22	Severe asthma with respiratory failure	Intubation ß-agonist vs. steroid	Heliox improved parameters
Hess et al./1999/Chest The effect of Heliox on nebulizer function using a beta-agonist bronchodilator		-	-	Powering of nebulizers with the use of Heliox
Kukudis et al./1997/J Pediatr Inhaled helium-oxygen revisited: effect of inhaled helium-oxygen during the treatment of status asthmaticus in children	18	Status asthmaticus	Nebulized ß-agonist and steroid	Parameters in favor of Heliox improved

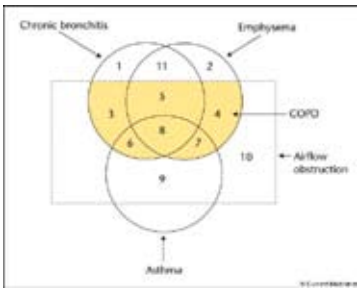
Source/Year/Title	Patients	Disease	Intervention	Results
Browne-Heitschmidt et al./1997/ Pediatr Nurs Heliox: a new treatment for life-threatening asthma		Acute asthma	Conventional therapy	Improved peak flow readings and reduction in dyspnea and pulsus paradoxus
Manthous et al./1995/ Am J Respir Crit Care Heliox improves pulsus paradoxus and peak expiratory flow in nonintubated patients with severe asthma	22	Status asthmaticus	ß-agonist and iv steroid	Greater improvement after 15 min in Heliox group
Kass et al./1995/Chest Heliox therapy in acute severe asthma	12	Acute exacerbation of asthma	Conventional treatment plus different concentrations of Heliox	Greater improvement

4b. Clinical studies with no difference in therapies or not in favor of medicinal helium/oxygen mixtures - references to chapter 4

Source/Year/Title	Patients	Disease	Intervention	Results
Rodrigo et al./2003/Chest Use of helium-oxygen mixtures in the treatment of acute asthma	392	Acute asthma	Conventional therapy vs. Heliox	Review of 7 clinical trials compared Heliox to placebo used in conjunction with other standard acute treatments
L' her et al./ 2000/Am J Respir Crit Care Helium-oxygen breathing in the early emergency care of acute severe asthma	16	Severe asthma	Nebulized broncho-dilators driven by test gas, supplemental oxygen	No difference in most parameters with Heliox at conc. 40%
Carter et al./1996/Chest Evaluation of Heliox in children hospitalized with acute severe asthma	11	Acute asthma	Nebulized albuterol vs. steroid	Parameters improved more after Heliox than air; no difference between gases

5. Medicinal helium/oxygen mixtures in chronic obstuctive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

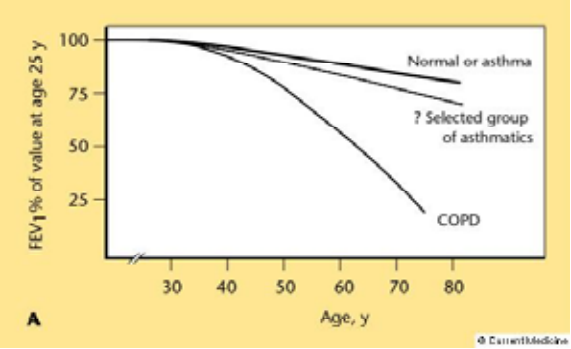


Non-proportional Venn diagram showing subsets of patients with bronchitis, emphysema, asthma, and combinations of these components of COPD. The subsets comprising COPD are shaded. Patients with reversible asthma (subset 9) do not have COPD, whereas patients with emphysema and/or bronchitis (subsets 6, 7 and 8) are considered to have "asthmatic bronchitis". Most patients with COPD have chronic bronchitis and emphysema (subset 5).

Chronic bronchitis is an inflammation or irritation of the airways in the lungs. When the airways are irritated, thick mucus forms in them. The mucus blocks the airways and makes it hard to get air into the lungs. Symptoms of chronic bronchitis include a cough that produces mucus (sputum), breathing difficulties, and a feeling of tightness in the chest.

