"Helium ventilation in obstructive respiratory diseases : evaluation of ventilation/perfusion relationships with the MIGET : from the animal model to the clinical application"

Watremez, Christine

Abstract
To briefly guide the reader along this thesis on the contribution of helium ventilation in bronchospastic diseases, we provide a short outline in five steps as following: - First, we will review briefly the basis of asthma disease and COPD. - Second, we will describe some respiratory measurements we have at one’s disposal to evaluate the level of the disease and the extent of therapy effect. - Third, we will make a recall of measurement of the ventilation-perfusion relationships by the Multiple Inert Gas Elimination Technique. - Fourth, we will explain what is helium and how it will be theoretically interesting to use it in the clinical setting. - Finally, we will expose our works whose begin with the development of an animal model of bronchospasm, continue with the application of helium ventilation in this model, and reach completion with helium ventilation of COPD patients.

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Evaluation of ventilation/perfusion relationships with the MIGET

From the animal model to the clinical application

Christine WATREMEZ

Thèse présentée en vue de l'obtention du grade de Docteur en Sciences Biomédicales et Pharmaceutiques

Promoteur: Prof. M De Kock
Co-Promoteur: Prof. G Lister

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Faculty

Promotor:
Marc De Kock, MD, PhD
Head of Anesthesiology Unit
Department of Acute Medicine
Cliniques Universitaires Saint Luc
Université Catholique de Louvain

Co-promotor:
Giuseppe Liistro, MD, PhD
Head of Pneumology Unit
Department of Internal Medicine
Cliniques Universitaires Saint Luc
Université Catholique de Louvain

President of the Jury:
Jean Paul Thissen, MD, PhD
Endocrinology Unit
Department of Internal Medicine
Cliniques Universitaires Saint Luc
Université Catholique de Louvain

Jury:

Philippe Jolliet, MD, PhD
Head of Intensive Care Unit
Centre Hospitalier Universitaire Vaudois
Lausanne - Switzerland

Vincent Ninane, MD, PhD
Head of Pneumology Unit
Centre Hospitalier Universitaire Saint Pierre
Bruxelles

Philippe Baele, MD, PhD
Anesthesiology Unit
Department of Acute Medicine
Cliniques Universitaires Saint Luc
Université Catholique de Louvain

Marc Reynaert, MD, PhD
Emergency Unit
Department of Acute Medicine
Cliniques Universitaires Saint Luc
Université Catholique de Louvain

Jean Roeseler, CPT
Intensive Care Unit
Department of Acute Medicine
Cliniques Universitaires Saint Luc
Université Catholique de Louvain
Preface

To briefly guide the reader along this thesis on the contribution of helium ventilation in bronchospastic diseases, we provide a short outline in five steps as following:

- First, we will review briefly the basis of asthma disease and COPD.

- Second, we will describe some respiratory measurements we have at one’s disposal to evaluate the level of the disease and the extent of therapy effect.

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<tr>
<td>ASA</td>
<td>Acute Severe Asthma</td>
</tr>
<tr>
<td>APCs</td>
<td>Antigen Presenting Cells</td>
</tr>
<tr>
<td>BTPS</td>
<td>Body temperature and pressure conditions</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic Adenosine Monophosphate</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive Heart Faillure</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>ECF</td>
<td>Eosinophil Chemotactic Factors</td>
</tr>
<tr>
<td>EPR-2</td>
<td>Expert Panel Report 2</td>
</tr>
<tr>
<td>FEF\textsubscript{25-75%}</td>
<td>Forced midexpiratory flow rate</td>
</tr>
<tr>
<td>FEV\textsubscript{1}</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>He</td>
<td>Helium</td>
</tr>
<tr>
<td>HFOV</td>
<td>High Frequency Oscillary Ventilation</td>
</tr>
<tr>
<td>HPNS</td>
<td>High Pressure Nervous Syndrome</td>
</tr>
<tr>
<td>MCh</td>
<td>Methacholine</td>
</tr>
<tr>
<td>MHC</td>
<td>Histocompatibility complex molecule</td>
</tr>
<tr>
<td>MCT</td>
<td>Methacholine Challenge Testing</td>
</tr>
<tr>
<td>MIGET</td>
<td>Multiple Inert Gas Elimination Technique</td>
</tr>
<tr>
<td>NANC</td>
<td>Non adrenergic non cholinergic</td>
</tr>
<tr>
<td>NCF</td>
<td>Neutrophil Chemotactic Factors</td>
</tr>
<tr>
<td>NPPV</td>
<td>Non-invasive Positive Pressure Ventilation</td>
</tr>
<tr>
<td>Pab</td>
<td>Abdominal pressure</td>
</tr>
<tr>
<td>Palv</td>
<td>Alveolar pressure</td>
</tr>
<tr>
<td>Pdi</td>
<td>Trans diaphragmatic pressure</td>
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<tr>
<td>Pes</td>
<td>Esophageal pressure</td>
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<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
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<td>PEEPe</td>
<td>External PEEP</td>
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<td>Abbreviations</td>
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<tr>
<td>PEFR</td>
<td>Peak Expiratory Flow Rate</td>
</tr>
<tr>
<td>PF</td>
<td>Peak flow</td>
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<tr>
<td>PHM</td>
<td>Peptide histamine methionine</td>
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<tr>
<td>Pga</td>
<td>Gastric pressure</td>
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<tr>
<td>Ppl</td>
<td>Pleural pressure</td>
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<tr>
<td>Ptp</td>
<td>Transpulmonary pressure</td>
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<tr>
<td>Q</td>
<td>Blood flow</td>
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<tr>
<td>RV</td>
<td>Residual volume</td>
</tr>
<tr>
<td>$sG_{AW}$</td>
<td>Specific airway conductance</td>
</tr>
<tr>
<td>$T_H$</td>
<td>T helper cells</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>$V_A$</td>
<td>Alveolar ventilation</td>
</tr>
<tr>
<td>$V_a/Q$</td>
<td>Ventilation-perfusion ratio</td>
</tr>
<tr>
<td>$V_{max_{50%}}$</td>
<td>Maximal expiratory flow rate at 50% of the FVC</td>
</tr>
<tr>
<td>$V_{max_{75%}}$</td>
<td>Maximal expiratory flow rate at 75% of the FVC</td>
</tr>
<tr>
<td>VIP</td>
<td>Vasoactive intestinal polypeptide</td>
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Introduction

Helium was first isolated from the mineral cleveite in 1895. Barach first described its use in place of nitrogen as a carrier gas for oxygen in the early 1930s. It was recommended as an adjunct to the treatment of respiratory failure, in particular for obstructive lesions of the larynx, trachea, and lower airways. Enthusiasm for its use tailed off in the 1940s for two main reasons. The first was the onset of the Second World War when main sources of helium were lost, but more significant was the subsequent development of potent bronchodilators and mucolytic agents that proved far more effective.

Despite a lapse of over 70 years since Barach first described the use of helium-oxygen mixtures for the management of obstructive disorders of the respiratory tract, its use remains sporadic and undefined. The properties of helium make it an ideal agent for use as a carrier gas for oxygen in place of nitrogen for various conditions affecting the respiratory tract. The low density of Heliox helps to promote greater and smoother gas flow, decrease airway resistance, and decrease the work of breathing in selected patients.

Helium is an inert agent and has neither bronchodilator nor 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 activities. Additionally, research using Heliox mixtures has demonstrated a higher percentage of lung particle retention and a large delivery of albuterol from both metered-dose inhalers and nebulizers.

The success of bronchodilators and anti-inflammatory agents as well as inconsistent results in clinical studies have resulted in limited application of helium in the mechanically ventilated critically ill patient. Recently some reviews of literature have been made in order to determine the effect of adding helium to standard medical care in the course of acute asthma. They concluded that the existing evidence does not provide support for the
administration of helium oxygen mixtures to patients presenting to the emergency department with moderate to severe acute asthma, but recognised that further research is warranted. Guidelines published in 2007 for the management of acute exacerbations reflect this uncertainty and the use of helium in acute adult asthma is not recommended on the basis of the current evidence.

But the complex physiopathology of asthma, the variability of disease presentation between patients and their response to therapy make the study of a single agent during acute severe bronchospasm difficult to extrapolate to the clinical setting. Furthermore it would be a crime in emergency state to take time for studying helium before administration of any therapy (helium has neither bronchodilator nor anti-inflammatory effect; it has a purely physical effect). That’s why it was necessary, and that was the first step of this work, to develop a stable animal model of severe induced bronchospasm in the aim of studying specific effect of helium. Furthermore and to have a complete study of helium’s effects, it was necessary to study the consequences of helium’s physical properties on the respiratory mechanic and to observe its impact on ventilation-perfusion relationships.
Introduction

Reference List


1 – Obstructive airway diseases
1 – Obstructive airway diseases

1.1 Mechanisms of airway obstruction.

Increased resistance to airflow can be caused by conditions 1) inside the lumen, 2) in the wall of the airway, and 3) in the peribronchial region (Fig. 1).

1) The lumen may be partially occluded by excessive secretions, such as in chronic bronchitis. Partial obstruction can also occur acutely in pulmonary edema, asthma or after aspiration of foreign material and postoperatively, with retained secretions.

2) Causes in the wall of the airway include contraction of bronchial smooth muscle, as in asthma, hypertrophy of the mucous glands, as in chronic bronchitis, and inflammation and edema of the wall, as in bronchitis and asthma.

3) Outside of the airway, destruction of the lung parenchyma may cause loss of radial traction and consequent narrowing, as in emphysema. Peribronchial edema can also cause narrowing.

Figure 1: Mechanisms of airway obstruction.
(A) The lumen is partly blocked, for example, by excessive secretions. (B) The airway wall is thickened, for example, by edema or muscle hypertrophy. (C) The abnormality is outside the airway; in the example shown, the lung parenchyma is partly destroyed and the airway has narrowed because of loss of radial traction.
1.2 Asthma

Asthma is a disease of the human respiratory system in which the airways narrow, often in response to a "trigger" such as exposure to an allergen, cold air, exercise, or emotional stress. This narrowing causes symptoms such as wheezing, shortness of breath, chest tightness, and coughing, which are the hallmarks of asthma. Between episodes, most patients feel fine.

The disorder is a chronic inflammatory condition in which the airways develop increased responsiveness to various stimuli, characterized by bronchial hyper-responsiveness, inflammation, increased mucus production, and intermittent airway obstruction. The symptoms of asthma, which can range from mild to life threatening, can usually be controlled with a combination of drugs and lifestyle changes.

Public attention in the developed world has recently focused on asthma because of its rapidly increasing prevalence, affecting up to one in four urban children². Susceptibility to asthma can be explained in part by genetic factors, but no clear pattern of inheritance has been found. Asthma is a complex disease that is influenced by multiple genetic, developmental, and environmental factors, which interact to produce the overall condition³ (Fig.2).

![Figure 2: Factors influencing symptoms appearance.](Image)
1.2.1 History

The word *asthma* is derived from the Greek *aazein*, meaning "sharp breath". The word first appears in Homer's *Iliad*. Hippocrates was the first to use it in reference to the medical condition. Hippocrates thought that the spasms associated with asthma were more likely to occur in tailors, anglers, and metalworkers. Six centuries later, Galen wrote much about asthma, noting that it was caused by partial or complete bronchial obstruction. Moses Maimonides, an influential medieval rabbi, philosopher, and physician, wrote a treatise on asthma, describing its prevention, diagnosis, and treatment. In the 17th century, Bernardino Ramazzini noted a connection between asthma and organic dust. The use of bronchodilators started in 1901, but it was not until the 1960s that the inflammatory component of asthma was recognized, and anti-inflammatory medications were added to the regimen.

1.2.2 Epidemiology

The risk factors for asthma include:

- a personal or family history of asthma or atopy;
- triggers;
- premature birth or low birth weight;
- viral respiratory infections in early childhood;
- maternal smoking;
- being male, for asthma in prepubertal children; and
- being female, for persistence of asthma into adulthood.

1.2.3 Signs and symptoms

An acute exacerbation of asthma is referred to colloquially as an *asthma attack*. The clinical hallmarks of an attack are dyspnea and wheezing, the latter "often being regarded as the *sine qua non*". A cough—sometimes producing clear sputum—may also be present. The onset is often sudden; there is a "sense of constriction" in the chest, breathing becomes difficult, and wheezing occurs (typically in both respiratory phases).
Signs of an asthmatic episode are wheezing, tachypnea, prolonged expiration, tachycardia, rhonchous lung sounds, and over-inflation of the chest. During a severe asthma attack, the accessory muscles of respiration may be used, shown as in-drawing of tissues between the ribs and above the sternum and clavicles, and the presence of a paradoxical pulse (a pulse that is weaker during inhalation and stronger during exhalation). Status asthmaticus refers to an attack that continues for hours or even days without remission despite bronchodilator therapy. There are often signs of exhaustion, dehydration, and marked tachycardia. The chest may become ominously silent, and vigorous treatment is urgently required.

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 initiation of mechanical ventilation in patients with severe asthma may save lives, but is associated with increased morbidity.

Despite the severity of symptoms during an asthmatic episode, between attacks an asthmatic may show few signs of the disease.

Virtually all of the functional disturbances of asthma derive from the airway narrowing, which affects all parts of the tracheobronchial tree but is probably maximal in small bronchi 2 to 5 mm in diameter. Airway resistance is increased, and maximal expiratory flow is reduced at all lung volumes. Narrowed peripheral airways close at higher lung volumes, causing marked increases in residual volume. Also contributing to thoracic hyperinflation is the tendency to breathe at a higher lung volume, as an adaptive mechanism to reduce excessive airway narrowing by increasing circumferential traction on intrapulmonary airways.

These changes greatly increase the work of breathing: resistive work is increased because of the high pressures required to move air through narrowed airways, and elastic work is increased because of the lower compliance of both the lungs and the thoracic cage at high volumes. Overinflation of the thorax places the diaphragm and intercostal muscles at a mechanical disadvantage, so that they must function over a suboptimal
range of their length-tension curve. The increase in the work of breathing and the loss in muscle efficiency cause fatigue and can lead to exhaustion and respiratory failure.

1.2.4 Blood Gas Abnormalities

Asthma causes important impairments of gas exchange only during severe attacks. The degree of arterial hypoxemia roughly correlates with the severity of airways obstruction that is not homogeneous throughout the lungs. Often, some airways are completely occluded, others severely narrowed, and still others unobstructed. The resulting mismatch of ventilation (Fig. 3) and perfusion widens the alveolar-arterial oxygen difference, accounting for the oxygen tensions of 60-69 mm Hg (8.0-9.2 kPa) typically found during severe attacks of asthma.

Figure 3: Possible explanation to the bimodal VA/Q distribution in asthma.

As a result of mucus, oedema, and spasm, airways may be completely occluded. The alveolar units (denoted as A) may, however, still be ventilated via interbronchial channels and alveolar pores – so called collateral ventilation. This ventilation is executed with gas that has already participated in exchange of O2 and CO2 in other alveolar units (denoted B). This is why the collateral ventilated lung regions show up as a distinct mode with low VA/Q ratios.
The hypocapnia that is almost invariably found in mild to moderate attacks reflects an increase in respiratory drive. An elevated arterial PCO₂ indicates that airways obstruction is so severe that the muscles of respiration cannot maintain the ventilation rate set by the respiratory drive (alveolar hypoventilation). Any worsening of airways obstruction or muscle fatigue, or any decline in respiratory drive (as from administration of a narcotic or sedative drug), can then cause a further fall in alveolar ventilation. The rise in arterial PCO₂ then further inhibits muscle performance and respiratory drive ("CO₂ narcosis"), precipitating respiratory failure and death. Arterial hypercapnia thus indicates an attack of extreme severity that requires aggressive management.

1.2.5 Diagnosis

In most cases, a physician can diagnose asthma on the basis of typical findings in a patient's clinical history and examination. Asthma is strongly suspected if a patient suffers from eczema or other allergic conditions—suggesting a general atopic constitution—or has a family history of asthma. While measurement of airway function is possible for adults, most new cases are diagnosed in children who are unable to perform such tests. Diagnosis in children is based on a careful compilation and analysis of the patient's medical history and subsequent improvement with an inhaled bronchodilator medication. In adults, diagnosis can be made with a peak flow meter, looking at both the diurnal variation and any reversibility following inhaled bronchodilator medication.

Testing peak flow at rest and after exercise can be helpful, especially in young asthmatics who may experience only exercise-induced asthma. If the diagnosis is in doubt, or if chronic obstructive pulmonary disease is suspected, a complete lung function testing should be conducted. Once a diagnosis of asthma is made, a patient can use peak flow meter testing to monitor the severity of the disease.

During an attack, all indices of expiratory flow rate are reduced significantly, including the FEV1, FEV1/FVC%, FEF₂₅₋₇₅%, Vmax₅₀%, and
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V_{max}^{75\%}\). The FVC is also usually reduced because airways close prematurely toward the end of a full expiration. (Fig. 4)

**Figure 4:** Flow-volume curve which is typical of a patient with obstructive airway disease. Note the diminished vital capacity and flattening of the effort independent sector of the curve (compared with the broken curve which shows the normal). The expiratory curve is characteristically concave upwards.

Between attacks, some impairment of ventilatory capacity can usually be demonstrated although the patient may claim to feel normal. The response of these indices to bronchodilator drugs is of great importance in asthma. They may be tested by administering a short-acting \(\beta_2\) agonist by aerosol for 2 minutes. Typically, all indices increase substantially when a bronchodilator is administered to a patient during an attack, and the change is a valuable measure of the responsiveness of the airway. The extent of the increase varies according to the severity of the disease. In status asthmaticus, little change may be seen because the bronchi have become
unresponsive. Again, patients in remission may show only minor improvement, although generally there is some.

There is some evidence that the relative change in FEV1 and FVC after bronchodilator therapy indicates whether the bronchospasm has been completely relieved (Fig.5). During an asthma attack, both the FEV1 and FVC tend to increase by the same fraction, with the result that FEV1/FVC% remains low and almost constant. However, when the tone of airway muscle is nearly normal, the FEV1 responds more than the FVC, and the FEV1/FVC percent approaches the normal value of approximately 75%.

![Figure 5: Changes in FEV1 after bronchodilator therapy.](image)

The flow-volume curve in asthma has the typical obstructive pattern although it may not exhibit the scooped out appearance seen in emphysema. After a bronchodilator, flows are higher at all lung volumes, and the whole curve may shift as the TLC and RV are reduced.

Static lung volumes are increased, and remarkably high values for FRC and TLC during asthma attacks have been reported. The increased RV
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is caused by premature airway closure during a full expiration as a result of the increased smooth muscle tone, edema and inflammation of the airway walls, and abnormal secretions. The cause of the increased FRC and TLC is not fully understood. However, there is some loss of elastic recoil, and the pressure-volume curve is shifted upward and to the left. This tends to return toward normal after a bronchodilator. There is some evidence that changes in the surface tension of the alveolar lining layer may be responsible for the altered elastic properties. The rise in lung volume tends to decrease resistance of the airways by increasing their radial traction. The FRC measured by helium dilution is usually considerably below that found with the body plethysmograph, reflecting the presence of occluded airways or the delayed equilibration of poorly ventilated areas.

Airway resistance as measured in the body plethysmograph is raised, and it falls after a bronchodilator. It is likely that the bronchospasm affects airways of all sizes, and the relationship between airway conductance and elastic recoil pressure is significantly abnormal. Narrowing of the large and medium-sized bronchi can be seen directly at bronchoscopy.

Provided patients remain calm, they can withstand surprisingly high airway resistance. However, once they are alarmed and start to struggle, they may enter a vicious cycle of raised oxygen consumption, increased ventilatory demand and increased work of breathing leading to a further increase in oxygen consumption, which cannot be met.

1.2.6 Methacholine challenge

Methacholine chloride is a synthetic choline ester that acts as a non-selective muscarinic receptor agonist in the parasympathetic nervous system. It is highly active at all of the muscarinic receptors, but has little effect on the nicotinic receptors. Methacholine has a charged quaternary amine structure (Fig.6), rendering it insoluble to lipid cell membranes. Clinically, this means that it will not cross the blood-brain barrier and has
poor absorption from the gastrointestinal tract. It is broken down at a relatively slow rate within the body, due to its resistance to acetylcholinesterases.

Figure 6: Quaternary structure of methacholine.

The primary clinical use of methacholine is to diagnose bronchial hyperreactivity, which occurs in asthma. This is accomplished through the methacholine challenge test. Other therapeutic uses are limited by its adverse cardiovascular effects, such as bradycardia and hypotension, which arise from its function as a cholinomimetic.

Use of methacholine, as well as all other muscarinic receptor agonists, is contraindicated in patients with coronary insufficiency, gastroduodenal ulcers, and incontinence. The parasympathomimetic action of this drug will exacerbate the symptoms of these disorders.

Methacholine challenge testing is one method of assessing airway responsiveness. Airway hyperresponsiveness is one of the features that may contribute to a diagnosis of asthma. It may vary over time, often increasing during exacerbations and decreasing during treatment with antiinflammatory medications.