Emphysema is a chronic disease that interferes with normal breathing. It occurs when the delicate alveoli walls become inflamed, causing them to lose their natural elasticity. They over-expand and lose the ability to fill up and contract properly. As air gets trapped in the alveoli, some rupture to form one large air space instead of many small ones. The trapped air cannot be fully released when a patient exhales, and breathing then becomes incresingly labored.

A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production or dyspnea, and/or history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry.

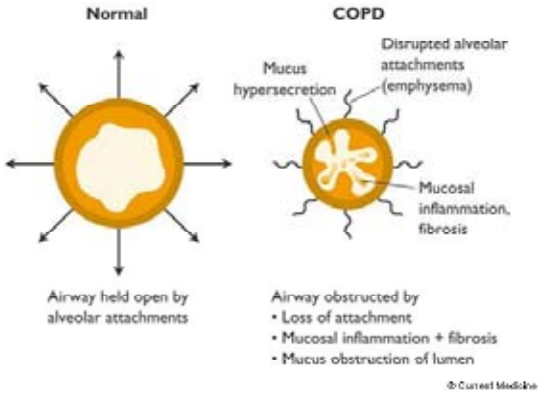


Clinical course of airway function in asthma, COPD, smoking, and after smoking cessation.

Long-term clinical course of patients with asthma and COPD. It is generally thought that patients with asthma have a change in pulmonary function with aging that is comparable to that of normal non-smoking individuals. Questions have been raised as to whether a select group of asthmatics have decreases in pulmonary function that are excessive for their age. However, patients with COPD have a much more dramatic decline in pulmonary function over time. (Courtesy of Gregory R. Owens.)

Mechanisms of airflow limitation in COPD:

The airway in normal subjects is distended by alveolar attachments during expiration, allowing alveolar emptying and lung deflation. In COPD, these attachments are disrupted because of emphysema, thus contributing to airway closure during expiration, trapping gas in the alveoli and resulting in hyperinflation. Peripheral airways are also obstructed and distorted by airway inflammation and fibrosis (chronic obstructive bronchiolitis) and by occlusion of the airway lumen by mucus secretions, which may be trapped in the airways because of poor mucociliary clearance.



The classification of severity follows simply the given symptoms despite the fact that there is only an imperfect relationship between the degree of airflow limitation and the presence of symptoms.

The benefits of medicinal helium/oxygen mixtures in COPD are less clearly reported, although there is ongoing research into its use in place of oxygen in acute exacerbations. Some studies show that medicinal helium/oxygen mixtures consistently improve both inspiratory and expiratory flow, producing a reduction in dynamic hyperinflation with a consequent improvement in gas exchange. Reduction in hyperinflation improves mechanical advantage by increasing respiratory muscle efficiency and decreasing the work of breathing. Decreased work of breathing will reduce the volume of carbon dioxide produced. The major problem is in most cases not just oxygen transport to the alveoli, but also the inability to exhale carbon dioxide properly.

In summary, there is currently insufficient evidence to support the use of medicinal helium/oxygen mixtures in the standard treatment of acute exacerbations of COPD, but future randomized trials would be of value.

References:

Celli BR, Snider GL, Heffner J. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152:S77-S121.

Hogg JC. Chronic obstructive pulmonary disease: an overview of pathology and pathogenesis. Novartis Found Symp 2001; 234:4-19.

5a. Clinical studies in favour of medicinal helium/oxygen mixtures - references to chapter 5

Source/Year/Title	Patients	Disease	Intervention	Results
Maggiore et al./2004/Poster Effect of helium-oxygen during non-invasive ventilation for acute exacerbation	195	Acute exacerbation of hypercapnic respiratory failure	NIV with and without Heliox	Trend in favor of Heliox but not statistically significant
Diehl et al./2003/Crit Care Med Helium/oxygen mixture reduces the work of breathing at the end of the weaning process in patients with severe chronic obstructive pulmonary disease	12	COPD	Sequentially helium-oxygen and air-oxygen	In spontaneously breathing intubated patients with COPD, helium-oxygen mixtures reduce the work of breathing, as well as intrinsic positive end-expiratory pressure, without modifying the breathing pattern
Jolliet et al./2003/Crit Care Med Helium-oxygen vs. air-oxygen noninvasive pressure support in decompensated chronic obstructive disease: a prospective, multicenter study	123	COPD Decompensated	Heliox with NIPSV vs. air-oxygen	Helium/oxygen did not significantly reduce intubation rate or intensive care unit stay, but hospital stay was shorter and total costs were lower
Jolliet et al./2003/Intensive Care Med Comparative effects of helium/oxygen and external positive end-expiratory pressure on respiratory mechanics, gas exchange, and ventilation-perfusion relationships in mechanically ventilated patients with chronic obstructive pulmonary disease	10	COPD	Heliox compared to PEEP	Helium/oxygen mixtures and PEEP comparably reduced PEEPi and trapped gas volume; helium/oxygen decreased airway resistance and intra thoracic pressures
Austan et al./2002/Heart & Lung Management of respiratory failure with non-invasive positive pressure ventilation and Heliox adjunct	Case report	COPD Exacerbation	Heliox	Non-invasive positive pressure ventilation and combination with Heliox recommended
Gerbaux et al./2001/Crit Care Med Use of Heliox in patients with severe exacerbation of chronic obstructive pulmonary disease	81	COPD	Heliox as an adjunctive Therapy	Heliox seems to improve prognosis in patients with severe acute exacerbation of chronic obstructive pulmonary disease

Source/Year/Title	Patients	Disease	Intervention	Results
Tassaux et al./2000/Crit Care Med Effects of helium/oxygen on intrinsic positive end-expiratory pressure in intubated and mechanically ventilated patients with severe chronic obstructive pulmonary disease	23	COPD Intubated and ventilated patients	Heliox vs. air-oxygen	In mechanically ventilated COPD patients with intrinsic positive end-expiratory pressure, helium/oxygen can markedly reduce trapped lung volume, PEEPi and peak and mean airway pressures
Piva et al./2000/J Pediatr (Rio J) The use of helium- oxygen mixture in the ventilation study of children with chronic obstructive lung disease	20	COPD Children	Nebulizing of micro-particles in scinti-graphy	Nebulization with Heliox was more effective than with oxygen; benefits are more evident in the presence of lower obstruction
Jolliet et al./1999/Crit Care Med Beneficial effects of Helium:oxygen versus air: oxygen non-invasive pressure support in patients with decompensated chronic obstructive pulmonary disease	19	COPD Decompensated	Heliox vs. air-oxygen	In decompensated COPD patients, non-invasive pressure support ventilation with helium-oxygen reduced dyspnea and $PaCO_2$ more than air-oxygen
Jaber et al./1999/ Am J Respir Crit Care Med Noninvasive ventilation with helium-oxygen in acute exacerbation of COPD	10	COPD Exacerbation	Heliox and NIV vs. air-oxygen	Use of Heliox during non-invasive ventilation markedly enhances the ability of NIV to reduce patient effort and to improve gas exchange
Polito et al./1995/N Engl J Med Heliox in respiratory failure from obstructive lung disease	Case report	Respiratory failure from COPD	Heliox treatment	Averts need to intubate, or allows earlier extubation

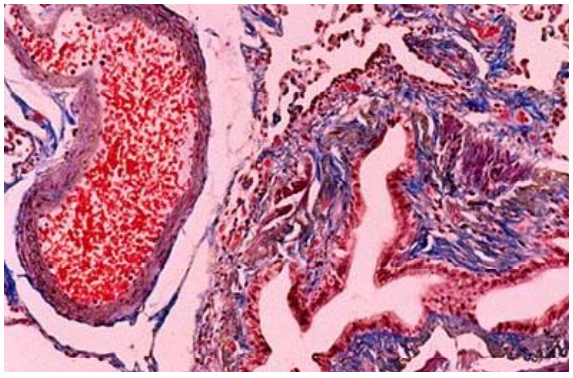
5b. Clinical studies with no difference in therapies or not in favor of medicinal helium/oxygen mixtures - references to chapter 5