Methacholine challenge testing (MCT) is most often considered when asthma is a serious possibility and traditional methods, most notably spirometry performed before and after administration of a bronchodilator,
have not established or eliminated the diagnosis. Symptoms that suggest asthma include wheezing, dyspnea, chest tightness, or cough in the following circumstances:

1- with exposure to cold air,
2- after exercise,
3- during respiratory infections,
4- following inhalant exposures in the workplace, and
5- after exposure to allergens and other asthma triggers.

A history of such symptoms increases the pretest probability of asthma. The optimal diagnostic value of MCT (the highest combination of positive and negative predictive power) occurs when the pretest probability of asthma is 30–70%. Methacholine challenge testing is more useful in excluding a diagnosis of asthma than in establishing one because its negative predictive power is greater than its positive predictive power.

Methacholine challenge testing is also a valuable tool in the evaluation of occupational asthma. Methacholine challenge testing is sometimes used to determine the relative risk of developing asthma, assess the severity of asthma, and assess response to asthma therapy although its clinical use in these areas has not been well established.

However, bronchial hyperresponsiveness is also seen in a wide variety of other diseases, including smoking-induced chronic airway obstruction (COPD), congestive heart failure (CHF), cystic fibrosis, bronchitis, and allergic rhinitis.

Many different dosing protocols have been used. Each has advantages and disadvantages and the committee was unable to come to a single recommendation. Two methods are accepted: the 2-min tidal breathing method and the five-breath dosimeter method. Other drugs can be used like Histamine, Acetylcholine or Carbachol.
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Figure 7: Lung mechanics before and after intravenous methacholine infusion. Resistance of the respiratory system (Rrs) was significantly increased and dynamic compliance (Cdyn) was significantly decreased. The static compliance (Cst) was unchanged after methacholine administration.

Figure 8: Effects of intravenous methacholine infusion on auto-positive end-expiratory pressure (auto-PEEP), end-expiratory transpulmonary pressure (Ptp, exp), and end-expiratory abdominal pressure (Pabd, exp). Methacholine induced no significant hyperinflation according to the auto-PEEP and Ptp, exp measurements. However, expiratory muscle activity significantly increased after methacholine administration, as demonstrated by the increase in Pabd, exp. *P < 0.01.
Figure 9: Videomicroscopy of methacholine-induced contraction of individual airways. Precision-cut lung slices showing a bronchus (B); a bronchiole (b) and a pulmonary vein (PV) treated with increasing concentrations of methacholine.

Figure 10: Concentration-response curve of airway and vessel treated by methacholine. Concentration-response curve obtained from calculation of the relative airway (■) and vessel (△) area shown in previous image. Airway and vessel were treated with increasing molar concentrations of methacholine.
1.2.7 Pathophysiology

Macroscopically in patients who have died of asthma the lung is overinflated, with both large and small airways being filled with plugs comprised of a mixture of mucus, serum proteins, inflammatory cells, and cell debris. The mucous is increased in amount and abnormal; it is thick, tenacious, and slow-moving. In severe cases, many of the airways are occluded by mucous plugs, some of which may be coughed up in the sputum. Microscopically there is usually extensive infiltration of the airway lumen and wall with eosinophils and lymphocytes accompanied by vasodilatation, evidence of microvascular leakage, and epithelial disruption. Trophic changes identified in postmortem studies include smooth muscle hypertrophy, new vessel formation, increased numbers of epithelial goblet cells, and the deposition of interstitial collagens beneath the epithelium (basement membrane thickening), changes which may arise as the result of injury and may lead to remodelling (Fig.11 and 12).

![Figure 11: Changes leading to remodelling](image)

Thus, there is evidence of both acute and chronic inflammation that is irregularly distributed throughout the airways, including the smallest
airways (less than 2 mm in diameter), and the parenchyma. This wide distribution of inflammation carries implications for delivery of inhaled medications to the appropriate areas of the lung.

**Figure 12: Pathological features of asthma.**

1.2.7.1 Bronchoconstriction

In essence, asthma is the result of an abnormal immune response in the bronchial airways. The airways of asthmatics are "hypersensitive" to certain triggers, also known as stimuli. In response to exposure to these triggers, the bronchi contract into spasm (Fig.13). Inflammation soon follows, leading to a further narrowing of the airways and excessive mucus production, which leads to coughing and other breathing difficulties.
An important component of asthma underlying the instability of the airways is the presence of an exaggerated bronchoconstrictor response to a wide variety of exogenous and endogenous stimuli.

The stimuli often used to reveal the hyperresponsiveness act by highly specific mechanisms (Fig. 14). They may be classified as causing airflow limitation directly by stimulating airway smooth muscle (e.g., methacholine and histamine); indirectly by releasing pharmacologically active substances from mediator-secreting cells, such as mast cells (exercise, hyper- and hypo-osmolar stimuli) or nonmyelinated sensory neurons (sulfur dioxide and bradykinin); or by a combination of both mechanisms (Fig. 11).

**Figure 13: Main asthma triggers.**
1.2.7.1.1 Parasympathetic system.

This system is of major importance in the control of bronchomotor tone. Afferents arise from receptors under the tight junctions of the bronchial epithelium and pass centrally in the vagus. The system responds to a great
number of noxious stimuli, and histamine also acts directly on the parasympathetic afferents in addition to its direct action on airway smooth muscle. Efferent preganglionic fibres also run in the vagus to ganglia located in the walls of the small bronchi. Thence, short postganglionic fibres lead to nerve endings which release acetylcholine to act at muscarinic receptors in the bronchial smooth muscle. Stimulation of any part of the reflex arc results in bronchoconstriction, and some degree of resting tone is normally present. The muscarinic receptors can be stimulated with methacholine and blocked with atropine. The parasympathetic reflex arc plays a major part in the bronchoconstrictor response to inhaled irritants. Its action may be enhanced in a number of pathological states, including loss of bronchial epithelium, but is seldom primarily responsible for conditions of airway hypersensitivity.

1.2.7.1.2 Sympathetic system.

In contrast to the parasympathetic system, the sympathetic system is poorly represented in the lung and not yet proven to be of major importance in man. Indeed it appears unlikely that there is any direct sympathetic innervation of the airway smooth muscle, although there may be an inhibitory effect on cholinergic neurotransmission in some species. Beta-blockers may cause mild bronchoconstriction in healthy subjects, but there may be severe bronchoconstriction in some patients with asthma and bronchitis. In spite of the minimal significance of sympathetic innervation, bronchial smooth muscle has plentiful β₂-adrenergic receptors, which are highly sensitive to adrenaline, a therapeutic standby for almost a century. Adrenaline also inhibits mediator release from mast cells. There are a few α-adrenergic receptors which are bronchoconstrictor but unlikely to be of much clinical significance.

1.2.7.1.3 Non-adrenergic non-cholinergic (NANC) system.

The airways are provided with a third autonomic control, which is neither adrenergic nor cholinergic. This is the only effective bronchodilator nervous pathway in man. The efferent fibres run in the vagus and pass to the smooth muscle of the airway where the neurotransmitters probably
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Include vasoactive intestinal polypeptide (VIP) and peptide histamine methionine (PHM). Stimulation of NANC efferents or administration of VIP will both cause prolonged relaxation of bronchi. There is also a bronchoconstrictor part of the NANC system but its clinical significance is not yet clear.

1.2.7.1.4 Mast cells (type MC₂)

They are plentiful in the wall of airways and alveoli and also lie free in the lumen of the airways where they may be recovered by bronchial lavage. The surface of the mast cell contains a very large number of binding sites for the immunoglobulin IgE. Activation of the cell results from antigen bridging of only a small number of these receptors. The triggering mechanism is thus extremely sensitive. Activation may also be initiated by a wide range of compounds, including the complement fractions C₃a, C₄a and C₅a, substance P, physical stimulation and many drugs and other organic molecules. In many respects basophils behave like mast cells, both in their activation and in the pattern of their response.

The response of the mast cell to activation is probably mediated by an increase in cAMP and intracellular calcium ions. Within 30 seconds of activation, there is degranulation with discharge of a range of preformed mediators. Histamine acts directly on H₁ receptors in the bronchial smooth muscle fibres to cause contraction, and on other H₁ receptors to increase vascular permeability. Histamine also acts on H₂ receptors to increase mucus secretion. In the granules, histamine is associated with heparin, which is probably not released but remains associated with the membrane of the mast cell. The granules also contain proteases, mainly tryptase, which detach epithelium from the basement membrane, resulting in desquamation and possibly activating an axonal reflex causing local release of substance P. Among other constituents are serotonin and chemotactic factors for both neutrophils and eosinophils.

The second major event after mast cell activation is the initiation of synthesis of arachidonic acid derivatives. The most important derivative in the cyclo-oxygenase pathway is prostaglandin PGD₂, which is a
bronchoconstrictor, although its clinical significance is not clear. The lipo-oxygenase pathway results in the formation of LTB₄ and the three sulphidopeptide leukotrienes, LTC₄, LTD₄ and LTE₄, formerly known collectively as slow-reacting substance (SRS-A), until the constituents were identified. The sulphidopeptide leukotrienes cause a slow but sustained contraction of bronchial muscle, which can be inhibited by non-steroidal anti-inflammatory drugs usually abbreviated to NSAIDs (i.e. indomethacin and aspirin).

1.2.7.1.5 Neutrophils and eosinophils.

Mast cell granules contain chemotactic factors for both these cells (NCF and ECF), and this effect is reinforced by histamine. Eosinophils are freely distributed alongside mast cells in the submucosa, and make their own contribution to bronchoconstriction, particularly by releasing leukotrienes. Neutrophils contribute to proteolytic damage and may release oxygen-derived free radicals.

1.2.7.1.6 Bronchial muscle receptors.

Muscarinic and β-adrenergic receptors may have directly competing effects on the activation of the membrane-bound adenylate cyclase and thus the synthesis of cyclic adenosine monophosphate (cAMP), which controls the degree of relaxation of the bronchial smooth muscle (Fig.15). Cyclic AMP is converted to 5’AMP by the enzyme phosphodiesterase, which is inhibited by theophylline, the active component of the well-tried preparation aminophylline. However, inhibition of phosphodiesterase occurs only at concentrations greatly in excess of those at which theophylline is an effective bronchodilator. Mackay, Baldwin and Tattersfield ²³ have presented evidence for believing that theophylline causes bronchodilatation by more than one mechanism, of which catecholamine release is one. In addition, it may block histamine release from the mast cell and it may also affect calcium entry. Furthermore, theophylline probably blocks the bronchoconstrictor effect of adenosine in asthmatics and also appears to drive the diaphragm, even in the long term.
The sensitivity of the smooth muscle receptors to circulating substances and to drugs is probably of greater clinical relevance than their activation by the autonomic nervous system. The $\beta_2$-adrenergic receptors are highly sensitive to adrenaline, salbutamol and isoprenaline but this is prevented by beta-blockers. The muscarinic receptors are sensitive to methacholine and blocked by atropine (Fig.15). The $H_1$ receptor is sensitive to histamine but blocked by a wide range of antihistamines. Serotonin and $\alpha$-adrenergic receptors are also bronchoconstrictor.

**Figure 15: Mechanisms of action of bronchodilators agents.**

Bronchodilation may be caused by administering one of the following types of drugs: (1) an agonist of $\beta_2$-adrenoceptors (e.g., albuterol), which subserve relaxation of airway smooth muscle, (2) an antagonist (e.g., ipratropium), which blocks the muscarinic cholinoreceptor (M)-mediated airway smooth muscle contractile activity of acetylcholine released from cholinergic nerves, (3) an antagonist of cysteinyl leukotriene receptors (cysLT), which blocks airway smooth muscle contractile activity of leukotrienes $C_4$, $D_4$, or $E_4$ (LT) released.
from mast cells, or (4) an inhibitor of phosphodiesterase isoymes 3 (PDE3) and 4 (PDE4), which promotes airway smooth muscle relaxation by increasing intracellular levels of cyclic adenosine 3',5'-monophosphate (cAMP). The interaction between receptor activation, adenyl cyclase, cAMP, intracellular calcium ion concentrations, and the process of contraction are shown. Stimulation is indicated by “+” and inhibition by “-”.

1.2.7.1.7 Physical and chemical factors.
Physical factors capable of stimulating vagal afferents include:
- mechanical stimulation of the upper airway (i.e. laryngoscopy)
- presence of foreign bodies in the trachea.
- Inhalation of cold air is a potent stimulus in the sensitive subject, and can be used as a provocation test.
- Inhalation of particulate matter or even an aerosol of pure water will cause bronchoconstriction.
- An aerosol of histamine produces part of its effect by stimulation of vagal afferents.
Many chemical stimuli result in bronchoconstriction.
- Gases include sulphur dioxide, ozone and nitrogen dioxide.
- Liquids with pH of less than about 2.5 provoke Mendelson’s syndrome, of which bronchoconstriction is a prominent feature in the early stages.
- Even more low PaCO₂ may induce bronchoconstriction called hypocapnic bronchoconstriction.
Nitrous oxide is a bronchodilator as well as an anesthetic gas.
Many drugs may activate the mast cell. This way follows sensitisation of the cell but may also occur when a drug is first administered. Several drugs used by anaesthetists have this effect as a rare though frightening complication. In some cases the drug responsible for the reaction may be identified by skin testing, undertaken with care because this procedure may initiate bronchospasm. Splitting of complement C3 into C3a and C3b may be demonstrated soon after injection and the peripheral leucocyte count may decrease because of margination. The reaction usually
occurs within a minute of administration and there is sometimes transient circulatory failure due to sudden vasodilatation. Alarming though this response may be, the mortality is apparently low.

1.2.7.1.8 **Hyper-reactive airways.**

Asthmatics, some patients with chronic bronchitis and others exhibit exaggerated responses to a wide variety of the factors, which can cause bronchoconstriction. This may be demonstrated with provocation tests using histamine, methacholine or cold air. There is no single cause of the condition and possible factors include a reduction in resting airway calibre, increased sensitivity of the mast cell, loss of bronchial epithelium and an increased responsiveness of the airway smooth muscle. Autonomic imbalance is now considered to be an uncommon cause. Hyper-reactive airways may be considered an essential precursor and feature of asthma.

1.2.7.1.9 **Resting calibre of the airways.**

In the healthy subject, the small airways make only a small contribution to total airway resistance because their aggregate cross-sectional area increases to very large values after about the eighth generation. However, they are the site of most of the important causes of obstruction in a range of pathological conditions, including chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis, asthma and bronchiolitis. These airways have been termed the “quiet zone” because they must undergo a considerable increase in their resistance before the change can be detected by tests of overall airway resistance that, in the healthy subject, is dominated by the resistance of the larger airways. Once their calibre is reduced sufficiently to exert a significant effect on airway resistance, further small changes in calibre have a major effect due to the relationship between flow and fourth or fifth power of the radius (Poiseuille’s law).

1.2.7.2 **The immune response**

When an inhaled antigen becomes trapped in the airways, it is enzymatically degraded into shorter peptides by the antigen-presenting cells
(APCs) such as dendritic cells. APCs express the peptides derived from the antigen on the cell surface, in what is known as the binding groove of the class II major histocompatibility complex (MHC) molecule. Now located on the cell surface, the antigen-MHC complex is presented to T cells, which express a receptor that is specific to the MHC II peptide.

Presented with the antigen-MHC II complex, T helper 0 (T\textsubscript{H}0) cells become activated and start to differentiate into either T helper type 1 (T\textsubscript{H}1) or type 2 (T\textsubscript{H}2) cells. The selective differentiation of T\textsubscript{H}0 cells has profound consequences for the immune system: T\textsubscript{H}1 cell production leads to cell-mediated immunity, while the production of predominantly T\textsubscript{H}2 cells provides humoral immunity. The resulting balance of T\textsubscript{H}1 or T\textsubscript{H}2 cells is a crucial variable in the development of asthma; the dominance of the T\textsubscript{H}2 cell type appears to be necessary for the development of asthma. In one study, mice that lacked the ability to create T\textsubscript{H}1 cells displayed an asthma-like phenotype.

One cytokine secreted by T\textsubscript{H}2 cells—IL-4—combined with the action of other cytokines induces synthesis by antigen-stimulated B cells of IgE, an allergen-specific antibody. IgE binds allergens and then receptors on mast cells, basophils, and eosinophils in the airway epithelium. Subsequent exposure of the same antigen to these cells in the airway epithelium initiates the acute-phase reaction of asthma. Stimulated mast cells in the airway release preformed granules of mediators such as histamine, eicosanoids, and cytokines. These molecules are responsible for the symptoms of asthma. They affect the mucosa of the airways, increasing mucosal edema, and mucus production, smooth muscle constriction, and recruit other immune cells, thereby exacerbating the reaction.

The late phase of an asthmatic reaction is characterized by an influx of inflammatory and immune cells during the first several hours after antigen exposure (Fig.16). These cells—particularly eosinophils—secrete a series of cytokines, leukotrienes, and polypeptides, which contribute to the development of asthma.
hyperresponsiveness, mucus secretion, bronchoconstriction, and sustained inflammation.

Figure 16: Inflammatory and immune responses after antigen exposure.

1.2.8 Pathogenesis

The fundamental problem in asthma appears to be immunological: young children in the early stages of asthma show signs of excessive inflammation in their airways. Epidemiological findings give clues as to the pathogenesis: the incidence of asthma seems to be increasing worldwide, and asthma is now very much more common in affluent countries.

One theory of pathogenesis is that asthma is a disease of hygiene. In nature, babies are exposed to bacteria and other antigens soon after birth, "switching on" the T\textsubscript{H}1 lymphocyte cells of the immune system that deal with bacterial infection. If this stimulus is insufficient—as it may be in modern, clean environments—then T\textsubscript{H}2 cells predominate, and asthma and other allergic diseases may develop. This "hygiene hypothesis" may explain the increase in asthma in affluent populations. The T\textsubscript{H}2 lymphocytes and eosinophil cells that protect us against parasites and other infectious agents...
are the same cells responsible for the allergic reaction. In the developed world, these parasites are now rarely encountered, but the immune response remains and is wrongly triggered in some individuals by certain allergens.

The trigger for the development of airway inflammation cannot always be identified. It is well recognized in some instances, as in the case for some antigens in allergic asthmatics. However, in other types of asthma, such as exercise-induced asthma and asthma following a viral respiratory tract infection, the trigger is not recognized.

Another theory is based on the correlation of air pollution and the incidence of asthma. Atmospheric pollutants, especially submicronic particles in automobile exhaust gases, may also play a role. Although it is well known that substantial exposures to certain industrial chemicals can cause acute asthmatic episodes, it has not been proved that air pollution is responsible for the development of asthma. In Western Europe, most atmospheric pollutants have fallen significantly over the last 40 years, while the prevalence of asthma has risen.

Asthma also has a genetic component. Population studies show that it is a complex genetic disorder with both environmental and genetic components. The latter is not a single gene trait but is polygenic. Associations of asthma with a variety of chromosomal loci through linkage analysis have been demonstrated.

1.2.9 Treatment

The most effective treatment for asthma is identifying triggers, such as allergens (pets...) or drugs (aspirin...), and limiting or eliminating exposure to them. Desensitization may be attempted, but is effective only in allergic patients sensitized to few allergens. As is common with respiratory disease, smoking adversely affects asthmatics in several ways, including an increased severity of symptoms, a more rapid decline of lung function, and decreased response to preventive medications. Asthmatics who smoke...
typically require additional medications to help control their disease. Furthermore, exposure of both nonsmokers and smokers to secondhand smoke is detrimental, resulting in more severe asthma, more emergency room visits, and more asthma-related hospital admissions\textsuperscript{26}. Smoking cessation and avoidance of those who smoke is strongly encouraged in asthmatics\textsuperscript{27,28}.

The specific medical treatment recommended to patients with asthma depends on the severity of their illness and the frequency of their symptoms. Specific treatments for asthma are broadly classified as relievers, preventers and emergency treatment. The Expert panel report 3: Guidelines for the diagnosis and management of asthma (EPR-2)\textsuperscript{29} of the U.S. National Asthma Education and Prevention Program, and the British guideline on the management of asthma are broadly used and supported by many doctors. Bronchodilators are recommended for short-term relief in all patients. For those who experience occasional attacks, no other medication is needed. For those with mild persistent disease (more than two attacks a week), low-dose inhaled glucocorticoids—or alternatively, an oral leukotriene modifier, a mast-cell stabilizer, or theophylline—may be administered. For those who suffer daily attacks, a higher dose of glucocorticoid in conjunction with a long-acting inhaled β-2 agonist may be prescribed; alternatively, a leukotriene modifier or theophylline may substitute for the β-2 agonist. In severe asthmatics, oral glucocorticoids may be added to these treatments during severe attacks\textsuperscript{3}.

For those in whom exercise can trigger an asthma attack (exercise-induced asthma), higher levels of ventilation and cold, dry air tend to exacerbate attacks. For this reason, activities in which a patient breathes large amounts of cold air, such as cross-country skiing, tend to be worse for asthmatics, whereas swimming in an indoor, heated pool, with warm, humid air, is less likely to provoke a response\textsuperscript{3}.