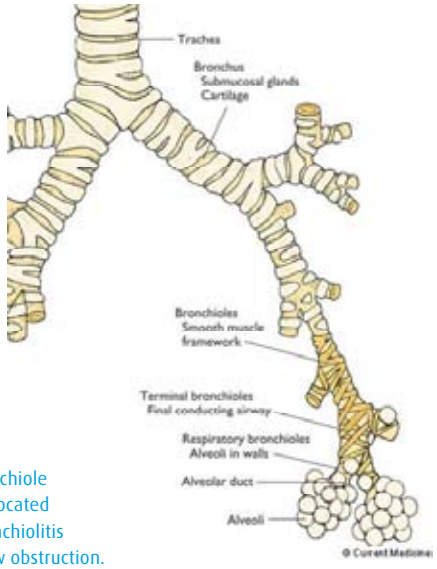
Source/Year/Title	Patients	Disease	Intervention	Results
Andrews et al./2004/Emerg Med J Heliox in the treatment of chronic obstructive pulmonary disease	121	COPD	Heliox vs. air-oxygen mixtures	Definitive evidence of a beneficial role of Heliox in treatment of severe COPD is lacking; however beneficial effect of HELIOX breathing was reported in all trials
Johnson et al./2002/Chest Effects on training with Heliox and non invasive positive ventilation on exercise ability in patients with severe COPD	39	Severe COPD	Heliox or non-invasive positive pressure ventilation	No immediate training advantage with exercise in with exercise in patients with COPD
Rodrigo et al./2000/Cochrane database Heliox for treatment of exacerbations of chronic obstructive pulmonary disease	68 review	COPD Exacerbation	Heliox or air-oxygen mixtures	Insufficient evidence to support use of helium/ oxygen mixtures to treat acute exacerbations of COPD in either ventilated or non-ventilated patients
deBoisblanc et al./2000/Crit Care Med Randomized trial of the use of Heliox as a driving gas for updraft nebulization of bronchodilators in the emergent treatment of acute exacerbations of chronic obstructive pulmonary disease	50	COPD Exacerbation	Nebulizing of albuterol or ipratropium with Heliox as driving gas	Heliox as driving gas for the updraft of bronchodilators during the first 2 hours of treatment of an acute exacerbation failed to improve FEV1 faster then air; the improvement in FEF 25-75 was small and with uncertain clinical significance

6. Medicinal helium/oxygen mixtures in bronchiolitis

Bronchiolitis is the inflammation of the respiratory bronchioles, which produces airway obstruction from bronchial wall edema and mucus occluding the airways. The main viral pathogens responsible for bronchiolitis are respiratory syncytial virus (RSV) and parainfluenza virus.

Constrictive bronchiolitis is a late, fibrotic, concentric bronchiolitis that occurs with or without complete obliteration [1]. There is no primary involvement of the distal alveolar ducts and alveoli. The histological changes associated with constrictive bronchiolitis vary from mild bronchiolar inflammation and scarring to concentric fibrosis with complete obliteration of the bronchioles [1], [2], [3]. Irreversible scarring and alteration of the bronchioles varies from one airway to the next. The effect of obstruction may appear in distal air spaces.





Trichrome stain from a patient with constrictive bronchiolitis. The lumen of the bronchiole is irregular and distorted by a dense band of submucosal collagen that stains blue located between the reddish-staining muscle and the luminal mucosa. The constrictive bronchiolitis occurred in a patient with chronic severe asthma who developed irreversible airflow obstruction.

References:

[1] Popper HH. Bronchiolitis, an update. Virchows Arch 2000; 437:471-81.
[2] Colby TV. Bronchiolitis. Am J Clin Pathol 1998; 109:101-9.
[3] Swensen SJ. Bronchiolar disorders. Am J Respir Crit Care Med 2003; 168:1277-92.

6a. Clinical studies in favor of medicinal helium/oxygen mixtures

Source/Year/Title	Patients	Disease	Intervention	Results
Martinon-Torres et al./2002/Pediatrics Heliox therapy in infants with acute bronchiolitis	38	Bronchiolitis Children	Heliox vs. conventional therapy	Heliox therapy enhanced the clinical respiratory status, shown by the marked improvement in clinical scores and the reduction of the accompanying tachycardia and tachypnea

6b. Clinical studies with no difference in therapies or not in favour of medicinal helium/oxygen mixtures

Source/Year/Title	Patients	Disease	Intervention	Results
Gross et al./2000/Crit Care Helium-oxygen mixtures do not improve gas exchange in mechanically ventilated children with bronchiolitis	10	Bronchiolitis	Heliox in different mixtures vs. nitrogen	The use of different Heliox mixtures with nitrogen-oxygen in mechanically ventilated children with bronchiolitis did not result in a significant or noticeable decrease in ventilation or oxygenation

7. Medicinal helium/oxygen mixtures in pediatric respiratory disorders

Diseases, indications: See also chapters 3, 4, 5 and references

7a. Clinical studies in favor of medicinal helium/oxygen mixtures

Source/Year/Title	Patients	Disease	Intervention	Results
Gupta et al./2005/ Pediatr Crit Care Med Heliox administration in the pediatric intensive care unit: An evidence-based review	Review Children	Asthma	Heliox therapy	Heliox has positive effects with no adverse effects; more studies are needed to define the potential benefits
		Aerosol delivery		Heliox improves delivery of inhaled bronchodilators to the lower airway and improved gas movement as measured by spirometry
		Upper airway obstruction		Heliox relieves respiratory distress, decreases the work of breathing, improves gas exchange, may alleviate the need for re-intubation in the post-op period
		Croup		Heliox improves the work of breathing as evidenced by croup score, but not to a greater degree than seen with conventional therapy
		High-frequency ventilation		Heliox cannot be recommended
Myers/2003/Respiratory care Therapeutic gases for neonatal and pediatric respiratory care	Review Children	Asthma, airway obstruction, post-extubation stridor, croup bronchiolitis, delivery		Benefits of Heliox reported; clinical studies are requested to show clear evidence to make Heliox a first line therapy
Grosz et al./2001/Laryngoscope Use of helium-oxygen mixtures to relieve upper airway obstruction in a pediatric population	42	Airway obstruction	Heliox therapy	Helium/oxygen therapy is a useful adjunct therapy for upper airway obstruction

Tobias/2001/Pediatr Emerg Care Heliox in children with airway obstruction	Case report	Airway obstruction Children	Heliox as additional therapy tool	Positive effects from Heliox
Piva et al./2000/J Pediatr (Rio J) The use of helium- oxygen mixture in the ventilation study of children with chronic obstructive lung disease	20	COPD Children	Nebulizing of micro-particles in scinti-graphy	Nebulization with Heliox was more effective than with oxygen; benefits are more evident in the presence of lower airway obstruction
Orsini et al./1999/Crit Care Heliox improves pulmonary mechanics In a pediatric porcine model of induced severe bronchospasm and independent lung mechanical ventilation	Animal model	Severe bronchospasm	Heliox therapy	In a pediatric porcine model of acute, severe methacholin-induced bronchospasm and independent lung mechanical ventilation, administration of Heliox improved pulmonary mechanics, gas flow and ventilation
Habib et al./1999/ Pharmacotherapy Effect of helium-oxygen on delivery of Albuterol in a pediatric, volume-cycled, ventilated lung model	Lung model		Albuterol nebulization with Heliox	Positive effect compared to air

7b. Clinical studies with no difference in therapies or not in favor of medicinal helium/oxygen mixtures

Carter et al./1996/Chest Evaluation of Heliox in children hospitalized with acute severe asthma	11	Acute asthma	Nebulized albuterol vs. steroid	Parameters improved more after Heliox than air; no difference between gases

8. Medicinal helium/oxygen mixtures in airway obstruction (accident, croup, post-extubation stridor, pneumothorax, cancer)

Upper airway obstruction is the most common condition for which medicinal helium/oxygen mixtures are used. The literature supporting their use was reviewed by Smith and Buros, who reported that the greater the severity of the obstruction, the more dramatic the benefit from breathing medicinal helium/oxygen mixtures. In contrast with widely held beliefs, they also suggested that medicinal helium/oxygen mixtures could be of benefit at comparatively low concentrations of helium.

Many published case series and reports have described the rapid and dramatic response to inhaled medicinal helium/oxygen mixtures in patients with upper airway obstruction, with improvement in respiratory distress that often averts the need for intubation. It is reported that patients become less anxious, more comfortable and more cooperative as the work of breathing is decreased.

There is also growing support for the use of medicinal helium/oxygen mixtures as an adjunct to ventilation in cases of iatrogenic upper airway obstruction such as bronchoscopy.