\subsection{Relief medication}

Symptomatic control of episodes of wheezing and shortness of breath is generally achieved with fast-acting bronchodilators. These are
typically provided in pocket-sized, metered-dose inhalers (MDIs). In young sufferers, who may have difficulty with the coordination necessary to use inhalers, or those with a poor ability to hold their breath for 10 seconds after inhaler use (generally the elderly), an asthma spacer is used. The spacer is a plastic cylinder that mixes the medication with air in a simple tube, making it easier for patients to receive a full dose of the drug and allows for the active agent to be dispersed into smaller, more fully inhaled bits. A nebulizer—which provides a larger, continuous dose—can also be used. Nebulizers work by vapourizing a dose of medication in a saline solution into a steady stream of foggy vapor, which the patient inhales continuously until the full dosage is administered. There is no clear evidence, however, that they are more effective than inhalers used with a spacer. Nebulizers may be helpful to some patients experiencing a severe attack. Such patients may not be able to inhale deeply, so regular inhalers may not deliver medication deeply into the lungs, even on repeated attempts. Since a nebulizer delivers the medication continuously, it is thought that the first few inhalations may relax the airways enough to allow the following inhalations to draw in more medication.

Relievers include:

- Short-acting, selective beta₂-adrenoceptor agonists (salbutamol [albuterol], levalbuterol, terbutaline, bitolterol, pirbuterol, procaterol, fenoterol, bitolterol, reproterol). Tremors, the major side effect, have been greatly reduced by inhaled delivery, which allows the drug to target the lungs specifically; oral and injected medications are delivered throughout the body. There may also be cardiac side effects at higher doses, such as elevated heart rate or blood pressure; with the advent of selective agents, these side effects have become less common. Patients must be cautioned against using these medicines too frequently, as with such use their efficacy may decline, resulting in an exacerbation of symptoms which may lead to refractory asthma and death.
Older, less selective adrenergic agonists, such as inhaled epinephrine and ephedrine tablets are available. Cardiac side effects, although uncommon, occurred more often with the less selective drugs. They also have the disadvantage of providing a shorter period of relief than the selective bronchodilators. Nowadays, they are usually avoided in patients with heart disease. In emergencies, these drugs were sometimes administered by injection in severe attacks. Their use in this situation has declined.

Anticholinergic medications, such as ipratropium bromide may be used instead. They have no cardiac side effects and thus can be used in patients with heart disease; however, they take up to an hour to achieve their full effect and are not as powerful as the $\beta_2$-adrenoreceptor agonists.

### 1.2.9.2 Prevention medication

Current treatment protocols recommend prevention medications such as an inhaled corticosteroid, which helps to suppress inflammation and reduces the swelling of the lining of the airways, in anyone who has frequent (greater than twice a week) need of relievers or who has severe symptoms. If symptoms persist, additional preventive drugs are added until the asthma is controlled. With the proper use of prevention drugs, asthmatics can avoid the complications that result from overuse of relief medications.

Asthmatics sometimes stop taking their preventative medication when they feel fine and have no problems breathing. This often results in further attacks, and no long-term improvement. Preventive agents include the following.

- Inhaled glucocorticoids.
- Antimuscarinics/anticholinergics (ipratropium), which have a mixed reliever and preventer effect. They are rarely used in asthma.
- Leukotriene modifiers (montelukast, zafirlukast).
- Mast cell stabilizers (cromoglicate).
• Methylxanthines (theophylline and aminophylline), which are sometimes considered if sufficient control cannot be achieved with inhaled glucocorticoids and long-acting β-agonists alone.
• Antihistamines, often used to treat allergic symptoms that may underlie the chronic inflammation. In more severe cases, hyposensitization ("allergy shots") may be recommended.
• Omalizumab, an IgE blocker; this can help patients with severe allergic asthma that does not respond to other drugs. However, it is expensive and must be injected.
• Methotrexate is occasionally used in some difficult-to-treat patients.
• If chronic acid indigestion (GERD) contributes to a patient's asthma, it should also be treated, because it may confound the respiratory problem.

1.2.9.3 Long-acting β₂-agonists

Long-acting bronchodilators (LABD) give a 12-hour effect, and are used to give a smoothed symptomatic effect (used morning and night). While patients report improved symptom control, these drugs do not replace the need for routine preventers, and their slow onset means the short-acting dilators may still be required.

Combinations of inhaled steroids and long-acting bronchodilators are becoming more widespread. Recently, Bateman et al.\(^{30}\) in a meta-analysis showed that salmeterol combined with inhaled corticosteroids decreases the risk for severe exacerbations, does not seem to alter the risk for asthma related hospitalizations, and may not alter the risk for asthma-related deaths or intubations compared with inhaled corticosteroids alone. The most common combination currently in use is fluticasone/salmeterol.

Currently available long-acting beta₂-adrenoceptor agonists include salmeterol, formoterol, and sustained-release oral albuterol. But a recent Cochrane meta-analysis\(^{31}\) founded an increased risk of serious adverse events with regular salmeterol used alone, risks which are not clearly
abolished by inhaled corticosteroids. Therefore regular salmeterol should be discontinued if no symptomatic benefit is achieved.

1.2.9.4 Emergency treatment

When an asthma attack is unresponsive to a patient's usual medication, other treatments are available to the physician or hospital:

- oxygen to alleviate the hypoxia (but not the asthma *per se*) that results from asthma attacks;
- nebulized salbutamol (2.5-5 mg), usually three in rapid succession ("back-to-back") or continuous nebulization;
- systemic steroids, oral or intravenous (prednisone, prednisolone, methylprednisolone, dexamethasone, or hydrocortisone);
- other bronchodilators that are occasionally effective when the usual drugs fail:
  - nonspecific beta-agonists, injected or inhaled (epinephrine, isoproterenol);
  - anticholinergics, IV or nebulized, with systemic effects (glycopyrrolate, atropine);
  - methylxanthines (theophylline, aminophylline);
  - inhalation anesthetics that have a bronchodilatory effect (isoflurane, halothane, sevoflurane, desflurane);
  - the dissociative anesthetic ketamine, often used in endotracheal tube induction
  - magnesium sulfate, intravenous
- intubation and mechanical ventilation, for patients in or approaching respiratory arrest.

The severity of asthma exacerbations may range from mild to life threatening. Deterioration usually progresses over hours or days, but may occasionally occur precipitously over some minutes. Acute exacerbations usually reflect exposure to a trigger, most often a viral infection or an allergen, but an exacerbation with a more gradual pattern of deterioration
may reflect failure of long-term management. Morbidity and mortality are most often associated with failure to recognize the severity of the exacerbation, inadequate action at its onset, and undertreatment of it. The aims of treatment are to relieve airflow obstruction and hypoxemia as quickly as possible, and to plan the prevention of future relapses. Crucial to successful treatment is close monitoring of the patient's condition and response to treatment with serial measurements of lung function. Assessment of the patient's pulse, respiratory rate, and current symptoms also guides treatment decisions, but measurements of lung function and oximetry are critical.

- Treatment of exacerbations depends on the patient, experience of the health care professional, therapies that are most effective for the particular patient, availability of medications, and emergency facilities.
- Primary therapies for exacerbations are the repetitive administration of rapid-acting inhaled \( \beta_2 \)-agonist, the early introduction of systemic glucocorticosteroids, and oxygen supplementation.
- Crucial to successful treatment of exacerbations is close monitoring of the patient's condition and response to treatment with serial measurements of lung function.
- Severe exacerbations of asthma are lifethreatening medical emergencies.

### 1.3 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\(^{33}\).

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Chronic inflammation causes remodeling and narrowing of the small airways. Destruction of the lung parenchyma, also by inflammatory
processes, leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration. Airflow limitation is measured by spirometry, as this is the most widely available, reproducible test of lung function (Table 1).

COPD has a variable natural history and not all individuals follow the same course. However, COPD is generally a progressive disease, especially if a patient's exposure to noxious agents continues. If exposure is stopped, the disease may still progress due to the decline in lung function that normally occurs with aging. Nevertheless, stopping exposure to noxious agents, even after significant airflow limitation is present, can result in some improvement in function and will certainly slow or even halt the progression of the disease.

Table 1: Spirometric classification of COPD severity based on postbronchodilator FEV1

<table>
<thead>
<tr>
<th>Stage I: Mild</th>
<th>FEV₁/FVC &lt; 0.70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV₁ ≥ 80% predicted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage II: Moderate</th>
<th>FEV₁/FVC &lt; 0.70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage III: Severe</th>
<th>FEV₁/FVC &lt; 0.70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage IV: Very Severe</th>
<th>FEV₁/FVC &lt; 0.70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV₁ &lt; 30% predicted or FEV₁ &lt; 50% predicted plus chronic respiratory failure</td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO₂) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO₂ (PaCO₂) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.33
1 – Obstructive airway diseases

1.3.1 Differences with asthma

Although inflammation is important in both diseases, the inflammatory response in COPD is markedly different from that in asthma.

Asthma and COPD have their major symptoms in common, but these are generally more variable in asthma than in COPD. The underlying chronic airway inflammation is also very different (Table 2): that in asthma is mainly eosinophilic and driven by CD4+ T lymphocytes, while that in COPD is neutrophilic and characterized by the presence of increased numbers of macrophages and CD8+ T lymphocytes. In addition, airflow limitation in asthma is often completely reversible, either spontaneously or with treatment, while in COPD it is never fully reversible and is usually progressive if exposure to noxious agents continues. Finally, the responses to treatment of asthma and COPD are dramatically different, in terms of both the overall magnitude of the achievable response and the qualitative effects of specific treatments such as anticholinergics and glucocorticosteroids. However, there is undoubtedly an overlap between asthma and COPD.

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells</td>
<td>Neutrophils</td>
<td>Eosinophils</td>
</tr>
<tr>
<td></td>
<td>Large increase in macrophages</td>
<td>Small increase in macrophages</td>
</tr>
<tr>
<td></td>
<td>Increase in CD8+ T lymphocytes</td>
<td>Increase in CD4+ T lymphocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activation of mast cells</td>
</tr>
<tr>
<td>Mediators</td>
<td>LTB4</td>
<td>LTD4</td>
</tr>
<tr>
<td></td>
<td>IL-8</td>
<td>L-4, IL-5</td>
</tr>
<tr>
<td></td>
<td>TNFalpha</td>
<td>(Plus many others)</td>
</tr>
<tr>
<td>Consequences</td>
<td>Squamous metaplasia of epithelium</td>
<td>Frabil epithelium</td>
</tr>
<tr>
<td></td>
<td>Paranchymal destruction</td>
<td>Thickening of basalemea membrane</td>
</tr>
<tr>
<td></td>
<td>Mucus metaplasia</td>
<td>Mucous metaplasia</td>
</tr>
<tr>
<td></td>
<td>Glandular enlargement</td>
<td>Glandular enlargement</td>
</tr>
<tr>
<td>Responses to Treatment</td>
<td>Glucocorticosteroids have little or no effect</td>
<td>Glucocorticosteroids inhibit inflammation</td>
</tr>
</tbody>
</table>

Table 2: Characteristics of inflammation in COPD and asthma.

Since inflammation is a feature of COPD, it follows that anti-inflammatory therapies may have clinical benefit in controlling symptoms, preventing exacerbations, and slowing the progression of the disease.
1 – Obstructive airway diseases

However, the inflammatory response in COPD appears to be poorly responsive to the glucocorticosteroids that are effective anti-inflammatory medications in asthma.

1.3.2 Risk factors

In addition to inflammation, two other processes thought to be important in the pathogenesis of COPD are an imbalance of proteinases and antiproteinases in the lung, and oxidative stress.

The best-documented host factor is a severe hereditary deficiency of alpha-1 antitrypsin. The major environmental factors are tobacco smoke, occupational dusts and chemicals (vapors, irritants, fumes), and indoor and outdoor air pollution. However, it is very difficult to demonstrate that a given risk factor is sufficient to cause the disease.

Exposure to inhaled noxious particles and gases causes inflammation of the lungs that can lead to COPD if the normal protective and/or repair mechanisms are overwhelmed or defective.

Exacerbations of COPD are associated with an increase in airway inflammation.

1.3.3 Pathology

Pathological changes characteristic of COPD are found in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature. The peripheral airways become the major site of airways obstruction in COPD. The structural changes in the airway wall are the most important cause of the increase in peripheral airways resistance in COPD. Inflammatory changes such as airway edema and mucus hypersecretion also contribute to airway narrowing.

Most common in COPD patients is the centrilobular form of emphysema, which involves dilatation and destruction of the respiratory bronchioles.

Physiological changes characteristic of the disease include mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and
cor pulmonale, and they usually develop in this order over the course of the disease.

The irreversible component of airflow limitation is primarily due to remodeling of the small airways. Parenchymal destruction (emphysema) also contributes but plays a smaller role.

In advanced COPD, peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, producing hypoxemia and, later on, hypercapnia. Inequality in the ventilation/perfusion ratio (VA/Q) is the major mechanism behind hypoxemia in COPD (Fig.17).
Figure 17: Typical patterns of ventilation-perfusion ratios in patients with COPD. 
Upper panel: Pattern typical of patients with type A presentation (hyperinflation, well-preserved blood gases, and evidence of pathological emphysema). Lower panel: Pattern typical of a patient with type B presentation (chronic bronchitis). The type A patient usually shows areas of abnormally high ventilation-perfusion ratio. As in this example, right-to-left shunts are minimal. The type B patient, on the other hand, commonly has areas of abnormally low ventilation-perfusion ratio as shown, but, again, generally no shunting.

Pulmonary hypertension develops late in the course of COPD. It is the major cardiovascular complication of COPD and is associated with a poor prognosis.

COPD is associated with systemic inflammation and skeletal muscle dysfunction that may contribute to limitation of exercise capacity and decline of health status.

1.3.3.1 Central airways

The central airways include the trachea, bronchi, and bronchioles greater than 2-4 mm in internal diameter. In patients with chronic bronchitis,
an inflammatory exudate of fluid and cells infiltrates the epithelium lining the central airways and associated glands and ducts \(^{34,35}\). The predominant cells in this inflammatory exudate are macrophages and CD8+ T lymphocytes \(^{36,37}\). Chronic inflammation in the central airways is also associated with an increase in the number (metaplasia) of epithelial goblet and squamous cells; dysfunction, damage, and/or loss of cilia; enlarged submucosal mucus-secreting glands \(^{38}\); an increase in the amount of smooth muscle and connective tissue in the airway wall \(^{38}\); degeneration of the airway cartilage \(^{39}\); and mucus hypersecretion. The mechanisms of mucus gland hypertrophy and goblet cell metaplasia have not yet been identified, but animal studies \(^{40,41}\) show that irritants including cigarette smoke \(^{42}\) can produce these changes. The various pathological changes in the central airways are responsible for the symptoms of chronic cough and sputum production, which identify people at risk for COPD and may continue to be present throughout the course of the disease. Thus, these pathological changes may be present either on their own or in combination with the changes in the peripheral airways and lung parenchyma described below.

### 1.3.3.2 Peripheral Airways

The peripheral airways include small bronchi and bronchioles that have an internal diameter of less than 2 mm. The early decline in lung function in COPD is correlated with inflammatory changes in the peripheral airways, similar to those that occur in the central airways: exudate of fluid and cells in the airway wall and lumen, goblet and squamous cell metaplasia of the epithelium \(^{43}\), edema of the airway mucosa due to inflammation, and excess mucus in the airways due to goblet cell metaplasia.

However, the most characteristic change in the peripheral airways of patients with COPD is airway narrowing. Inflammation initiated by cigarette smoking \(^{44}\) and other risk factors \(^{45}\) leads to repeated cycles of injury and repair of the walls of the peripheral airways. Injury is caused either directly by inhaled toxic particles and gases such as those found in cigarette smoke, or indirectly by the action of inflammatory mediators; this injury then initiates repair processes. Although airway repair is only partly understood, it seems...
likely that disordered repair processes can lead to tissue remodeling with altered structure and function.

1.3.3.3 Lung Parenchyma

The lung parenchyma includes the gas-exchanging surface of the lung (respiratory bronchioles and alveoli) and the pulmonary capillary system. The most common type of parenchymal destruction in COPD patients is the centrilobular form of emphysema, which involves dilatation and destruction of the respiratory bronchioles. These lesions occur more frequently in the upper lung regions in milder cases, but in advanced disease they may appear diffusely throughout the entire lung and also involve destruction of the pulmonary capillary bed. Panacinar emphysema, which extends throughout the acinus, is the characteristic lesion seen in alpha-1 antitrypsin deficiency and involves dilatation and destruction of the alveolar ducts and sacs as well as the respiratory bronchioles. It tends to affect the lower more than upper lung regions. Because this process usually affects all of the acini in the secondary lobule, it is also referred to as panlobular emphysema. The primary mechanism of lung parenchyma destruction, in both smoking-related COPD and alpha-1 antitrypsin deficiency, is thought to be an imbalance of endogenous proteinases and antiproteinases in the lung. Oxidative stress, another consequence of inflammation, may also contribute.

1.3.3.4 Pulmonary Vasculature

Pulmonary vascular changes in COPD are characterized by a thickening of the vessel wall that begins early in the natural history of the disease, when lung function is reasonably well maintained and pulmonary vascular pressures are normal at rest. In patients with emphysema, the destruction of alveolar walls results in a reduction of the capillary bed, increasing vascular resistance.
1.3.4 Pathophysiology

Physiological changes characteristic of the disease include mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale, and they usually develop in this order over the course of the disease.

1.3.4.1 Mucus Hypersecretion and Ciliary Dysfunction

Mucus hypersecretion in COPD is caused by the stimulation of the enlarged mucus secreting glands and increased number of goblet cells by inflammatory mediators such as leukotrienes, proteinases, and neuropeptides. Ciliated epithelial cells undergo squamous metaplasia leading to impairment in mucociliary clearance mechanisms. These changes are usually the first physiological abnormalities to develop in COPD, and can be present for many years before any other physiological abnormalities develop.

1.3.4.2 Airflow Limitation and Pulmonary Hyperinflation

Expiratory airflow limitation is the hallmark physiological change of COPD. The airflow limitation characteristic of COPD is primarily irreversible, with a small reversible component. Several pathological characteristics contribute to airflow limitation and changes in pulmonary mechanics, as summarized in Table 3. The irreversible component of airflow limitation is primarily due to remodelling – fibrosis and narrowing – of the small airways that produces fixed airways obstruction and also to the loss of the elastic support with alveolar destruction, and a consequent increase in airways resistance. The sites of airflow limitation in COPD are the smaller conducting airways, including bronchi and bronchioles less than 2 mm in internal diameter. These initial changes progress to the larger bronchi when the disease worsens. In the normal lung, resistance of these smaller airways makes up a small percentage of the total airways resistance.
Obstructive airway diseases

Table 3: Causes of airflow limitations in COPD

<table>
<thead>
<tr>
<th>Irreversible</th>
<th>Reversible</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fibrosis and narrowing of airways</td>
<td>- Accumulation of inflammatory cells, mucus, and plasma exudate in bronchi</td>
</tr>
<tr>
<td>- Loss of elastic recoil due to alveolar destruction</td>
<td>- Smooth muscle contraction in peripheral and central airways</td>
</tr>
<tr>
<td>- Destruction of alveolar support that maintains patency of small airways</td>
<td>- Dynamic hyperinflation during exercise</td>
</tr>
</tbody>
</table>

Airway smooth muscle contraction, ongoing airway inflammation, and intraluminal accumulation of mucus and plasma exudate may be responsible for the small part of airflow limitation that is reversible with treatment. Inflammation and accumulation of mucus and exudates may be particularly important during exacerbations. The progressive course of COPD is complicated by exacerbations that have many causes and occur with increasing frequency as the disease progresses.

Small-airway narrowing (with or without chronic bronchitis) and emphysema caused by smoking are the common conditions resulting in COPD. Chronic bronchitis is daily sputum production for at least three months of two or more consecutive years. Emphysema is a pathological diagnosis, and consists of alveolar dilatation and destruction. Breathlessness with exertion, chest tightness and wheeze are the results of airway narrowing and impaired gas exchange. The loss of lung elastic tissue in emphysema may result in airway wall collapse during expiration, leading to dynamic hyperinflation and consequent increased work of breathing.

The irreversible component of airflow limitation is the end result of inflammation, fibrosis and remodelling of peripheral airways. Airflow limitation leads to non-homogeneous ventilation, while alveolar wall destruction and changes in pulmonary vessels reduce the surface area
available for gas exchange. In advanced COPD there is a severe mismatching of ventilation and perfusion leading to hypoxemia. Hypercapnia is a late manifestation and is caused by a reduction in ventilatory drive. Pulmonary hypertension and cor pulmonale are also late manifestations, and reflect pulmonary vasoconstriction due to hypoxia in poorly ventilated lung, vasoconstrictor peptides produced by inflammatory cells and vascular remodelling. The clinical features and pathophysiology of COPD can overlap with asthma, as most COPD patients have some reversibility of airflow limitation with bronchodilators. By contrast, some non-smokers with chronic asthma develop irreversible airway narrowing. The overlap between chronic bronchitis, emphysema and asthma and their relationship to airflow obstruction and COPD are illustrated in Figure 18. Patients with chronic bronchiolitis, bronchiectasis and cystic fibrosis may also present with similar symptoms and partially reversible airflow limitation.

Figure 18: Non-proportional Venn diagram showing the overlap of chronic bronchitis, emphysema and asthma within COPD. Chronic bronchitis, airway narrowing and emphysema are independent effects of cigarette smoking, and may occur in various combinations. Asthma is, by definition, associated with reversible airflow obstruction. Patients with asthma...
1 – Obstructive airway diseases

whose airflow obstruction is completely reversible do not have COPD. In many cases it is impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity.

1.3.4.3 Gas Exchange Abnormalities

In advanced COPD, peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, producing hypoxemia and, later on, hypercapnia. The correlation between routine lung function tests and arterial blood gases is poor, but significant hypoxemia or hypercapnia is rare when FEV1 is greater than 1.00 L54.

Hypoxemia is initially only present during exercise, but as the disease continues to progress it is also present at rest.

Inequality in the ventilation/perfusion ratio (VA/Q) is the major mechanism behind hypoxemia in COPD, regardless of the stage of the disease 55. In the peripheral airways, injury of the airway wall is associated with VA/Q mismatching, as indicated by a significant correlation between bronchiolar inflammation and the distribution of ventilation. In the parenchyma, destruction of the lung surface area by emphysema reduces diffusing capacity and interferes with gas exchange 56. High VA/Q units probably represent emphysematous regions with alveolar destruction and loss of pulmonary vasculature (Fig.17).

1.3.4.4 Pulmonary Hypertension and Cor Pulmonale

Pulmonary hypertension develops late in the course of COPD (Stage IV: Very Severe COPD), usually after the development of severe hypoxemia (PaO2 < 8.0 kPa or 60 mm Hg) and often hypercapnia as well. It is the major cardiovascular complication of COPD and is associated with the development of cor pulmonale and with a poor prognosis 57.

Factors that are known to contribute to the development of pulmonary hypertension in patients with COPD include pulmonary hypoxic vasoconstriction; remodeling of pulmonary arteries, which thickens the
vessel walls and reduces the lumen; and destruction of the pulmonary capillary bed by emphysema, which further increases the pressure required to perfuse the pulmonary vascular bed.

Pulmonary hypertension is associated with the development of cor pulmonale, defined as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart, as in congenital heart disease."

1.3.4.5 Systemic Effects

COPD is associated with systemic (i.e., extrapulmonary) effects, such as systemic inflammation and skeletal muscle dysfunction. Evidence of systemic inflammation includes the presence of systemic oxidative stress, abnormal concentrations of circulating cytokines, and activation of inflammatory cells. Evidence of skeletal muscle dysfunction includes the progressive loss of skeletal muscle mass and the presence of several bioenergetic abnormalities. These systemic effects have important clinical consequences, as they contribute to the limitation of patients’ exercise capacity and thus the decline of health status in COPD.
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1 – Obstructive airway diseases


2 - Respiratory mechanics

I will attempt here to give a summary of respiratory mechanics and how to measure them. These measurements were necessary to demonstrate the efficiency and the reproducibility of our animal model of induced bronchospasm and to allow studying the physical properties of helium and its impact on respiratory mechanics.

The contraction of the diaphragm muscles causes a pressure variation, which is equal to the sum of pressures caused by elastic \((P_e)\), resistive \((P_r)\) and inertial \((P_i)\) components of the respiratory system. Where \(P_e\) equals the product of elastance \(E\) (inverse of compliance) and volume of the system \(V\), \(P_r\) equals the product of flow resistance \(R\) and time derivate of volume \(V\) (which is equivalent to the flow), \(P_i\) equals the product of inertance \(I\) and second time derivate of \(V\). \(R\) and \(I\) are sometimes referred to as Rohrer's constants.

\[
PTP = E \cdot V + R \cdot V' + I \cdot V''
\]

2.1 Devices for measuring pressures

The balloon catheter system is the most widely used method for recording esophageal pressure \((P_{es})\) as a reflection of pleural pressure \((P_{pl})\), and gastric pressure \((P_{ga})\) as a reflection of abdominal pressure \((P_{ab})\) \(^1\). (Table 4 and Fig. 19). Air-containing latex balloons are sealed over catheters, which in turn transmit pressures to the transducers. When choosing or preparing a balloon catheter system, careful attention must be given to its physical characteristics. Indeed, the volume of the balloon, its volume-pressure characteristics, and the dimensions of the catheter can influence the measurement of pressure and introduce major errors. Standardization has been proposed \(^2\).

For the measurement of \(P_{es}\), good results have been provided by latex balloons 5-10 cm long, 3.5-5 cm in perimeter, and with a thin wall \(^3\). For
accurate transmission of pressure, air should be introduced into the balloon until it is fully distended to smooth out folds, and then most of the air removed so that a volume is retained at which the rubber is unstretched without distending the esophagus significantly. A volume of 0.5 ml is adequate for balloons with these characteristics. If high positive pressures are to be measured, a volume of 0.5 ml may be inadequate. Balloons volumes should be checked repeatedly during measurements. For the measurement of Pga, balloon volume is less crucial and measurements can be made with a balloon volume of 1-2 ml. If studies of relatively long duration are planed, the walls of the gastric balloon should be thicker than those of esophageal balloons to increase resilience to gastric secretions.

Polyethylene catheters with an internal diameter 1.4-1.7 mm and 70-100 cm in length provide, when associated with adequate transducers, an appropriate frequency response.

**Pressures at a location**
- Pao = airway opening pressure
- Palv = alveolar pressure
- Ppl = pleural pressure
- Pab = abdominal pressure
- Pbs = body surface pressure

**Pressure differences across structures**
- Pel = elastic recoil pressure of the lung (pressure across lung tissue)
- Ptp = transpulmonary pressure (also Pₜₚ)
- Prc = pressure across the rib cage
- Paw = flow resistive pressure in airways
- Pcw = pressure across the chest wall
- Pdi = transdiaphragmatic pressure
- Prs = transrespiratory system pressure
- Pabw = transabdominal wall pressure
- Peq = pressure across the equipment
Relationships among pressures

\[
\begin{align*}
\text{Paw} &= \text{Pao} - \text{Palv} \\
\text{Pel}(L) &= \text{Palv} - \text{Ppl} \\
\text{Prc} &= \text{Ppl} - \text{Pbs} \\
\text{Pdi} &= \text{Ppl} - \text{Pab} \\
\text{Pabw} &= \text{Pab} - \text{Pbs} \\
\text{Ptp} &= \text{Pao} - \text{Ppl} \\
\text{Pcw} &= \text{Ppl} - \text{Pbs} \\
\text{Prs} &= \text{Pao} - \text{Pbs} = -\text{Peq}
\end{align*}
\]

**Table 4** Pressures for basic respiratory mechanics

**Figure 19:** Locations at which pressures can be measured, and pressure differences from them. 
AbW = abdominal wall; aw = airway; Di = diaphragm; Eq = equipment; Lt = lung tissue; Pab = abdominal pressure; Palv = alveolar pressure; Pao = pressure at airway opening; Pbs = body surface pressure; Ppl = pleural pressure; rc = rib cage.

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2.2 Measurement of ventilation

Ventilation is the amount of gas exchanged between the lungs and the environment.

The devices usually used to measure ventilation are spirometers. The classic water-sealed spirometers are too cumbersome for the purpose of our study. We used 3 different devices to measure the ventilation: the spirometer of the mechanical ventilator, a Fleisch pneumotachograph and a gasometer. These 3 devices helped us to control the quality of the measurements because volume and flow measurements can be subject to artefacts.

Temperature, humidity, pressure, viscosity, and density all affect the recording of gas volume, and thus of ventilation (volume per unit time).

To measure the volume (Fig.20) or ventilation inside the lung, it is necessary either to maintain the expired gas at body temperature and 100% water saturation until its volume has been measured, or to correct the volume that was measured at ambient temperature and humidity back to body temperature and saturated with water vapour. This is achieved by using the BTPS factor (Body Temperature Pressure Saturated) \(^6\).

\[
V_{\text{BTPS}} = V_{\text{ATPS}} \times \frac{(P_{\text{atm}} - P_{\text{H2O}})}{(P_{\text{atm}} - 47)} \times \frac{273 + 37}{273 + T^\circ}
\]

Where \(P_{\text{atm}}\) is the atmospheric pressure, \(P_{\text{H2O}}\) is the water vapour pressure at ambient temperature, \(T\) is the ambient temperature expressed in °Celsius, 47 is the water vapour pressure in mmHg at standard body temperature (37°C).

The effect of an increase in airway pressure is the compression of gas that takes place in the ventilator, tubing, and any humidifier and CO\(_2\) absorber that may be in the respiratory circuit. Using Boyle’s law, it can be seen that, 1 ml of gas will be compressed per litre of gas in the system per centimetre H\(_2\)O pressure increase. The pressure that counts is the end inspiratory pressure, because it determines how much is compressed in the ventilatory system when expiration is to start. There will be no
underestimation if ventilation is measured in the expiratory tubing, because flow or volume is measured after pressure release to atmospheric pressure.

**Figure 20: Neoprene balloon and gasometer.**
*In our studies, minute ventilation was measured by filling a neoprene balloon connected to the expiratory port of the ventilator for 2 minutes and measuring the volume of the gas with a dry gasometer after correction for the BTPS.*

If a PEEP device has been applied after the flow/volume meter, it will cause an underestimation of expired ventilation in proportion to the PEEP level. Another approach is to measure ventilation near the patient, for example, using a pneumotachograph at the tracheal tube. If ventilation is measured by gas flowmeter, it must have been calibrated for specific gases. This can be appreciated by looking at Poiseuille’s law which can be applied to laminar gas flow:

\[ P = V \times \left( \frac{8 \times \eta \times l}{\pi \times r^4} \right) \]

Where \( P \) = driving pressure for gas flow, \( V \) = gas flow, \( \eta \) = viscosity of gas, \( l \) = length of airway, \( r \) = airway radius. This is the reason why we calibrated our devices twice: with air and with the helium-oxygen mixture. The pneumotachograph measures the flow, and the volume is obtained by integration of flow by time, which is an additional cause of error. To avoid
this, all the devices were calibrated before and after the measurements, and cross-checks were performed.

2.3 Compliance

2.3.1 Recording pressure

The compliance of the lung is the slope of the volume/pressure relationship of the lung. Different methods of measurement exist, but in mechanically ventilated subjects, lung compliance (Clung) is simply the difference in lung volume between two respiratory levels, divided by the pressure difference needed to keep the lung at these two levels:

\[ \text{Clung} = \frac{\Delta V}{\Delta P_{\text{tp}}} \]

The pressure that keeps the lung expanded at a certain volume is the transpulmonary pressure (Ptp), which is pleural pressure (Ppl) minus alveolar pressure (Palv). With no flow and an unobstructed airway, the alveolar and mouth pressures are equal, so that the pressure measured at the airway opening can be used for measuring compliance. Volume may be measured with a spirometer, a body plethysmograph or by integration of a pneumotachogram. Point zero air flow are best indicated by a pneumotachogram (the tracing of flow vs. time). Static pressures can be measured with a simple water manometer but electrical transducers are more usual today.

The pleural pressure (Ppl) can be substituted by esophageal pressure (Pes), which is measured via a catheter with a balloon threaded over its tip. The catheter is positioned in the lower third of the esophagus (about 45 cm in our pigs). The best way of doing this is to let the catheter be swallowed down to the stomach (about 60 cm in our pigs). On arrival at the stomach, it can be easily detected because the pressure swing is now positive during an inspiration. On withdrawal, the pressure becomes negative when the balloon has been pulled up as far as the esophagus. The catheter is pulled out for another 5 cm, to ensure that it is positioned in the esophagus. The balloon is emptied and then reinflated with about 0.5-1.0 ml air. This volume should have been tested in advance to ensure that it does
not cause any internal pressure in the balloon, and that the pressure remains zero (or atmospheric). The variation in oesophageal pressure during breathing seems to reflect the pleural pressure excursions.

In man, it is usual to measure the pressure 32-35 cm beyond the nostrils, the highest point at which the measurement is free from artefacts due to mouth pressure and tracheal and neck movements. In the supine position the weight of the heart may introduce an artefact but there is usually a zone some 32-40 cm beyond the nares where the esophageal pressure is close to atmospheric and probably only about 0.2 kPa (2 cmH₂O) above the neighbouring intrathoracic pressure. Alveolar pressure equals mouth pressure when no gas is flowing; it cannot be measured directly.

### 2.3.2 Procedure

Compliance is a static variable, that is, airflow should be zero at the two volume points, for example, end inspiration and end expiration. Measurements are, however, often made when there is no guarantee that flow is zero on measuring pressure and volume. To circumvent this problem, such compliance is called dynamic. Comparison of dynamic compliance values obtained at different moments may thus not inform on changes in compliance, but rather on variations in resistance.

The measurements are made during rhythmic breathing, but compliance is calculated from pressure and volume measurements made when no gas is flowing, usually at end-inspiratory and end-expiratory “no flow” points. Three methods are in general use.

- **Loops.** The required pressure gradient and the respired volume are displayed simultaneously as X and Y coordinates. The resultant trace forms a loop as in Figure 21 (a), the “no flow” points being where the trace is horizontal. The dynamic lung compliance is the slope of the line joining these points when the pressure gradient is ambient/intrathoracic. The area of the loop is mainly a function of airway resistance.
Figure 21: Measurements of dynamic compliance of lung by simultaneous measurement of tidal excursion (lung volume relative to FRC) and intrathoracic pressure (relative to atmosphere).

In (a) these variables are displayed as the Y and X coordinates on a two-dimensional plotting device (e.g., cathode ray oscillograph). In (b) they are displayed simultaneously against time on two-channel oscillograph. In each case, lung compliance is derived as lung volume change divided by transmural pressure gradient change. The transmural pressure gradient is indicated by the intrathoracic pressure (relative to atmosphere) when the
lung volume is not changing. At these times the alveolar pressure must equal the atmospheric pressure since no gas is flowing. End-expiratory and end-inspiratory 'no-flow' points are indicated in (b). They correspond to horizontal parts of the loop in (a).

- **Multichannel recording of volume, pressure gradient and flow rate.**

This method differs from the one described above only in the manner of display; the principles are the same. Volume and pressure are displayed separately (figure 21 (b) and 22) The volume change is derived from the volume trace and is divided by the difference in pressure at the two “no flow” points. In figure 21, these points are identified as the horizontal part of the volume trace but are more precisely indicated by a pneumotachogram which may be integrated to give volume and thereby dispense with a spirometer. This method was introduced in 1927 by Von Neergaard and Wirz and may be used for both spontaneous and artificial breathing. The calculations may conveniently be undertaken on-line with a microcomputer interfaced to the volume and pressure transducers.

- **The third method** was used during our experiments. Thanks to the development of numerical integration, we can now either digitise the tracings of flow, volume and pressure on paper (Fig.22) or digitise directly the signals obtained via an analog-to-digital converter. The variables obtained are processed by a software fitting the simplified equation of motion of the respiratory system: \( \text{PTP} = \text{V.E} + \text{V'.RI} + \text{K} \), where PTP is the transpulmonary pressure, V the volume, E, elastance, V’ flow and RI, lung resistance. The inertial component is negligible. The software extracts the dynamic elastance and resistance.
Compliance is lung volume dependant. If lung volume changes between measurements, it can explain a possible change in compliance but it can also cause erroneous interpretation of the progress of lung disease. Compliance should be measured at the same lung volume over time to enable comparisons. A way of taking lung volume into account is to divide compliance by the lung volume, to give the specific compliance. The compliance/volume relationship is not, however, linear (compare the pressure/volume curve of the lung), so a perfect compensation for the lung volume change may not be obtained.

The shape of the pressure-volume curve could indicate changes in respiratory-system compliance. The shape of the pressure-volume curve
during volume-controlled ventilation (Fig.23(B)) differs from that during pressure-controlled ventilation (Fig.23(A)).

**Figure 23:** The two panels show alterations in the shape of the pressure-volume curve with alterations in respiratory-system compliance. WOB = work of breathing. VT = tidal volume. PIP = peak inspiratory pressure.
2.3.3 Compliance of the chest

In the anaesthetized, paralysed, or sedated patients, chest wall compliance can be measured together with the recording of lung compliance. The pressure that expands the chest wall (rib cage and diaphragm) is oesophageal pressure minus the pressure that surrounds the body (normally atmospheric, and set equal to zero in the calculations of compliance).

2.3.4 Compliance of the total respiratory system

Total compliance (Ctot) is calculated as a change in volume (ΔV) divided by change in airway pressure (ΔP), under the assumption of zero airflow:

\[ C_{tot} = \left( \frac{\Delta V}{\Delta P} \right) \]

For the lung the appropriate pressure gradient is alveolar/intrapleural (or intrathoracic) and for the total compliance alveolar/ambient. There is a relationship between total compliance (Ctot) and its two components, according to:

\[ \frac{1}{C_{tot}} = \left( \frac{1}{Clung} \right) + \left( \frac{1}{Ccw} \right) \]

where Clung is lung compliance and Ccw is chest wall compliance.

2.4 Intrinsic PEEP

In conjunction with the calculation of compliance, it might be wise to mention that any persisting end expiratory flow, just before the start of the next inspiration, signals a higher alveolar pressure than upper airway pressure. This increased alveolar pressure is called “intrinsic” or “auto” PEEP. It can be measured by occluding the airway tube for a second to allow pressure equilibration between the alveoli and the airway tube. Pressure must then be measured in the tube. Thus, an expiratory hold, which is a feature in some ventilators, can be used for the assessment of intrinsic PEEP (Fig.24).
Figure 24: Assessment of the intrinsic PEEP (auto PEEP or PEEPi) during mechanical ventilation (a, b) and spontaneous breathing (c).

(a) Note that there is an end expiratory flow and that airway pressure has to increase to a certain level before inspiratory flow starts. This is because of an intrinsic PEEPi which must be exceeded by airway pressure before a flow can be created. (b) If expiratory flow is halted by occluding the expiratory outlet on the ventilator, airway pressure will increase as a result of the transmission of the alveolar pressure to the upper airways and ventilator tubings, corresponding to the intrinsic PEEP. It should be noted that, in the presence of a range of intrinsic PEEP levels (as can be expected in obstructive lung disease), the measured intrinsic PEEP will be a weighted mean of all values. (c) The detection of an intrinsic PEEP during spontaneous breathing requires the recording of oesophageal pressure (Poeso). Note that the inspiratory flow (Vinsp) has not started until a certain decrease in Poeso, corresponding to the intrinsic PEEP.
The airway resistance can be calculated during inspiration and used to calculate the alveolar pressure needed to create the flow that is measured at end expiration. There are limitations to the technique, mainly because inspiratory and expiratory resistances are not the same, and because resistances increase with decreasing lung volume. It is thus higher at the end of expiration than at any other point during the breath. Despite these limitations, it seems to be most important to measure intrinsic PEEP, which can climb to over 10 cm H₂O in obstructive patients. Uncontrolled, the intrinsic PEEP may be an unexpected cause of baro-/volo-trauma.

2.5 Resistance

If a fluid flows through a tube, a difference of pressure exists. Resistance is the slope of the pressure/flow relationship. However, the pressure difference, and consequently, the resistance, depends on the pattern of flow. When the flow is laminar, which is thought to be the case in small airways, resistance may be defined as pressure divided by flow (R = P/V).

\[ R = \frac{8 \pi n l}{\pi r^4} = \frac{P}{V'} \]

The Poiseuille’s law states that there is a critical importance of the tube radius (r): if the radius is halved, the resistance increases 16-fold. However, doubling the length (l) only doubles resistance. The viscosity (n) of the gas, but not its density, affects the pressure-flow relationship. The P / V' relationship in laminar flow patterns is the basic principle of pneumotachography.

When the flow rate increases, or passes through irregular airways, the flow pattern becomes turbulent. Here, the pressure is proportional to the square of flow, \( P = V'^2 K \) and the density of the gas becomes relevant according to the Bernoulli’s principle. Between laminar and turbulent flow patterns, we have the transitional flow. The Rohrer’s equation for flow resistance states: \( P = K_1 V + K_2 V'^2 \). The advantage of this equation is that
it takes into account the turbulent and laminar components of flow patterns. See paragraph 2.8 for more informations on resistance.

The resistance to breathing is often divided into three components: 1) airway resistance, 2) lung tissue resistance, and 3) chest wall resistance. The airway resistance can also be partitioned into that of the upper and lower airways. In addition, a considerable resistance to airflow is often exerted by the artificial airway, such as the endotracheal tube and valves in the respiratory circuit.

### 2.5.1 Airway resistance

Pressure is required to force air through the airways. Airway resistance is the pressure difference between the alveoli and the mouth divided by the flow rate. Although mouth (or airway opening) pressure is easy to measure with a manometer, alveolar pressure is not, at least not during breathing. There are two methods of measuring the alveolar pressure: the body plethysmography (considered a “gold standard”, but requires complicated and bulky equipment) and the shutter or interruptive method.