In summary, the use of medicinal helium/oxygen mixtures for upper airway obstruction is described to relieve respiratory distress, decrease the work of breathing and improve gas exchange. Results from studies suggest medicinal helium/oxygen mixtures can improve exercise capability, SaO_2 and dyspnea scores in lung cancer patients. They may alleviate the need for re-intubation in the post-extubation period.

8a. Clinical studies in favor of medicinal helium/oxygen mixtures - references to chapter 8

Source/Year/Title	Patients	Disease	Intervention	Results
Ahmedzai et al./2004/ Br J Cancer A double-blind, randomised, controlled Phase II trial of Heliox28 gas mixture in lung cancer patients with dyspnoea on exertion	12	Lung cancer	Heliox vs. oxygen and vs. air	Breathing Heliox gave a significant improvement in exercise capability, $SaO_2$and dyspnea scores of lung cancer patients
Weir M/2002/Clin Pediatr Vocal cord dysfunction mimics asthma and may respond to Heliox	5	Vocal cord dysfunction	Heliox therapy	Heliox reduced symptoms, resulting in dramatic improvement in wheezing and less anxiety
Ho et al./2002/Resucitation Use of Heliox in critical upper airway obstruction. Physical and physiologic considerations in choosing the optimal helium:oxygen mix	Review	Critical upper airway obstruction	Heliox therapy	Heliox improves ventilation rapidly
Connolly et al./2001/ Ann Otol Rhinol Laryngol Avoiding intubations in the injured subglottis: the role of Heliox therapy	14	Injured subglottis	Heliox therapy	Heliox may be a important adjunct of the medical treatment of upper airway obstruction
Hess et al./2000/ Int Anesthesiol Clin Techniques to avoid intubation: non-invasive positive pressure ventilation and Heliox therapy	Review	Acute respiratory	Heliox therapy	Heliox therapy may be beneficial for patients with large airway obstructions or asthma
Ulhoa et al./2000/ Journal dePediatria Helium-oxygen mixture in airway obstruction	Case report	Airway obstruction	Heliox therapy	Heliox is a promising treatment for severe airway obstructions, presenting positive outcomes in a short period of time
Smith et al./1999/ Acad Emerg Med Relief of imminent respiratory failure from upper airway obstruction by use of helium-oxygen: a case series and brief review	Review	Airway obstruction	Heliox therapy	The greater the severity of the obstruction the more dramatic the benefit from breathing Heliox

8b. Clinical studies with no difference in therapies or not in favor of medicinal helium/oxygen mixtures - references to chapter 8

Source/Year/Title	Patients	Disease	Intervention	Results
Weber et al./2001/Pediatrics A randomized comparison of helium-oxygen mixture and racemic epinephrine for the treatment of moderate to severe croup	29	Croup	Heliox vs. racemic epinephrine	Administration of Heliox resulted in similar improvements in severe croup compared with patients given RE
Barr et al./1997/ Annals of Emergency Medicine Heliox therapy for pneumothorax: new indication for an old remedy	Animal trial	Pneumothorax	Heliox vs. oxygen and air	Heliox was as effective as oxygen in reducing volume of an experimental pneumothorax

9. Medicinal helium/oxygen mixtures and mechanical ventilation

The physical properties of helium (particularly its low density and increased thermal conductivity) interfere with key parameters of mechanical ventilator function and monitoring, the extent of which depends on the ventilator technology.

The most frequently observed problems are underestimation of delivered tidal volume, inadequate alarming, valve/gas-delivery problems, inaccuracy of fraction of inspired oxygen, and malfunction of hot wire pneumotachometers. Few ventilators are designed for helium/oxygen application.

The results of all evaluations suggest that safe use of medicinal helium/oxygen mixtures with mechanical ventilators is possible, but only if the physical properties of the gas, the basic principles underlying the machine's valve and monitoring device technology, and the appropriate correction factors are known by the user.

In summary, the use of medicinal helium/oxygen mixtures cannot be recommended with existing ventilators as a standard operating procedure. There are several reports of malfunctions and technical problems. (Gupta et al.).