The most common measurements made using the body plethysmograph are VTG (expressed in liters BTPS, or body temperature and pressure saturated) and $R_{aw}^{1,2}$ (reported cm H$_2$O · L$^{-1}$ · s$^{-1}$) Airways conductance ($G_{aw}$) is also commonly calculated as the reciprocal of $R_{aw}$ ($1/R_{aw}$). Specific airways conductance (ie, conductance/unit of lung volume) is routinely reported as $sG_{aw}$ (reported in L · s$^{-1}$ · cm H$_2$O$^{-1}$).

The body plethysmograph (Fig.25) measures changes in volume of the whole body and is essentially a rigid box in which the patient sits while the small changes of pressure in the box can be measured as he or she makes respiratory manoeuvres.
The basic principle is Boyle’s law, that is, that the pressure and volume of a gas are inversely related \((P_1V_1=P_2V_2)\) at constant temperature. Briefly, to measure lung volume, the patient makes an inspiratory effort against a closed airway and the resulting slight increase in volume of the lung reduces the free volume of air in the box, thereby increasing its pressure. To achieve this, we set the initial pressure in the box times the initial volume of the box (both of which we know), equal to the pressure times volume of the box at the end of a chest expansion (of which we know only the pressure). At the same time, the increase in volume of the lung results in a reduction of pressure in airway; from the changes in the two pressures and the volume of the box, the volume of the lung can be derived. We set the initial volume of the chest (unknown) times the initial pressure at the mouth (known), equal to the inspiratory volume of the chest (the same unknown volume plus the change in the volume of the chest, which we have just computed) times the pressure at the mouth during the inspiratory effort.
(known). Now we solve for the unknown volume, which will be the original volume of gas present in the lungs when the shutter was closed. The shutter is usually closed at the end of a normal exhalation, or at FRC.

The calculation is simplified by displaying the two pressures on the $x$ and $y$ axes of an oscilloscope. In the modern pulmonary function laboratory, this is a much easier way of measuring lung volume than gas dilution techniques using, for example, helium equilibration or nitrogen washout.

The plethysmograph method measures the total volume of compressible gas in the thorax, whether the gas is in communication with the airways or not. This is a valuable feature of the method in clinical practice because a comparison of the thoracic volume by this technique and by the helium dilution method measures the amount of non-ventilated or poorly-ventilated lung. This is useful information in some types of lung disease. Body plethysmography is particularly appropriate for patients who have air spaces within the lung that do not communicate with the bronchial tree. In these individuals, gas dilution methods of measurement would give an erroneously low volume reading.

Airway resistance is measured in a somewhat similar way. The patient is asked to make rapid shallow breaths and, during inspiration, as the alveolar gas slightly expands, the box pressure rises slightly (Fig. 26). This allows alveolar pressure to be calculated. The difference between alveolar and mouth pressure divided by flow rate is equal to airway resistance.
Figure 26: Principles of body plethysmography. The patient sits in the box, which has the pressure transducer in the wall of the device, and breathes through a mouthpiece connected to a device that contains an electronic shutter and a differential pressure pneumotachometer. The mouth pressure and box pressure changes that are measured during tidal breathing and panting maneuvers which are performed during the test by the patient at the end of expiration are sent to a microprocessor unit that calculates thoracic gas volume.
When the subject breathes, airflow is recorded on the Y axis of the cathode ray oscillograph and plethysmograph pressure (which is proportional to alveolar pressure) is recorded on the X axis. The slope of the line generated on the cathode ray oscillograph is $\frac{V}{P_p}$ where "V is air flow and $P_p$ is plethysmograph pressure."
that in the alveoli the moment before the occlusion, airway resistance can be calculated. The halt should be no longer than a few tenths of a second in order to avoid a deviating mouth pressure caused by the ongoing inspiratory or expiratory effort. Although this may give reasonable results in the absence of airways disease, the “shutter method” mostly underestimates airway resistance in patients with obstructive lung disease. This is because there is no complete pressure equilibration between mouth and alveoli in the presence of airway narrowing during the short flow interruption.

Figure 29: The shutter technique for the assessment of airway resistance (Raw). When airflow is briefly halted by a shutter at the mouth, mouth pressure increases during an expiratory manoeuvre and decreases during an inspiratory manoeuvre. This is because, during the no flow period, the alveolar pressure will be transmitted to the mouth. The mouth pressure will, however, also be affected by the ongoing movement of the chest, so that a biphasic pressure change can be seen, as shown in the insert. The rapid pressure change is assumed to alveolar pressure, whereas the slower change is caused by chest movement.

As the airways penetrate toward the periphery of the lung, they become more numerous but much narrower. Based on Poiseuille’s equation
with its (radius)^4 term, it would be natural to think that the major part of the resistance lies in the very narrow airways. Indeed, this was thought to be the case for many years. However, it has now been shown by direct measurements of the pressure drop along the bronchial tree (Fig.30) that the major site of resistance is the medium-sized bronchi and that the very small bronchioles contribute relatively little to resistance.

![Figure 30: Location of the chief site of airway resistance. Note that the intermediate-sized bronchi contribute most of the resistance and that relatively little is located in the very small airways.](image)

Figure 30 shows that the most of the pressure drop occurs in the airways up to the seventh generation. Less than 20% can be attributed to airways less than 2 mm in diameter. The reason for this apparent paradox is the prodigious number of small airways.

The fact that the peripheral airways contribute so little to resistance is important in the detection of early airway disease. Because they constitute a “silent zone”, it is probable that considerable small airway disease can be...
present before the usual measurements of airway resistance can detect an abnormality.

Lung volume has an important effect on airway resistance (Fig. 31 and 33). Like the extra-alveolar blood vessels, the bronchi are supported by the radial traction of the surrounding lung tissue, and their calibre is increased as the lung expands.

Figure 31 shows that as lung volume is reduced, airway resistance rise rapidly. If the reciprocal of resistance (conductance) is plotted against lung volume, an approximately linear relationship is obtained. At very low lung volumes, the small airways may close completely, especially at the bottom of the lung, where the lung is less well expanded. Patients who have
increased airway resistance often breathe at high lung volumes; this helps to reduce their airway resistance. Contraction of bronchial smooth muscle narrows the airways and increases airway resistance. The density and the viscosity of the inspired gas affect the resistance offered to flow. The resistance is increased during a deep dive because the increased pressure raises gas density, but it is reduced when a helium-O₂ mixture is breathed. The fact that changes in density rather than viscosity have such an influence on resistance shows that flow is not purely laminar in the medium-sized airways, where the main site of resistance lies.

2.5.2 Lung resistance

Lung resistance is the sum of airway and lung tissue resistances. The driving force is pleural pressure minus mouth pressure (transpulmonary pressure Ptp), but this pressure difference is also used for expansion of the lung. Thus, the resistive pressure component must be separated from the elastic component, which can be done if the static pressure-volume curve of the lung is known or assumed. If resistance is measured during quiet breathing, it is customary to link end inspiratory and end expiratory pressure-volume points by a straight line, and calculate resistive pressure as the difference in pressure between the straight line and the measured transpulmonary pressure at that lung volume (or part of the tidal volume) (Fig. 32). If the airflow is regulated, resistance can be defined in terms of lung volume and airflow, both of which play a most important role in the resistance value. 
Figure 32: (a) Pressure-volume and (b) pressure-flow loops during a tidal breath.
Assuming that the elastance is constant over the tidal volume, a straight line can be drawn between the maximum and minimum transpulmonary pressure (Pt) on the pressure-volume loop. The difference in pressure between the loop and the straight line corresponds to the pressure needed to overcome resistive forces. These pressures (P_{insp}, P_{exp}) can be divided by the simultaneously measured airflows (V_{insp}, V_{exp}) to yield pulmonary resistance (airway and lung tissue resistance). Letters A, B, C, and D show simultaneous events in (a) and (b).
Figure 33: Shutter technique for assessment of the pressure-volume curve of the lung and lung resistance over the vital capacity. By rapid airway occlusions and a flow regulator that maintains expiratory flow at a predetermined level, a volume-resistance curve can also be constructed. Note the increase in resistance with decreasing lung volume, an effect of the airway narrowing during expiration. Ptp, transpulmonary pressure.
To calculate the resistance of the lung tissue itself, airway resistance has to be subtracted from lung resistance. In the anesthetised, paralysed, and sedated patient who is undergoing mechanical ventilation, another simplified approach can be used to separate airway resistance from that of the tissue. As the recording is mostly done together with the measurement of total respiratory resistance, the method is described later.

2.5.3 Chest wall resistance

Chest wall resistance is accessible during mechanical ventilation, as is the possibility of measuring chest wall compliance. Here the driving pressure is pleural or oesophageal pressure minus atmospheric pressure. Again, the pressure comprise both the elastic and the resistive components, and they have to be separated to calculate the resistance. As with the analysis of lung resistance, a pressure-volume curve of the chest wall can be measured, or assumed to be linear between volume end points. The remaining pressure at a given volume is the resistive pressure which, divided by flow, gives the chest wall resistance. A complicating factor is the relatively large oesophageal pressure excursions caused by the beating heart. These variations can be almost half the magnitude of the pressure variations induced by the tidal volume. As the pressure waves from the ventilator and the heart are on the whole not in phase, an averaging procedure over several breaths may eliminate the influence of the heart beats.

2.5.4 Total respiratory resistance

Total respiratory resistance (Rtot) is the sum of airway (Raw), lung tissue (Rlung tis), and chest wall (Rw) resistances:

\[ R_{\text{tot}} = R_{\text{raw}} + R_{\text{lung tis}} + R_{\text{w}}. \]

It can be assessed only in the relaxed patient, and needs only the recording of airway pressure and airflow.
2.5.5 Principles of measurement of flow resistance

Simultaneous measurement of air flow rate and intrathoracic-to-mouth pressure gradient (Fig. 34). It was shown how simultaneous measurement of tidal volume and intrathoracic pressure yielded the dynamic compliance of the lung. For this purpose, pressures were selected at the time of zero airflow when pressures were uninfluenced by air flow resistance. The same apparatus may be employed for the determination of flow resistance by subtracting the pressure component used in overcoming elastic forces.

The shaded areas in the pressure trace indicate the components of the pressure required to overcome flow resistance and these may be related to the concurrent gas flow rates. Alternatively, the intrathoracic-to-mouth pressure gradient and respired volume may be displayed as X and Y coordinates of a loop. Figure 21 showed how dynamic compliance could be derived from the no-flow points of such a loop.
Figure 34: The measurement of pulmonary resistance and dynamic compliance by simultaneous measurement of air flow and intrathoracic-to-mouth differential pressure (Von Neergaard and Wirz, 1927). The spirogram is conveniently obtained by integration of the pneumotachogram. In the pressure trace, the dotted line shows the pressure changes which would be expected in a hypothetical patient with no pulmonary resistance. Pulmonary resistance is derived as the difference between the measured pressure differential and that which is required for elastic forces (shaded area) compared with the flow rate shown in the pneumotachogram. Note that the pneumotachogram is a much more sensitive indicator of the no-flow points than the spirogram.

The area of the loop is a function of the work performed against flow resistance.
A convenient technique to measure simultaneously resistance and compliance of the lung is done by fitting the equation of motion of the lung:

\[ P_{\text{TP}} = E_d \cdot V + R_l \cdot V' + K \]

The data of volume (V) and flow (\(V'\)) are summarized and the fitting is done by a statistical software, giving the two constants of the equation: elastance (\(E_d\)) and resistance (\(R_l\)). K is a constant term reflecting the error due to the residual of the least squares adjustment method\textsuperscript{12}.

### 2.6 Power and work of breathing

In a fluid system, the mechanical work \((W)\) is the integral of the pressure applied \((P)\) and the resulting volume change \((V)\):

\[ W = \int P \, dV \]

The work per unit time is termed power.

\[ W / t = \text{power} = P \cdot V' \]

Power is then the product of pressure and flow.

Both pulmonary resistive power and work are of definite importance in determining respiratory muscle performance and work. In the ventilator treated patient, total respiratory work can be determined as the product of airway pressure and volume.
Figure 35: Pressure-volume curve of the lung showing the inspiratory work done overcoming elastic forces (area OAECDO) and viscous forces (hatched area ABCEA).

This can be illustrated on a pressure-volume curve (Fig. 35). During inspiration, the intrapleural pressure follows the curve ABC, and the work done on the lung is given by the area 0ABCD0. Of this, the trapezoid 0AECD0 represents the work required to overcome the elastic forces, and the hatched area ABCEA represents the work overcoming viscous (airway and tissue) resistance. The higher the airway resistance or the inspiratory flow rate, the more negative (rightward) would be the intrapleural pressure excursion between A and C and the larger the area.

On expiration, the area AECFA is work required to overcome airway (+ tissue) resistance. Normally, this falls within the trapezoid 0AECD0, and thus this work can be accomplished by the energy stored in the expanded elastic structures and released during a passive expiration. The difference between the areas AECFA and 0AECD0 represents the work dissipated.

The higher the breathing rate, the faster the flow rates and the larger the viscous work area ABCEA. On the other hand, the larger the tidal volume, the larger the elastic work area 0AECD0. It is of interest that patients who have a reduced compliance tend to take small rapid breaths,
while patients with severe airway obstruction tend to breathe slowly (Fig.37). These patterns tend to reduce the work done on the lungs.

Two different pressure volume diagrams are shown in figure 36. During normal inspiration (left graph) transpulmonary pressure increases from 0 to 5 cm H\textsubscript{2}O while 500 ml of air is drawn into the lung. Potential energy is stored by the lung during inspiration and is expanded during expiration; as a consequence, the entire expiratory cycle is passive. The hatched area plus the triangular area ABC represents pressure multiplied by volume and is the work of breathing. The triangular area ABC is the work required to overcome elastic forces (C\textsubscript{T}), whereas the hatched area is the work required to overcome airflow or frictional resistances (R\textsubscript{L}). The graph on the right applies to an anaesthetized patient with diffuse obstructive airway disease resulting from the accumulation of mucous secretions. There is a marked increase in both the elastic (triangle ABC) and airway (hatched area) resistive components of respiratory work. During expiration, only 250 ml of air leaves the lungs during the passive phase when intrathoracic
pressure reaches the equilibrium value of 0 cm H₂O. Active effort-producing work is required to force out the remaining 250 ml of air, and intrathoracic pressure actually becomes positive.

**Figure 37:** The diagrams show the work done against elastic and airflow resistance separately and summated to indicate the total work of breathing at different respiratory frequencies. The total work of breathing has a minimum value at about 15 breaths/min under normal circumstances. For the same minute volume, minimum work is performed at higher frequencies with stiff (less compliant) lungs and at lower frequencies when the airflow resistance is increased.

For a constant minute volume, the work done against elastic resistance is increased when breathing is deep and slow (Fig. 37). On the other hand, the work done against airflow resistance is increased when breathing is rapid and shallow. If the two components are summated and the total work is plotted against respiratory frequency, there is an optimal respiratory frequency at which the total work of breathing is minimal. In patients with diseased lungs in which elastance is high (pulmonary fibrosis, pulmonary edema, infants), the optimum frequency is increased, and rapid, shallow breaths are favored. When airway resistance is high (asthma,
obstructive lung disease), the optimum frequency is decreased, and slow, deep breaths are favored.

2.7 Trans-diaphragmatic pressure

Trans-diaphragmatic pressure (Pdi) is defined as the difference between pleural (Ppl) and abdominal (Pab) pressures and, in practice, is generally equated to the difference between Pes and Pga, so that

\[ Pdi = Pga - Pes \]

As the diaphragm is the only muscle in which contraction simultaneously lowers Pes and increases Pga, an increase in Pdi is, in principle, the result of diaphragmatic contraction unless there is passive stretching. An inspiratory effort produced with a completely passive unstretched diaphragm is associated with a negative change in Pes and Pga but no change in Pdi. This assumes that changes in Pes or Pga induced by mechanisms other than diaphragm contraction are uniformly transmitted across the diaphragm from one compartment to the other.

Pes and Pga are most often measured by passing a pair of probes, generally balloon catheters (Fig. 39). A simple technique is to advance both probes well into the stomach and then to withdraw one of them until a sniff-related pressure deflection becomes negative, indicating that the balloon has entered the esophagus. It is then withdrawn a further 10 cm. The validity of the Pes measurement can be checked by matching Pes to Pao during static Mueller (inspiratory) maneuvers (the dynamic occlusion test).

Displacement of balloons is minimized by taping the catheters to the nose. The distance between the nostril and the tip of the balloons varies with the size of the subject, but is usually 35-40 cm for Pes and 50-60 cm for Pga in adults.
Figure 38: The method for measuring diaphragm endurance.

\(P_{\text{di}}\) = transdiaphragmatic pressure; \(P_{\text{di max}}\) = maximum trans-diaphragmatic pressure; \(P_{\text{ga}}\) = gastric pressure; \(V\) = respiratory flow from a pneumotachograph; \(P_{\text{ETCO2}}\) = end-tidal carbon dioxide pressure; \(V_T\) = tidal volume.

Placing the probes becomes more difficult when the subject can not perform voluntary inspiration. The pressure signals during a swallow can be useful: a balloon is positioned in the esophagus when swallowing is associated with a slow, powerful rise in pressure, whereas if this does not occur the balloon is likely to be in the stomach.

It is advisable to measure \(P_{\text{es}}\) and \(P_{\text{ga}}\) separately by using two pressure transducers (Fig.38), with \(P_{\text{di}}\) derived from a third differential pressure transducer or reconstructed electronically off-line. This allows the investigator to monitor balloon position and detect confounding events such as esophageal spasm, as well as recording the three pressures independently. Resting \(P_{\text{ga}}\) is usually positive with respect to atmosphere due to the hydrostatic pressure in the abdomen. For respiratory muscle measurements \(P_{\text{ga}}\) is conventionally taken as zero at resting end expiration.
Pdi is specific for diaphragm contraction. Separate measurements of Pes and Pga provide information of the components of this contraction and Pes on the respiratory driving pressure.

**2.8 Reynolds number**

To understand the effect of changing gas density or viscosity on the pressure-flow characteristics of the lungs, a review of basic fluid dynamics is required.

Movement of gas through a rigid tube is modelled by two basic patterns of flow. In a given tube, laminar flow occurs at lower flow rates and is characterized by the existence of streamlines parallel to the sides of the tube. Gas in the centre of the tube moves more rapidly than gas at the edge of the tube (Fig. 39), and gas viscosity is the major determinant of flow rate.

In the same tube, turbulent flow predominates at higher flow rates, and the movement of individual particles is not organized around streamlines (Fig. 39). Gas density is a major determinant of flow rate in turbulent systems.

*Figure 39: Laminar and turbulent flows in a tube.*

The tendency for flow to be laminar or turbulent within a given region can be quantified by the Reynolds number (Re), named after Osborne Reynolds (1842-1912) who proposed it in 1883 as a dimensionless ratio of inertial (turbulent) to viscous (laminar) forces:
\[ \text{Re} = \frac{[\rho \cdot d \cdot v]}{[\pi \cdot \eta]} \]

where \( \rho = \text{density, } d = \text{tube diameter, } v = \text{fluid velocity, and } \eta = \text{viscosity.} \)

At any anatomical level within the tracheobronchial tree, gas velocity is equal to flow rate divided by total cross sectional airway area. Therefore Re can be expressed as follows:

\[ \text{Re} = \frac{[4 \cdot \rho \cdot \text{flow}]}{[\pi \cdot \eta \cdot d]} \]

where \( d = \text{airway diameter.} \)

When Re is high, the force required to generate a given flow rate is determined to a greater degree by fluid density, and flow is more turbulent. Conversely, at lower Re the flow rate is determined to a greater degree by fluid viscosity, and flow is more laminar. In a straight, smooth, unbranched tube, laminar flow predominates when Re is <2000. When Re is >4000, flow is mainly turbulent.

![Figure 40: Entry length of laminar (a) and turbulent (b) flows.](image)

The length of pipe before fully developed flow is achieved is different for the two types of flow (Fig. 40). The length is known as the entry length.
Re also determines the entrance length (EL) of a tube, which is the distance from the beginning of a tube for laminar flow to become established.

\[ EL = 0.03 \times d \times Re \]

Thus, when Re is low, not only is there less of a tendency for turbulent flow, but laminar flow will become established more quickly after changes in airway calibre or configuration.

In the normal human lung, most resistance is due to the large airways. Flow is primarily turbulent from the trachea to the start of the bronchioles, particularly when the flow rate is high. From the formula for Re, one can see that this results from a smaller overall cross-sectional area and thus higher flow velocity, leading to a higher Re. In addition, there are frequent branch points, and EL may be longer than the length of a particular airway. In combination, these factors inhibit the development of laminar flow.

So can be defined three patterns of air flow:

- **Laminar flow pattern** is seen mainly in very small airways.

Pressure/Flow Relationship for Laminar Flow is given by Poiseuille’s Law:

\[ V = P \pi r^4 / 8 \eta l \]

\[ \eta = \text{viscosity}, l = \text{length of tube or vessel} \]

With laminar flow, the gas flow rate is directly proportional to the driving pressure, the constant being thus defined as resistance to gas flow:

\[ \text{Pressure difference} = \text{flow rate} \times \text{resistance} \]
For gas flow in a straight unbranched tube, the value for resistance is:

\[
\frac{8 \times \text{length} \times \text{viscosity}}{\pi \times (\text{radius})^4}
\]

In this rearrangement of the Hagen-Poiseuille equation, the direct relationship between flow and the fourth power of the radius of the tube explains the critical importance of narrowing of air passages, as well as the choice of an appropriate cannula for an intravenous infusion.

Viscosity is the only property of a gas which is relevant under conditions of laminar flow. Helium has a low density but a viscosity close to that of air. Helium will not therefore improve gas flow where the flow is laminar.

- **Turbulent flow pattern** is seen in the trachea and larger airways, especially with higher velocity (e.g., exercise).

If Reynold's number \((\text{Re}) = \frac{2 \times r \times v \times \rho}{\eta} > 2000\), air flow is turbulent

\(r = \text{radius}, \ v = \text{velocity}, \ \rho = \text{density}, \ \eta = \text{viscosity}\)

The relationship between driving pressure and flow rate differs from the relationship described above for laminar flow in three important respects:

- the driving pressure is proportional to the square of the gas flow rate
- the driving pressure is proportional to the density of the gas and is independent of its viscosity
- the required driving pressure is, in theory, inversely proportional to the fifth power of the radius of the tube (Fanning equation)

Resistance, defined as pressure gradient divided by flow rate, is not constant as in laminar flow but increases in proportion to the flow rate.

- **Transitional flow pattern** (combination of laminar and turbulent) is seen in most medium-sized airways especially at branch points. Medium-sized airways offer the most resistance to air flow.
The following method of quantification of “resistance” should be used when flow is totally or partially turbulent. This method considers resistance as comprising two components, one for laminar flow and the other for turbulent flow. The simple relationship for laminar flow given above would then be extended as follows:

\[ \text{Pressure difference} = k_1 \text{(flow)} + k_2 \text{(flow)}^2 \]

In the Roher's equation, \( k_1 \) contains the factors of the Hagen-Poiseuille equation while \( k_2 \) includes factors in the corresponding equation for turbulent flow. Mead and Agostoni (1964) summarized studies of normal human subjects in the following equation:

\[ \text{Pressure gradient (kPa)} = 0.24 \text{(flow)} + 0.03 \text{(flow)}^2 \]

Or

\[ \text{Pressure gradient (cmH}_2\text{O)} = 2.4 \text{(flow)} + 0.3 \text{(flow)}^2 \]

Over a surprisingly wide range of flow rates, the equation above may be condensed into the following single-term expression with little loss of precision:

\[ \text{Pressure gradient} = K \text{(flow)}^n \]

The exponent \( n \) has a value ranging from 1 with purely laminar flow to 2 with purely turbulent flow, the value of \( n \) being a useful indication of the nature of the flow. The constants for the normal human respiratory tract are:

\[ \text{Pressure gradient (kPa)} = 0.24 \text{(flow)}^{1.3} \]

Or

\[ \text{Pressure gradient (cmH}_2\text{O)} = 2.4 \text{(flow)}^{1.3} \]

In theory, the benefits of heliox in patients with high airway resistance are due to decreasing Re and facilitating laminar flow, resulting in improved ventilation and a decreased work of breathing. By decreasing the density of the inhaled gas, heliox decreases the applied force required to achieve a given flow rate.
Figure 41 shows the nature of the gas flow for three different gas mixtures in terms of gas flow rate and diameter of tube. It will be seen that mixed flow patterns will often be present under conditions which are likely to occur in the clinical situation.  

Figure 41: Graphs to show the nature of the gas flow through tubes of various diameters for three different gas mixtures; 25 l/min is a typical peak flow rate during spontaneous respiration. It will be seen that the nature of flow in the trachea and in endotracheal tubes will be markedly dependent on the composition of the gas mixture.
The property of the gas which affects Reynold’s number is the ratio of density to viscosity. Viscosities of respirable gases do not differ greatly but there may be very large differences in density. Note that use of a less dense gas such as helium not only reduces resistance during turbulent flow but also renders turbulent flow less likely to occur.
Reference List


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3 - Analysis of distribution of ventilation-perfusion ratios with the MIGET

The gas exchange that takes place in any lung unit is determined not only by the ventilation or the blood flow, but also by their ratios. The importance of the ratio of ventilation to blood flow in determining gas exchange was first recognized nearly 90 years ago, but the multiple inert gas elimination technique (MIGET) was developed in the mid 1970s\textsuperscript{1-3}. This technique provides more information concerning the role of VA/Q relations on pulmonary gas exchange than previously available. The MIGET, in addition to its ability to estimate VA/Q distributions in real lungs, provides information on other pulmonary factors causing hypoxemia (Table 5) and also allows a numerical analysis of the influence of extra pulmonary factors on arterial PO\textsubscript{2}.

This technique, heavy and time consuming as you can see later, was essential to prove that our animal model of induced bronchospasm accurately mimics acute asthma crisis regarding its consequences on gas exchange. Furthermore it permits us to demonstrate the impact of helium on ventilation-perfusion relationships in many situations like induced bronchospasm in mechanical ventilation, asthmatic model in pressure support mode, or mechanically ventilated patients with COPD.

<table>
<thead>
<tr>
<th>Intrapulmonary factors</th>
<th>Extra pulmonary factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA/Q mismatching</td>
<td>↓ minute ventilation</td>
</tr>
<tr>
<td>Shunt</td>
<td>↓ cardiac output</td>
</tr>
<tr>
<td>Alveolar-end capillary</td>
<td>↓ inspired PO\textsubscript{2}</td>
</tr>
<tr>
<td>O\textsubscript{2} diffusion limitation</td>
<td>↑ O\textsubscript{2} uptake</td>
</tr>
</tbody>
</table>

Table 5: Factors determining arterial hypoxemia

3.1 Principles of the MIGET

If an inert gas (defined here as a gas that obeys Henry’s law, i.e. showing a linear relationship between partial pressure and concentration in
blood) is dissolved in 5% dextrose or normal saline and then infused at a constant rate into a peripheral vein, a steady state of gas exchange across the lung is reached within few minutes. In any single gas-exchange unit in that lung, the relationship among the alveolar (P_A), end-capillary (P_C), and mixed venous (P_V) partial pressures is given by equation:

\[ P_A \cdot P_C = P_V \cdot \frac{\lambda}{\lambda + \frac{V_A}{Q}} \]

This equation is derived from simple mass balance considerations on the assumption of a steady state of gas exchange in the lungs, continuous ventilatory and circulatory movement of gas and blood through the lungs, and alveolar-end-capillary diffusion equilibration of partial pressure for the gas. End-capillary and alveolar partial pressures of an inert gas are assumed to be equal in a single lung unit, and the equation become as follows:

\[ \frac{P_A}{P_V} = \frac{P_C}{P_V} = \frac{\lambda}{\lambda + \frac{V_A}{Q}} \]

This indicates that both end capillary and alveolar partial pressures of an inert gas depend on the partial pressure of this gas in the venous side of the capillary and the expression in the right hand side of the equation, which includes the solubility of the gas (\(\lambda\)) expressed as the partition coefficient, and the \(V_A/Q\) ratio of the lung unit.

The \(P_C/P_V\) ratio indicates the retention (R) of the gas in the blood while the \(P_A/P_V\) ratio express its excretion (E) to the ambient air. According to this mathematical expression, the retention and the excretion of an inert gas depend only on the solubility of the gas and the \(V_A/Q\) ratio of the lung unit.

The MIGET uses simultaneous venous infusion of six inert gases in trace concentrations (SF_6, ethane, cyclopropane, enflurane, diethyl ether and acetone) covering a broad spectrum of partition coefficients from 0.005 (SF_6) to 300 (acetone) to characterise the distribution of the \(V_A/Q\) ratios within the whole lung. For each inert gas the retentions are calculated as the ratio between arterial partial pressure and mixed venous partial pressure (R = Pa/Pv) and the excretions as the ratio between mixed expired partial
pressure and mixed venous partial pressure \( (E = P_e/P_v) \). The retentions of the six inert gases allow the estimation of a continuous distribution of the pulmonary blood flow against \( V_a/Q \) ratios on a logarithmic scale. Similarly, the excretions of the six inert gases provide an estimation of the distribution of the alveolar ventilation against \( V_a/Q \) ratios.

The technique requires the existence of steady state conditions in all \( V_a/Q \) units. This means that \( R \) and \( E \) must be constant during the period of measurement within a given experimental condition, though it is not necessary for absolute partial inert gas pressures to be constant.

Traditionally 50 "compartments" are used in all. The ordinate consists of both ventilation \( (V_a) \) and blood flow \( (Q) \) for each compartment, and the graph is then the frequency distribution of ventilation and blood flow as a function of the \( V_a/Q \) ratio. This graphical representation is useful in giving a general overview of the distribution. It suggests patterns of distribution as uni-modal, bimodal or tri-modal (from six gases it is mathematically impossible to resolve more than three modes). The graphical representation does not in itself quantify the degree of inequality.

The first moment of the distribution is simply the mean abscissa value, or mean \( V_a/Q \) ratio, of each curve.

The second moments of the distributions are more informative about their respective means on a log scale, and the square root of these moments have been called \( \logSD_Q \) and \( \logSD_V \) for blood flow \( (Q) \) and ventilation \( (V) \) curves respectively. The letters "SD" refer to standard deviation, which is applicable only if the entire distribution is logarithmically normal.

The fractions of total ventilation and blood flow within arbitrarily defined ranges of \( V_a/Q \) ratio \((V_a/Q \) ratio < 0.1 and \( V_a/Q \) ratio > 10.0\) are corresponding parameters for abnormal low or high \( V_a/Q \) regions.

The root mean square value (over the six gases) of retention minus excretion is an average alveolar-arterial difference for the inert gases.

Retention of \( SF_6 \) and excretion of acetone are essentially the markers of the amount of shunt \((\% Q_T \) to \( V_a/Q \) ratio < 0.005\) and dead space \((\% V_A \) to \( V_a/Q \) ratio > 100\), respectively. All perfusion in areas of very low
(< 0.005) or zero $V_a/Q$ (shunt or unventilated lung units) is combined into a single parameter referred to as shunt. Similarly, all ventilation in units of $V_a/Q > 100$ including unperfused lung ($V_a/Q$ infinitely high) is referred to as dead space.

Shunt, when present, can be due to perfusion of unventilated or extremely poorly ventilated lung regions or to direct vascular communications such as atrial septal defects with reverse (right to left) flow, or rarely to arterio-venous channels in the lung. Post-pulmonary shunt (through bronchial or thebesian circulations) is not detected by the MIGET$^9$.

In a corresponding manner the dead space value returned by the computer algorithm reflects anatomical (conducting airway) dead space, together with any external instrumental dead space and also that part of alveolar ventilation that reaches alveoli, which are, for any reason, completely unperfused (or which have a $V_a/Q$ ratio > 100).

3.2 Preparation of the inert gas solution for sterile infusion.

A mixture of the six inert gases is equilibrated with 1 litre of either normal saline or 5% dextrose. A tank of gas containing approximately 20% hexafluoride ($\text{SF}_6$, $\lambda \approx 0.005$), 20% cyclo propane ($\lambda \approx 0.5$), and 60% ethane ($\lambda \approx 0.1$) is connected to the plastic bag with the solvent by using sterile intravenous tubing with a 0.22 μm Millipore filter inserted. Gas from the tank is then pumped into the bag until the latter is somewhat distended. The bag is vigorously shaken for approximately one minute and the gas in the bag is then vented to the atmosphere. This cycle should be repeated once to reach full equilibration between the saline or dextrose and the tank gas mixture. Next, 0.7 ml liquid diethyl ether ($\lambda \approx 12$ /l saline is transferred into the bag, followed by the addition of 7 ml liquid acetone ($\lambda \approx 300$ /l, and finally, 3 ml liquid enflurane ($\lambda \approx 2$ /l. The bag is then gently inverted several times to facilitate the distribution of the last three gases into the liquid phase. Each of these steps must be done using sterile disposable material and following the necessary precautions to preserve sterility.
3.3 Infusion of the inert gas solution.

The solution is infused into a peripheral superficial vein. A constant and smooth rate of infusion of 3 ml/min is used. To achieve a steady state a period of about 20-30 minutes with the infusion running is usually required before any sampling is carried out.

3.4 Sampling procedure and measurements of inert gas concentrations.

After ensuring steady state, arterial (4-8 ml) and mixed-venous (4-8 ml) samples are drawn simultaneously using heparinized barrel matched ungreased glass syringes weighed both before and after heparinisation. In the same time, duplicate 15 ml samples of mixed expired gas are collected in matched barrel/plunger glass syringes from a mixing box (Fig.42).

![Figure 42: Picture of our mixing box.](image-url)

The mixed expired samples can be directly injected into the gas chromatograph to measure inert gas concentration. For the blood samples, each syringe is weighed a third time, after blood sampling, in order to
measure the volume of blood (calculated as weight divided by density). Approximately 10 ml of nitrogen is transferred into each syringe for equilibration of inert gases between blood and the nitrogen phase. This procedure is carried out in a shaking water bath at body temperature for approximately 40 minutes. The gas above the blood is anaerobically transferred to a dry syringe to be measured in the gas chromatograph. The peak of the least soluble gas, SF₆, is measured by an electron capture detector while the remaining five gases (all hydrocarbons) are measured by a flame ionisation detector¹⁰,¹¹.

The chromatographic peaks so measured from the gas phase after the equilibration procedure are not equal to Pa and Pv of each inert gas. These partial procedures must therefore be calculated using standard mass balance formulae¹⁰ that take into account (1) height or area of the chromatographic peaks (Fig.43), (2) partition coefficients of each inert gas, and (3) volumes of heparin, blood, and gas in the syringe during the equilibration procedure.

The residual sum of squares (RSS) is a quantitative estimation of the overall experimental error in the procedure. 50% of data sets should have RSS < 5.3, 90% of RSS should be less than 10.6, and 99% less than 16.8. The range of the second moment (log SDₐ and log SDᵥ) is from 0.30 in healthy young subjects to about 2.5 in extreme lung disease. The overall intrasubject coefficient of variation for log SDₐ and log SDᵥ is 6% if the mean of duplicate measurements is used ¹².
3.5 Information content of the MIGET

A qualitative and quantitative description of the $V_A/Q$ distribution pattern can be obtained by plotting $V_A$ and $Q$ against $V_A/Q$ compartment by compartment.

One can obtain parameters such as principal moments, describing the degree of $V_A/Q$ mismatch in terms that permit statistical inference regarding effects of manipulation or therapy.

One can assess the compatibility of the inert gas data with the basic conceptual model behind the MIGET: that the lung acts as a collection of distinct gas-exchange units (each governed by its own $V_A/Q$ ratio) arranged in either parallel or series networks. This assessment is based on the
residual sum of squares between the measured data and the least-squares best fit by the preceding model.

One can detect indications of diffusion limitation of the inert gases through the differential behaviour of high- and low-molecular-weight gases in the mixture. Thus, enflurane and SF₆ have several fold greater molecular weights than do the other gases. Such diffusion limitation would be evident by a preferential retention of enflurane and SF₆ after allowing for differences in \( \lambda \).

One can thus determine the diffusion limitation of \( \text{O}_2 \) exchange across the alveolar wall. In the absence of such limitation, the arterial \( \text{PO}_2 \) predicted by MIGET statistically agrees with that actually measured. In the presence of such limitation, the predicted arterial \( \text{PO}_2 \) is greater than that measured.

Finally, this method enables one to partition the causes of hypoxemia into intrapulmonary factors (\( V_A/Q \) mismatch, shunt, diffusion limitation) and extra pulmonary factors (altered cardiac output, metabolic rate, inspired \( \text{PO}_2 \) and ventilation) in a quantitative manner, and it also enables one to predict how changes in extra pulmonary factors would alter arterial \( \text{PO}_2 \).\textsuperscript{13,14}

### 3.5.1 Results in normal subjects

The characteristic \( V_A/Q \) distribution in normal seated subjects consist of narrow perfusion and ventilation curves (Fig.44) centred around a \( V_A/Q \) ratio of one\textsuperscript{15}. 
Figure 44: Distribution of ventilation–perfusion ratios in an upright, young, normal subject. There is little inequality evident and, in particular, no areas of very low or very high ventilation-perfusion ratio. Shunt is absent.

Mean values for the second moment of the distribution (logSD_Q and logSD_V) range from 1.35 to 0.43. The upper 95% confidence limit for logSD_Q is 0.60, and for logSD_V is 0.65. A logSD of 0.3 is consistent with an alveolo-arterial difference of about 5 mmHg, as commonly found in normal\textsuperscript{8,16}. No (or virtually no) perfusion to V_A/Q ratios < 0.005 (shunt) is present. Likewise, the amount of ventilation to V_A/Q ratios > 100 (including instrumental, anatomical, and physiological dead space) is approximately 30%. As figure illustrates, no perfusion to lung units with V_A/Q ratios < 0.1 (low V_A/Q) is observed; similarly ventilation to lung units with V_A/Q ratios > 10 (high V_A/Q) is not present.

In general, there is more mismatch than expected on just gravitational grounds\textsuperscript{8,16}, indicating probably some intraregional V_A/Q inequality as well.
3.5.2 Asthma

The main observations are:

- $V_a/Q$ mismatch is very commonly present in patients in all clinical circumstances from clinical remission to status asthmaticus.

- $V_a/Q$ mismatch is often typically reflected by a pattern in which a distinct population of low $V_a/Q$ ratio units exists separate from units with normal $V_a/Q$ ratios. This is the “bimodal” pattern\(^\text{17}\) (Fig. 45).

![Figure 45: An example of the distribution of ventilation-perfusion ratios in an asthmatic subject. Note the separate population of areas of low ventilation-perfusion ratio distinct from the main mode. The size of the low $V_a/Q$ mode varies considerably among individuals, but is commonly comprises about 20% of the cardiac output as indicated. Shunt is notably absent in most patients with asthma.](image)

- Shunting is notably absent until patients develop the most severe level such as status asthmaticus\(^\text{18}\).

- Across the spectrum of activity, the arterial $PO_2$ is accurately predicted by the $V_a/Q$ pattern, confirming $V_a/Q$ mismatch rather than shunt or diffusion limitation as the mechanism of hypoxemia.
Despite considerable V_A/Q inequality, hypoxemia is often attenuated by the presence of a higher-than-normal cardiac output that preserves PaO_2 due to maintenance of mixed venous PO_2^{17}.

Acute administration of bronchodilators to patients with naturally occurring asthma fails to improve V_A/Q relationships despite simultaneous restoration of airflow rates^{17}. This strongly suggests that airway mucus and/or oedema, rather than bronchoconstriction, causes the V_A/Q mismatch. The correlation between airflow rates and V_A/Q mismatch is almost non existent, even in a single patient over time, further suggesting that bronchoconstriction is relatively unimportant to V_A/Q relationships and that gas exchange is determined by events in the most peripheral airways poorly reflected by flow rate data. As a corollary, there is only a weak association between severity of V_A/Q mismatch and clinical severity of asthma^{17,18}.

Finally, sequential measurements over time in chronic symptomatic asthmatics reveal considerable week-by-week variability in V_A/Q inequality, mostly unrelated to clinical symptoms or airflow rate changes^{12,19}.

3.5.3 Chronic obstructive pulmonary disease (COPD)

To date, data support the finding of areas of abnormally high V_A/Q ratios in “emphysematous” patients (pink puffer, type A)^{20}. Type A patients rarely have abnormally low V_A/Q areas, but many “chronic bronchitic” patients (blue bloater, type B) commonly do (Fig.46). As in asthma true shunting (V_A/Q = 0) is rarely observed^{20}. 


Figure 46: Typical patterns of ventilation-perfusion ratios in patients with COPD. Upper panel: Pattern typical of patients with type A presentation (hyperinflation, well-preserved blood gases, and evidence of pathological emphysema). Lower panel: Pattern typical of a patient with type B presentation (chronic bronchitis). The type A patient usually shows areas of abnormally high ventilation-perfusion ratio. As in this example, right-to-left shunts are minimal. The type B patient, on the other hand, commonly has areas of abnormally low ventilation-perfusion ratio as shown, but, again, generally no shunting.
The pathological basis of these $V_a/Q$ changes is speculative, but the most likely hypothesis to explain high $V_a/Q$ areas is continued ventilation of the enlarged and putatively hypoperfused airspaces produced by emphysemous digestion of the associated alveolar walls\textsuperscript{21}. Competing hypotheses such as microvascular obstruction or the phenomenon of “auto-positive end-expiratory pressure” (auto-PEEP) due to hyperinflation remain to be excluded. The most likely cause of the low $V_a/Q$ areas in type B patients appears to be peripheral airway obstruction with mucus/oedema (or distortion of bronchioles), such as hypothesized for asthma\textsuperscript{22}. It is, however, difficult to explain the absence of low $V_a/Q$ areas in perhaps one third of the type B patients. The presence of high $V_a/Q$ areas in the type B patients is consistent with occult emphysema, often found at post mortem examination. $V_a/Q$ inequality is the sole basis for hypoxemia in COPD, and there is no evidence of $O_2$ diffusion limitation at rest or even during exercise\textsuperscript{20}. There is also no evidence for impaired diffusive gas mixing, as might have been expected in the presence of large emphysematous air spaces. This conclusion is based on the observation that in patients with COPD there is no systematically increased retention of high-molecular-weight inert gases\textsuperscript{20}.