9a. Clinical studies in favor of medicinal helium/oxygen mixtures - references to chapter 9

Source/Year/Title	Patients	Disease	Intervention	Results
Chupta ef al./2004/Respiratory Care Heliox administration during high-frequency jet ventilation augments carbon dioxide clearance.	Review	-	Heliox in high-frequency jet ventilation	Improved carbon dioxide clearance, respiratory stabilization
Jolliet et al./2003/ Curr Opin Crit Care Usefulness of helium-oxygen mixtures in the treatment of mechanically ventilated patients	Review	Upper airway obstruction Asthma COPD	Heliox therapy	Heliox can be a valuable adjunct for patients with asthma and COPD during both non-invasive ventilation and conventional mechanical ventilation in the latter
Stucki et al./2002/Crit Care Med Successful management of severe respiratory failure combining Heliox with non invasive high-frequency percussive ventilation	Case report	Cystic fibrosis	Heliox ventilation	Successful management of a severe respiratory failure
Katz et al./2001/ Am J Respir Crit Care Med Heliox improves gas exchange during high-frequency ventilation in a paediatric model of acute lung injury	Animal model	Acute lung injury	Heliox ventilation	Heliox improuves carbone dioxide elemination primarily through increased tidal volume delivery
Winters et al./2000/ Pediatr Crit Care Med Heliox improves ventilation during high-frequency oscillatory ventilation in paediatric patients	5	Hypoxic resp.	Heliox ventilation	Heliox improves ventilation and decrease ventilator-related trauma
Goode et al./2000/ Am J Respir Crit Care Med Improvement in aerosol delivery with helium-oxygen mixtures during mechanical ventilation	Lung model	Mechanical ventilation	Albuterol nebulization Heliox vs. oxygen-air	Heliox may improve the aerosol delivery in mechanically ventilated patients
Tassaux et al./1999/ Am J Respir Crit Care Med Calibration of seven ICU ventilators for mechanical ventilation with helium-oxygen mixtures	Lung model	Mechanical ventilation	Heliox ventilation Heliox vs. oxygen-air	Calibration is performed for seven different ICU ventilators

Tassaux et al./1999/ Am J Respir Crit Care Med of seven ICU ventilators for mechanical ventilation with helium-oxygen mixtures	Lung model	Mechanical ventilation	Heliox ventilation	Calibration is performed for seven different ICU ventilators

9b. Clinical studies with no difference in therapies or not in favor of medicinal helium/oxygen mixtures - references to chapter 9

Source/Year/Title	Patients	Disease	Intervention	Results
Gross et al./2000/Crit Care Helium-oxygen mixtures do not improve gas exchange in mechanically ventilated children with bronchiolitis	10	Bronchiolitis	Heliox in different mixtures vs. nitrogen	The use of different Heliox mixtures with nitrogen-oxygen in mechanically ventilated children with bronchiolitis did not result in a significant or noticeable decrease in ventilation or oxygenation

10. Summary of articles

- Biologically inert gas mixture with significant lower density
- Virtually insoluble in human tissues; non-reactive with biologic membranes and other common respiratory gases
- Long-term inhalation does not seem to show any negative side effects
- Therapeutic action due to high kinematic viscosity, high binary diffusion coefficient, low density and the subsequent effects of these properties on airway resistance and facilitated diffusion
- Increases the diffusion of carbon dioxide and may improve alveolar ventilation, resulting in improved gas exchange and higher carbon dioxide elimination
- Improves some physiological variables (peak flow, pulsus paradoxus, work of breathing)
- Reduce potential to the incidence of endotracheal intubation, avoiding mechanical ventilation (especially in acute exacerbations of asthma and COPD)
- Able to carry aerosols to support asthma therapy
- Acts as a therapeutic bridge until the effect of corticosteroids occurs, so unlikely to reduce hospital admissions, hospital or ICU length of stay, or hospital mortality
- Many episodic reports of helium/oxygen treatment with good results indicate its potential

- Method is not a standard procedure in most treatment schemes – not well known in target group
- Little documented data; current meta analysis shows mostly no significant outcome benefits of this intervention
- Lack of randomized controlled clinical trials
- Can only used by educated staff under supervision of a physician
- Lack of dedicated and proper devices on the market
- Additional technical equipment necessary (ventilator and flow meters, special gas supply, masks)
- Mucus plugging as a prominent feature in death due to status asthmaticus is probably intensified by helium
- Direct thermal debit for the body in high volumes
- Humidification has to be maintained

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