3.5.4 Interstitial pulmonary fibrosis

Despite the huge variety of pathological causes of fibrosis, patients with advanced disease show remarkably similar $V_a/Q$ patterns characterized by a relatively modest amount of $V_a/Q$ inequality manifest by areas of very low and of zero $V_a/Q$ ratio (Fig.6). Typically, only 10-20% of the cardiac output perfuses such abnormal regions, and the remainder of the $V_a/Q$ distribution lies within the normal range of $V_a/Q$ ratios. The usually very low arterial $PO_2$ requires additional explanation; using the MIGET, it has been noted that because of subnormal values of cardiac output, the mixed venous $PO_2$ is often reduced, even at rest\textsuperscript{23}. This explains how a modest amount of $V_a/Q$ mismatch can produce quite severe hypoxemia\textsuperscript{24}.
Figure 47: The typical pattern of V\textsubscript{A}/Q inequality in patients with interstitial pulmonary fibrosis. Such patients have relatively small amounts of V\textsubscript{A}/Q inequality, usually consisting of areas of very low or zero ventilation-perfusion ratios as shown. In this example, only 21% of the cardiac output is associated with unventilated or essentially unventilated areas, but this is sufficient to produce moderately severe hypoxemia.

3.5.5 Adult respiratory distress syndrome

True shunts (V\textsubscript{A}/Q = 0) are almost always observed (Fig.48) and likely reflect alveoli flooded with exudates, alveoli filled with cellular debris, atelectasis, or right-to-left shunt through a patent foramen ovale. Areas of low V\textsubscript{A}/Q are sometimes seen and may reflect relatively transient events. The pathological basis for such low V\textsubscript{A}/Q areas is speculative but may lie in partial alveolar filling, distal airway partial obstruction, or local reductions in lung compliance\textsuperscript{25,26}.

Areas of high V\textsubscript{A}/Q are also commonly seen (Fig.48) and most often correlate with the level of alveolar pressure imposed by the ventilator and the mechanical properties of the lungs. Another possibility for the presence of high V\textsubscript{A}/Q areas is pulmonary arterial microvascular obstruction or frank pulmonary embolus.
3.5.6 Pulmonary embolism

As expected, the $V_A/Q$ pattern is characterized by the appearance of high $V_A/Q$ areas\textsuperscript{27,28} (Fig.49). There is an association between the development of radiologically determined atelectasis and intrapulmonary shunts both appearing to increase in the days following the embolic event\textsuperscript{29}. The degree of $V_A/Q$ mismatch and the level of hypoxemia appear to be a little relation to the percentage obstruction of the vascular bed\textsuperscript{30}. Early in pulmonary embolism, hypoxemia is presumed to be due to just $V_A/Q$ mismatch produced by the embolus; later in the process, however, scattered atelectasis appears to play a role, causing shunt (Fig.49) and hence further hypoxemia.
Figure 49: Example of the distribution of ventilation-perfusion ratios in a patient with severe pulmonary embolus. The dominant abnormality is the appearance of a population of lung units with abnormally high ventilation-perfusion ratios (in this example, comprising more than 50% of the total alveolar ventilation). Areas of low and zero $V_A/Q$ are also seen.
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4 - Helium
Helium (He) is a colorless, odorless, tasteless, non-toxic, nearly inert monatomic chemical element that heads the noble gas series in the periodic table and whose atomic number is 2. Its boiling and melting points are the lowest among the elements and it exists only as a gas except in extreme conditions\(^1\). Extreme conditions are also needed to create the small handful of helium compounds, which are all unstable at standard temperature and pressure (0°C or 273.15 K, and 100 kPa or 1 bar). Its most abundant stable isotope is helium-4 and its rare stable isotope is helium-3. The behavior of liquid helium-4's two varieties—helium I and helium II—is important to researchers studying quantum mechanics (in particular the phenomenon of superfluidity) and those looking at the effects that near absolute zero temperatures have on matter (such as superconductivity).

Helium is the second most abundant and second lightest element in the Periodic Table. In the modern Universe almost all new helium is created as a result of the nuclear fusion of hydrogen in stars. On Earth it is created by the radioactive decay of much heavier elements (alpha particles are helium nuclei). After its creation, part of it is trapped with natural gas in concentrations up to 7% by volume. It is extracted from the natural gas by a low temperature separation process called fractional distillation.

In 1868 the French astronomer Pierre Janssen first detected helium as an unknown yellow spectral line signature in light from a solar eclipse\(^2\). Since then large reserves of helium have been found in the natural gas fields of the United States, which is by far the largest supplier of the gas. The first clinical use of helium is indicated by a patent filed by Charles Cook in 1923 for the use of a helium and oxygen mixture (heliox) to decrease the risk of decompression sickness in divers. In 1934, Barach first described the airway physiology of breathing heliox and advocated for its use in a variety of medical conditions\(^3\). Used sporadically for several decades, heliox has been
revisited as a therapeutic option for a variety of upper and lower airway conditions.

Helium is also used in cryogenics, in deep-sea breathing systems, to cool superconducting magnets, in helium dating, for inflating balloons, for providing lift in airships and as a protective gas for many industrial uses (such as arc welding and growing silicon wafers). Inhaling a small volume of the gas temporarily changes the quality of one’s voice.

4.1 History

4.1.1 Discoveries

Helium was first detected on August 18, 1868 as a bright yellow line with a wavelength of 587.49 nm in the spectrum of the chromosphere of the Sun, by French astronomer Pierre Janssen during a total solar eclipse in India. Janssen was at first ridiculed since no element had ever been detected in space before being found on Earth. October 20th the same year, English astronomer Norman Lockyer also observed the same yellow line in the solar spectrum and concluded that it was caused by an unknown element after unsuccessfully testing to see if it were some new type of hydrogen. Since it was near the Fraunhofer D line he later named the new line D₃, distinguishing it from the nearby D₁ and D₂ doublet lines of sodium. He and English chemist Edward Frankland named the element after the Greek word for the Sun god, Helios, and, assuming it was a metal, gave it an -ium ending (a mistake that was never corrected).

British chemist William Ramsay isolated helium on March 26, 1895 by treating cleveite (now known to be uranite) with mineral acids. Ramsay was looking for argon but noticed the yellow D₃ line after he removed nitrogen and oxygen from the gas liberated by the sulfuric acid he put on the cleveite sample. These samples were identified as helium by Lockyer and British physicist William Crookes. It was independently isolated from cleveite the same year by Swedish chemists. They collected enough of the gas to accurately determine its atomic weight.
An oil drilling operation in Dexter, Kansas created a gas geyser in 1903 that contained 12% by volume of an unidentified gas. American chemists Hamilton Cady and David McFarland of the University of Kansas discovered it was helium and published a paper in 1907 saying that helium could be extracted from natural gas. Also in 1907, Ernest Rutherford and Thomas Royds demonstrated that an alpha particle is a helium nucleus.

Helium was first liquefied by Dutch physicist Heike Kamerlingh Onnes in 1908 in Leiden by cooling the gas to less than one kelvin. He tried to solidify it by reducing the temperature to 0.8 K but failed because helium does not have a triple point temperature where the solid, liquid and gas phases are at equilibrium. It was first solidified in 1926 by his student Willem Hendrik Keesom who subjected helium to a similar amount of cooling as Kamerlingh Onnes but at 25 standard atmospheres of pressure.

In 1938, Russian physicist Pyotr Leonidovich Kapitsa discovered that liquid helium-4 has almost no viscosity at temperatures near absolute zero, a phenomenon now called superfluidity. In 1972, the same phenomenon was observed in liquid helium-3 by American physicists Douglas D. Osheroff, David M. Lee, and Robert C. Richardson.

The first clinical use of helium is indicated by a patent filed by Charles Cook in 1923 for the use of a helium and oxygen mixture (heliox) to decrease the risk of decompression sickness in divers. In 1934, Barach first described the airway physiology of breathing heliox and advocated for its use in a variety of medical conditions.

4.1.2 Production and use

Great quantities of helium were found in the natural gas fields of the American Great Plains, putting the United States in a very good position to become the leading world supplier. Following a suggestion by Sir Richard Threlfall, the United States Navy sponsored three small experimental helium production plants during World War I. Some of this gas was used in the world's first helium-filled airship.

Although the extraction process, using low-temperature gas liquefaction, was not developed in time to be significant during World War I,
production continued. Helium was primarily used as a lifting gas in lighter-than-air craft. This use increased demand during World War II, as well as demands for shielded arc welding. Helium was also vital in the atomic bomb Manhattan project.

Helium use following World War II was depressed but the reserve was expanded in the 1950s to ensure a supply liquid helium as a coolant to create oxygen/hydrogen rocket fuel (among other uses) during the Space Race and Cold War. Helium use in the United States in 1965 was more than eight times the peak wartime consumption.

After the "Helium Acts Amendments of 1960" (Public Law 86-777), the U. S. Bureau of Mines arranged for five private plants to recover helium from natural gas. For this helium conservation program, the Bureau built a 425-mile pipeline from Bushton, Kansas to connect those plants with the government's Cliffside partially depleted gasfield, near Amarillo, Texas. This helium-nitrogen mixture was injected and stored in the Cliffside gasfield until needed, when it then was further purified.

By 1995, 32 billion ft³ (1 billion m³) of the gas had been collected and the reserve was US$ 1.4 billion in debt, prompting the United States Congress to phase out the reserve starting the next year. The resulting "Helium Privatization Act of 1996" directed the United States Department of the Interior to start liquidating the reserve by 2005.

Helium produced before 1945 was about 98% pure (2% nitrogen), which was adequate for airships. In 1945 a small amount of 99.9% helium was produced for welding use. By 1949 commercial quantities of Grade A 99.995% helium were available.

For many years the United States produced over 90% of commercially usable helium in the world. Extraction plants created in Canada, Poland, Russia, and other nations produced the remaining helium. In the early 2000s, Algeria and Qatar were added as well. Algeria quickly became the second leading producer of helium (16% of total in 2002). Through this time helium consumption has increased, as well as costs.
4.1.3 Abundance

Helium is the second most abundant element in the known Universe after hydrogen and constitutes 23% of all elemental matter measured by mass even though there are 8 times as many hydrogen atoms as helium. It is concentrated in stars (especially hotter ones), where it is formed from hydrogen by the nuclear fusion of the proton-proton chain reaction and CNO cycle. This so-called ‘hydrogen burning’ process provides the energy stars need to shine. According to the Big Bang model of the early development of the Universe, the vast majority of helium was formed in the first three minutes after the Big Bang. Its widespread and large abundance is part of the evidence that supports this theory.

However, in the Earth’s atmosphere, the concentration of helium by volume is only 5.2 parts per million at sea level and up to 15 miles (24 km), largely because most helium in the Earth's atmosphere escapes into space due to its inertness and low mass. There is a layer in the heterosphere (a part of the Earth’s upper atmosphere) at about 1000 km where helium is the dominant gas (although the total pressure is very low). Helium is the 71st most abundant element in the Earth’s crust where it is found in 8 parts per billion ($10^9$). Helium only makes up 4 parts per trillion ($10^{12}$) in seawater.

Essentially all helium on Earth is a result of radioactive decay of elements such as uranium and radon. A type of radiation called alpha rays are made of two protons and two neutrons, which also makes them helium-4 nuclei. These +2 positive ions easily gain the two electrons needed to make complete helium atoms. In this way an estimated 0.5 ft$^3$ of helium is produced from every cubic mile of the Earth's crust (3.4 L/km$^3$) per year. This decay product is found in minerals of uranium and thorium, including cleveites, pitchblende, carnotite, monazite and beryl. There are also small amounts in mineral springs, volcanic gas and meteoric iron.
4.2 Notable characteristics

4.2.1 Gas and plasma phases

Helium is a colorless, odorless, and non-toxic gas. It is the least reactive member of group 18 (the noble gases) of the periodic table and therefore virtually inert. Under standard temperature and pressure helium behaves very much like an ideal gas. Under virtually all conditions helium is mono-atomic. It has a thermal conductivity that is greater than any gas except hydrogen and its specific heat is unusually high. Helium is also less water soluble than any other known gas and its diffusion rate through solids is three times that of air and around 65% that of hydrogen.

Helium is chemically unreactive under all normal conditions due to its valence of zero. It is an electrical insulator unless ionized.

4.2.2 Solid and liquid phases

Helium solidifies only under great pressure. The resulting colorless almost invisible solid is highly compressible; applying pressure in the laboratory can decrease its volume by more than 30%. With a bulk modulus on the order of $5 \times 10^7$ Pa it is 50 times more compressible than water. Unlike any other element, helium will fail to solidify and remain a liquid down to absolute zero at normal pressures.

4.3 Medical applications

Substituting helium for nitrogen in a gas mixture changes the physical properties of the inhaled gas, and underlies the theoretical rationale for the clinical application of heliox. Stated differently, by decreasing gas density, airway resistance can be decreased in the absence of any anatomical change.

Heliox is a gas that is composed of a mixture of helium (He) and oxygen (O₂). The term Heliox generally describes a mixture that is 21% O₂ (the same as air) and 79% He, although other mixtures are available (Fig.50). Heliox has been used in a medical context since the 1930s, and although the medical community adopted its use initially to alleviate the
symptoms of upper airway obstruction, its range of medical uses has since expanded greatly, most of which are dependent on the low density of heliox.

![Image of Helium and Oxygen container](image)

**Figure 50: Picture of our mixture of Helium and Oxygen container.**

Therapeutic use of heliox capitalizes on the physical effect of lowering gas density to improve air flow as predicted by the fluid dynamic paradigm. In contrast, the diagnostic use of helium to measure lung volumes by gas dilution is not based on low density, but on the fact that helium is inert and has low solubility in blood. The measurement of lung volume by the inert gas dilution technique is performed routinely in pulmonary function laboratories around the world, and accounts for the vast majority of helium used for medical purposes. There are four methods of measuring total lung capacity (TLC):

- Helium dilution
- Nitrogen washout
- Body plethysmography
• Chest radiograph measurements

The first 3 methods are used extensively in hospital pulmonary function laboratories, but Helium dilution and Nitrogen washout may underestimate the TLC in patients with moderate to severe COPD.

Measurements of TLC using the chest radiograph correlate within 15 percent of those obtained by body plethysmography and is not used in routine.

The energy expenditure required to overcome airway resistance is negligible during resting ventilation in the normal lung. Thus, the physical properties of the inspired gas do not ordinarily play a significant role in determining the work of breathing or in limiting ventilation. However, with alteration of airway geometry, particularly during excessive ventilatory demand, the resistive work of breathing can become sufficiently elevated to limit ventilation and fatigue the muscles of breathing. Under these circumstances, manipulation of the physical properties of the inspired gas mixture can have important clinical applications.

In theory, the benefits of heliox in patients with high airway resistance are due to decreasing Re and flow resistance, resulting in improved ventilation and a decreased work of breathing. By decreasing the density of the inhaled gas, heliox decreases the applied force required to achieve a given flow rate.

### 4.3.1 Use in children

There have been several reports describing the use of heliox in the following pediatric populations:

• Children with upper airway obstruction due to compression, postextubation stridor, and croup

• Children with lower airway obstruction due to bronchiolitis, status asthmaticus, or respiratory distress syndrome
• Children with bronchopulmonary dysplasia (in whom heliox decreases the work of breathing)\textsuperscript{18}

\subsection*{4.3.1.1 Postextubation stridor}

Two studies have found that heliox is beneficial in patients with postextubation stridor\textsuperscript{9,10}. One described the use of heliox in eleven children with postextubation stridor. Following initial extubation, none of the patients responded to nebulized racemic epinephrine, and all were subsequently reintubated\textsuperscript{10}. Eight patients developed recurrent stridor at the time of their second extubation, and again all eight failed to respond to treatment with nebulized racemic epinephrine. Following treatment with heliox, seven patients had improvement in their respiratory distress scores, and six (75 percent) avoided reintubation. Both of the patients in the trial who required reintubation were started on heliox much later than those who were successfully treated (10 and 20 hours, versus a mean of 1 hour).

A randomized, double-blind crossover trial studied the effects of heliox (70:30) in 13 children thought to be at high risk of postextubation stridor\textsuperscript{9}. Each patient served as his or her own control by breathing air-oxygen or heliox for 15 minutes following extubation. Respiratory distress scores were significantly lower while breathing heliox.

\subsection*{4.3.1.2 Croup}

While heliox improves respiratory distress, as evidenced by improvement in croup scores, heliox is not superior to other conventional therapies. Proponents of heliox argue that the combination of heliox and conventional therapies allows a substantial reduction in work of breathing, respiratory distress, and the likelihood of intubation while waiting for the corticosteroids to take effect\textsuperscript{19}.

\subsection*{4.3.1.3 Bronchiolitis}

The use of heliox in bronchiolitis is discussed separately. The use of heliox in the treatment of moderate or severe bronchiolitis has been evaluated in several small randomized trials with mixed results\textsuperscript{13,20}. One
study found no difference in the proportion of infants requiring mechanical ventilation, but the number of patients enrolled might have been too small to detect such a difference. Other studies noted clinical improvement in some parameters and decreased duration of ICU stay (3.5 versus 5.4 days). Administration of heliox is cumbersome and results in a relatively small benefit in a limited group of infants.

4.3.1.4 Asthma

In children with acute severe asthma, two double-blind randomized controlled trials and one meta-analysis have reported conflicting results. One trial enrolled 18 patients, aged 16 months to 18 years old, who presented to an emergency department with status asthmaticus. Treatment arms compared heliox (80:20) to room air at 10 L/min via a nonrebreathing face-mask. Patients breathing heliox had significantly greater reductions in pulsus paradoxus (from a mean of 23.3 to 10.6 mmHg) and in subjective dyspnea, as well as significantly greater increases in peak expiratory flow compared with patients breathing air. These variables returned to baseline values after heliox was discontinued. The authors estimated that intubation was avoided in three patients due to the beneficial effects of heliox.

In contrast, a crossover study of 11 children with acute asthma presenting with a mean FEV1 below 50 percent predicted randomly assigned subjects to treatment with either heliox (70:30) or 30 percent oxygen-enriched air. No differences in FEV1, FVC, clinical assessment of disease severity, or subjective dyspnea scores were noted. Although there was a significant increase in FEF25-75 and peak expiratory flow rates (PEFR), the clinical significance of these findings is unclear.

A systematic analysis pooled and analyzed results from seven trials enrolling nearly 400 patients with acute asthma. Studies included both adult and pediatric populations. No significant improvement in recovery of pulmonary function was noted in patients treated with heliox. No significant differences in outcome were noted when adults and pediatric populations were analyzed separately, or when high versus low helium ratio studies were compared.
4.3.1.5 Respiratory distress syndrome

The role of heliox has also been studied in infants with the respiratory distress syndrome (RDS). One study randomly assigned 30 infants with RDS to treatment with either heliox (78:22) or "AirOx" (78 percent nitrogen:22 percent oxygen). After two days of mechanical ventilation, there was a significant increase in the transcutaneous PO$_2$/FiO$_2$ ratio in the group receiving heliox. In addition, mean airway pressure required for ventilation was significantly lower in the heliox group by day four. Nonsignificant trends toward fewer days of mechanical ventilation, lower mortality, and decreased incidence of bronchopulmonary dysplasia were also noted.

4.3.1.6 Work of breathing

Breathing mechanics have been studied in infants with bronchopulmonary dysplasia treated with heliox. One group found that compared to breathing air, infants breathing heliox (either 80:20 or 70:30) had lower swings in esophageal pressure, as well as significant reductions in inspiratory and expiratory resistance. In addition, the mechanical power of breathing (work/minute) and the oxygen cost of breathing were reduced with heliox.

These changes were observed in the absence of any change in tidal volume, respiratory rate, or minute volume. Stated more simply, the infants breathing heliox had to work less in order to maintain the same ventilation. The authors calculated a caloric savings of 1.87 kcal/kg/day for infants with bronchopulmonary dysplasia treated with heliox. The decreased energy required to maintain ventilation in patients treated with heliox may increase calories available for growth and hasten recovery, but these findings are speculative.

4.3.2 Use in adults

There are numerous case reports of clinical improvement in patients treated with heliox following upper airway obstruction due to thyroid masses,
radiation injury, lymphoma, cancer, or angioedema. As noted, the greatest theoretical benefit of heliox is achieved by decreasing turbulent flow in large airways and at branch points in the tracheobronchial tree. Thus, patients with upper airway obstruction would be expected to derive the greatest benefit from heliox therapy. However, because upper airway compromise is relatively rare and often a medical emergency, few controlled studies of heliox treatment in this setting have been published. For this reason, the use of heliox in adults has primarily focused on treating patients with severe asthma as well as chronic obstructive pulmonary disease (COPD).

4.3.2.1 Asthma

Heliox is unlikely to be of substantial benefit in adults with asthma. As noted above, a systematic analysis pooled and analyzed results from seven trials enrolling nearly 400 patients and found no significant improvement in recovery of pulmonary function in patients with acute asthma who were treated with heliox. Furthermore, no significant difference in outcome was noted when adults were analyzed separately, or when high versus low dose studies were compared. Other systematic reviews have reached the same conclusions.

On the other hand, beneficial effects may be seen with heliox early in asthma therapy, before steroids are able to affect the underlying disease process. This was demonstrated in a randomized, controlled trial of heliox therapy in 23 adults with acute severe asthma and peak flow (PF) <200 despite treatment with 5 mg of nebulized albuterol. Heliox (70:30) was compared with standard oxygen supplementation. Patients in both the heliox and control groups had significant improvements in PF and dyspnea during the eight hours of the study. There were significant differences between the heliox and control groups only during the first 20 minutes of the study. By six hours, there were no differences between the groups.

As in the pediatric population, heliox has been shown to reduce pulsus paradoxus and improve PF rates and dyspnea scores in adults with asthma exacerbations. In a study of 27 patients, the improvements in
pulsus paradoxus and PF were significantly greater in patients breathing heliox than in controls. No significant change in PaCO₂ or PaO₂ was noted in the seven patients treated with heliox who had blood gases drawn.

4.3.2.2 Asthma complicated by respiratory failure

Two small, uncontrolled series investigated the effects of heliox in intubated patients with status asthmaticus and respiratory acidosis. Following ventilation with 60 to 80 percent helium, all patients in one series experienced significant improvement in respiratory acidosis (mean reduction in PaCO₂ 35 mmHg) in one series. In addition, six of seven patients had a dramatic reduction in peak airway pressures (mean fall 32 cmH₂O).

One series of twelve asthmatics presenting to an emergency department with hypercapnic respiratory failure analyzed both intubated and nonintubated patients treated with heliox (70:30 or 60:40) in one hour; however, results were not uniform, with eight patients demonstrating a positive response and four not improving.

4.3.2.3 Stable COPD

One study examined the effects of heliox (80:20) in 15 patients with stable, but severe, COPD. Heliox was associated with a small drop in CO₂ production and a reduction of the functional residual capacity (FRC), which implies decreased dynamic hyperinflation (ie, air trapping). The PaO₂, respiratory rate, minute ventilation, tidal volume, breathing pattern, and dead space fraction did not change. In contrast, another small study found no effect on dynamic hyperinflation.

Heliox may improve exercise performance. In a randomized crossover trial, 82 patients with moderate to severe COPD had their exercise performance measured and dyspnea evaluated while receiving one of four different gases: Heliox28 (72:28), Heliox21 (79:21), Oxygen28 (72 percent nitrogen:28 percent oxygen), or medical air (79 percent nitrogen:21 percent oxygen). Patients breathing Heliox28 had better exercise performance and...
less dyspnea than all other groups. All of the gases improved exercise performance and dyspnea compared to medical air.

Future studies will need to confirm these findings and determine whether the improved exercise performance and dyspnea warrants the additional cost (approximately 3.5 times more expensive than oxygen per tank and requires more tanks per day).

4.3.2.4 Acute exacerbation of COPD

Several trials have compared noninvasive positive pressure ventilation (NPPV) with either air or heliox in patients with exacerbations of chronic obstructive pulmonary disease.\(^{36,37}\)

In one well-designed trial, patients with acute exacerbations of COPD were treated with low or high pressure NPPV in combination with heliox or oxygen-supplemented air.\(^{36}\) Differences in breathing pattern, work of breathing, and gas exchange were measured in nine patients using an esophageal balloon technique. Heliox was not associated with changes in breathing pattern, whereas high pressure NPPV produced significant increases in tidal volume and minute ventilation.

Heliox was associated with a reduction in PaCO\(_2\) and improvement in all measured indices of respiratory effort and work. The beneficial effects on the measured variables were further increased when high pressure NPPV was combined with heliox. Compared to the low pressure/air group, respiratory effort was reduced by:

- 15 percent in the low pressure/heliox group
- 35 percent in the high pressure/air group
- 50 percent in the high pressure/heliox group

The authors suggest that the addition of heliox to NPPV may allow a larger number of patients to benefit from NPPV. In addition, heliox may allow the use of lower levels of pressure support, which could reduce complications and patient discomfort resulting from high pressures and flow rates.\(^{36}\).
A crossover study monitored the effects of NPPV plus either heliox (70:30) or air-oxygen (70:30) on gas exchange and dyspnea in 19 patients with severe COPD\textsuperscript{37}. The use of heliox decreased PaCO\textsubscript{2}, reduced dyspnea, and favorably changed the breathing pattern of patients. Peak inspiratory flow rates were higher, while inspiratory time and the ratio of inspiratory time to respiratory cycle length were both decreased. All of these findings suggest a reduced work of breathing.

A third series involving 23 intubated patients with COPD and respiratory failure found that the administration of heliox significantly reduced intrinsic PEEP, trapped lung volume, and peak and mean airway pressures\textsuperscript{38}. There was no effect on hemodynamics or arterial blood gases. Twelve patients had a pulmonary artery catheter in place at the time of study; no changes in mixed venous PO\textsubscript{2} were noted. Similar findings were noted in a second small study of 12 patients recovering from acute exacerbations of COPD. In this randomized prospective crossover trial, heliox decreased the resistive work of breathing and intrinsic positive end-expiratory pressure (auto-PEEP) without changing the breathing pattern\textsuperscript{39}.

The effect of heliox in the absence of positive pressure ventilation is less well studied. A retrospective review of 81 patients presenting to the emergency department with COPD and hypercarbic respiratory insufficiency found a significant reduction in the rates of intubation (8 versus 50 percent) and in-hospital mortality (3 versus 24 percent) in the patients who received heliox as compared to control patients\textsuperscript{40}. The retrospective nature of this article precludes causal inference between heliox use and the endpoints studied, but does support the need for larger randomized trials.

### 4.3.2.5 Work of breathing

In a study focusing on physiologic, rather than clinical endpoints, researchers used an esophageal balloon in recently extubated patients without significant lung disease to quantify intrathoracic pressure swings and estimate the work of breathing\textsuperscript{41}. Fifteen of 18 patients exhibited a drop in their work of breathing, although gas exchange parameters were
unchanged. In addition, patients reported decreased dyspnea while breathing heliox.

Finally, one study examined the impact of heliox on pulmonary function in ten patients with mild COPD during cardiopulmonary exercise testing. Heliox was associated with an increase in minute ventilation, in the absence of any change in the metabolic cost of breathing.

### 4.3.3 Technical issues

There are two technical issues concerning both the clinical and research application of heliox. First, significant changes in the delivery of nebulized medicine occur when heliox is employed as the driving gas. Second, because the difference in physical properties between air or oxygen and heliox, calibration and function of pneumotachometers and ventilator flow sensors can be significantly altered.

#### 4.3.3.1 Aerosol delivery

To understand the effects of heliox on nebulizer function and aerosol delivery, it is important to consider that nebulizers use Bernoulli’s principle to generate an aerosol. Mathematically, this can be described by the equation:

\[ (P_1 - P_2) = 0.5 \times m \times ((V_2)^2 - (V_1)^2) \]

where \( P_1 - P_2 \) is the pressure drop across the nebulizer orifice, \( m \) is the mass of the gas, and \( (V_2)^2 - (V_1)^2 \) is the change in velocity of the gas across the orifice.

For a given flow rate, the use of heliox as a driving gas results in a lower pressure drop across the nebulizer orifice. This causes a lower inhaled mass of medication, or longer nebulization time in order to deliver the same amount of drug. One group concluded that when heliox is used as a driving gas for nebulization, the flow rate should be increased by approximately 50 percent.

On the other hand, when heliox is used as the driving gas for aerosolization, the particle size of the nebulized solution is reduced, which may enhance drug delivery. This hypothesis was evaluated in two studies examining lung deposition of heliox-driven aerosols in humans. In one
report, nine subjects with stable asthma inhaled radiolabeled Teflon particles suspended in either air or heliox. Heliox inhalation resulted in significantly lower oral deposition as well as higher particle retention in the lungs at 24 hours. Another report found a similar increase in lung deposition in patients with induced bronchoconstriction who received heliox-driven nebulized therapy. However, the results of these clinical trials remain controversial.

4.3.3.2 Instrument sensitivity

Graham’s law states that the flow of gas through an orifice is inversely proportional to the square root of its density. Thus, the actual flow rate of heliox through an oxygen flow meter is 1.8 times greater than the indicated flow. For this reason, mechanical ventilators and pneumotachometers need to be recalibrated when heliox is being used.

The changes in delivered FiO₂ and tidal volume induced by heliox vary among ventilators. Suggested correction factors are available for most ventilators in the United States and Europe. In addition to errors of calibration, some of the most commonly used critical care ventilators, including the Puritan-Bennett 7200 series, are unable to function when heliox is used. Servo ventilators are able to deliver heliox and require relatively simple calibration.

High-frequency oscillatory ventilation (HFOV) with heliox requires a lower oscillation amplitude than HFOV using oxygen-enriched air to achieve the same minute ventilation.

The lack of a clearly defined calibration scheme for pneumotachometers has been raised as a possible confounder in many of the studies investigating the role of heliox in acute asthma. It is possible, particularly in studies where PEFR improved in the absence of a clear change in FEV₁, that much of this effect might be due to inaccurate sensing of low density gas flow rates.
4.3.4 Limitations of clinical studies

Most clinical trials of heliox have enrolled fewer than thirty patients. Furthermore, inclusion criteria and clinical outcomes are not standardized across studies, making direct comparison difficult. As an example, the ratio of helium to oxygen varies across and within the studies presented below. Most protocols employed an 80:20 or 70:30 helium to oxygen ratio, but little information exists regarding optimum dosing. This is an important consideration because increasing the oxygen fraction diminishes the beneficial effect of low density gas inhalation, while increasing the amount of helium can worsen alveolar hypoxia.

Heliox also affects the performance of diagnostic equipment, mechanical ventilators, and the delivery of aerosolized medication. These factors may introduce methodological error or uncontrolled variables, and further limit generalization of some study conclusions.

Finally, heliox may provide its greatest benefit in urgent cases, particularly acute upper airway obstruction. Randomized application of emergency therapy is difficult, and many patients are treated with multiple interventions simultaneously. With these limitations in mind, the following is a brief review of modern clinical trials of heliox therapy in both pediatric and adult patient populations.

4.4 Other applications

Pressurized helium is commercially available and is extracted from natural gas. Helium is used for many purposes that require one or more of its unique properties; low boiling point, low density, low solubility, high thermal conductivity, or its inertness.
4.4.1 Balloons

Airships (Fig.51) and balloons (toy, weather, and research) are inflated with helium because it is lighter than air (1 m³ of helium will lift 1 kg). Helium is currently preferred to hydrogen in airships because, while it is more expensive, it is not flammable and has 92.64% of the lifting power of hydrogen.

![USGS blimp](image)

*Figure 51: Because of its low density, helium is the gas of choice to fill Airships such as the USGS blimp.*

4.4.2 Scuba diving

Scuba (Self-Contained Underwater Breathing Apparatus) diving is used in commercial, recreational and scientific activities. The most widely gas mixture used by divers is air. However, N₂-O₂ has potentially fatal side-effects when the diver is exposed to high pressures.

*Trimix* (Fig.52), a mixture of helium, oxygen, and nitrogen, is used in deep-sea breathing systems to reduce the risk of nitrogen narcosis (high pressure nitrogen having a narcotic effect on the brain), the bends (a very painful and possibly disabling or fatal condition that occurs when nitrogen
comes out of solution in blood and collects in joints), and oxygen toxicity at high pressures.

Higher pressures require a greater proportion of helium and reduced amounts of nitrogen and oxygen (every ten meter increase in depth yields a one atmosphere increase of pressure). Heliox, a mixture of helium and oxygen, is also used in this way. Below 600 meters (2000 ft) a mixture of hydrogen, helium, and oxygen called hydreliox (Fig.53) is used to help prevent hight pressure nervous syndrome\textsuperscript{56}. All these uses rely on helium's very low solubility in water (the major component of blood).
4.4.3 Vocal effect and health precautions

The voice of a person who has inhaled helium temporarily sounds high-pitched. This is because the speed of sound in helium is nearly three times that in air. As a result, when helium is inhaled there is a corresponding increase in the resonant frequencies of the vocal tract. The higher perceived pitch is only due to a different frequency shaping of the voice, the fundamental frequency of the vocal cords remaining more or less the same.

Although the vocal effect of inhaling helium may be amusing, it can be dangerous if done to excess. The reason is not due to toxicity or any property of helium but simply due to it displacing oxygen needed for normal respiration. One must be aware that in mammals (with the notable exception of seals) the breathing reflex is not triggered by insufficient oxygen but rather excess of carbon dioxide. Unconsciousness, brain damage and even asphyxiation followed by death may result in extreme cases. Also, if helium is inhaled directly from pressurized cylinders the high flow rate can fatally rupture lung tissue.

Neutral helium at standard conditions is non-toxic, plays no biological role and is found in trace amounts in human blood. At high pressures, a mixture of helium and oxygen (heliox) can lead to high pressure nervous syndrome (HPNS). Adding 10 percent nitrogen to a helium/oxygen
mixture, combined with the use of a proper compression rate, ameliorates many of the serious symptoms of HPNS\textsuperscript{57}.

Containers of helium gas at 5 to 10 K should be treated as if they have liquid inside. This is due to the rapid and large increases in pressure and, if allowed, volume that occur when helium gas at that temperature is warmed to room temperature.

4.4.4 Other uses

- The extremely low boiling point makes helium useful as a coolant in magnetic resonance imaging, superconducting magnets, cryogenics, and to remove thermal noise from detectors used in astronomy. The extreme coldness of liquid helium is also used to produce superconductivity in some ordinary metals such as lead (lead becomes superconductive at 7.3 K), allowing for a completely free flow of electrons in the metal.
- Because of its high thermal conductivity and inertness, helium is used as a coolant in some nuclear reactors (for example, pebble-bed reactors) and in arc welding air-sensitive metals that require heavy welds.
- Its inertness makes it useful as a protective gas in growing silicon and germanium crystals, in titanium and zirconium production, in protecting important historical documents, and in gas chromatography. This property also makes it useful in pressurizing liquid fuel rockets (see below) and in supersonic wind tunnels.
- The gain medium of the helium neon-laser (the first gas laser) most commonly used to scan bar codes is a mixture of helium and neon.
- This gas’ rate of diffusion through solids is three times that of normal air, making it an excellent component in leak detection in high-vacuum equipment and high pressure containers.
- In rocketry helium is used as an ullage medium to displace fuel and oxidizers in storage tanks and to condense hydrogen and oxygen to make rocket fuel. It is also used to purge fuel and oxidizer from
ground support equipment prior to launch and to precool liquid hydrogen in space vehicles.

- Physics researchers use alpha particles (helium nuclei) in particle accelerators and nuclear reaction experiments.

- Helium gas is used to fill the space between lenses in some solar telescopes because its extremely low index of refraction reduces the distorting effect of temperature variations in the gas filling the telescope (some telescopes are filled with vacuum instead)\(^5\).

- Radioactive decay of uranium and thorium produces alpha particles that quickly become helium. This happens at a known constant rate so if the containing rock or mineral can retain its helium then the ratio of helium to its radioactive parent atoms indicates its age. Alternatively, if the helium is not well-retained, the ratio of helium-3 to helium-4 contains some of the same information, since only helium-4 is produced by radioactive decay. Use of helium in this way is called helium dating.
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5- Validation of a porcine model of induced bronchospasm

Introduction

The complex physiopathology of asthma, the variability of disease between patients and their response to therapy make the study of a single agent during acute severe bronchospasm difficult to extrapolate to the clinical setting. That is the reason why it was necessary to study the specific effects of helium in a stable model of induced bronchospasm. Furthermore and to have a complete view of helium's effects, it was necessary to study the consequences of helium’s physical properties on the respiratory mechanics and to observe its impact on ventilation-perfusion relationships. Because the technique of MIGET needs a stability period of at least 15 minutes, the first step of our work was to reproduce the physiopathological characteristics of acute severe asthma in an animal model with high level of stability.

Since the respiratory mechanics are more easy to study in a big animal and because the pig is physiologically close to human, we have chosen to study this animal.
5 – Animal model of bronchospasm
An improved porcine model of stable methacholine-induced bronchospasm

Abstract: Objective: To validate an animal model replicating the pathophysiological characteristics of severe induced bronchospasm observed in humans, with a high level of stability permitting measurements such as the assessment of ventilation-perfusion relationships with the multiple inert gas elimination technique. Design and setting: Experimental study in an animal research laboratory. Subjects: 13 pigs (age 3–4 months) were studied and 7 underwent the complete protocol intervention. The animals were anaesthetized and paralyzed. Mechanical ventilation was initiated in a volume-controlled mode. Ventilatory parameters were adjusted to obtain normocapnia and were maintained constant during the bronchospasm. Methacholine was administered via a synchronized nebulizer and progressively adjusted to obtain a stable twofold increase in peak inspiratory pressure. Measurements and results: Cardio-pulmonary physiological data including assessment of lung mechanics and measurement of ventilation-perfusion relationships were obtained before and during the bronchospasm. Peak inspiratory pressure increased from 19.4±2.9 to 44.4±7.1 cmH2O during the bronchospasm. The latter remained stable over 3 h. Respiratory mechanics, gas exchange, and ventilation-perfusion distribution changes typical of those observed in severe bronchospasm in humans were observed in all animals. Conclusion: The present experimental model replicates some of the pathophysiological characteristics of severe human bronchospasm, and its stability should facilitate studies of the effects of different ventilatory modes in the setting of acute severe asthma.

Keywords: Asthma physiopathology - Ventilation perfusion ratio - Animal model
5 – Animal model of bronchospasm

Introduction
Severe asthmatic attack is a life-threatening condition, whose rapid worsening can require endotracheal intubation and mechanical ventilation. The substantial increase in airway resistance and marked heterogeneity of the distribution of ventilation may cause baro and volutrauma [1], in turn leading to increased morbidity and mortality [2]. Ventilatory techniques such as controlled hyperventilation [3] and the use of helium-oxygen gas mixtures [4] have shown promising results in this setting, but documentation of their various effects on respiratory mechanics and gas exchange in the carefully controlled conditions of a stable animal model have been lacking. Several animal models have been used to assess the efficacy of various ventilatory modes during bronchospasm [5, 6, 7]. However, all such models have faced the difficult problem of maintaining a stable level of induced bronchospasm. The multiple inert gas elimination technique (MIGET) [8] is a robust tool to assess both ventilation-perfusion \( (V_{A}/Q) \) distributions and the role of extrapulmonary factors determining arterial oxygenation in acute severe asthma [9, 10]. However, this technique requires a steady state period of at least 20 min [9].

The aim of this study was to develop a model of stable methacholine (MCh) induced bronchospasm reproducing some of the physiopathological changes observed in human to allow future studies by the MIGET of the impact of various mechanical ventilation and gas mixture strategies on the ventilation-perfusion relationships.

Materials and methods

Study protocol
The ethics committee of our university approved the study protocol. Thirteen young pigs (age 3-4 months, weighing 30-35 kg) were used in this study. The animals came from a farm and stayed in the laboratory for a period ranging from 1 to 3 weeks prior to the study. They were fed with a standardized diet without antibiotics. The animals were caged for in accordance with the standards for care and use of laboratory animals set forth by the University of Louvain. They were anesthetized and mechanically ventilated. Baseline values were obtained after 30 min of stabilization, following which bronchospasm was induced. All the hemodynamic, gas exchange, and ventilatory parameters were measured after stabilization of the bronchospasm. At the end of the experiment the animals were killed using a solution of embutramide, nembutal, meprobamate, and etacaine (T6, Intervet, Michelon, Belgium).

Anesthesia
Animals were anesthetized with 2 mg/kg xylazine hydrochloride (Rompun, Bayer, Leverkusen, Germany) intramuscularly and a combination of thiopental/kepoxones (Zolurel, Vereca, Belgium) at 7.5 mg/kg intramuscularly. An intravenous catheter was placed in an auricular vein, permitting supplemental intravenous anesthesia with propofol (Diprivan, AstraZeneca, Belgium) at 2 mg/kg per hour. All the animals were placed in supine position and intubated with a 6.5 mm inner-diameter cuffed endotracheal tube (SIMS Portex, Hythe, UK) and mechanically ventilated by a Servo 900C ventilator (Siemens Elma, Solna, Sweden). Muscle paralysis was obtained with an intravenous bolus of 0.1 mg/kg pancuronium bromide (Pavulon, Organon Teknika, Oss, The Netherlands) and maintained with 0.2 mg/kg per hour. Intravascular catheters were surgically placed. An 8.5 Fr Swan-Ganz introducer was placed in the left external jugular vein for drug administration and inert gas solution infusion.

The catheter for invasive blood pressure measurement and sampling was placed in a carotid artery. A CCO-SVo, Swan-Ganz catheter (Edwards Lifesciences, Germany) was introduced via the right internal jugular vein into the pulmonary artery, enabling on-line measurements of cardiac output, blood temperature, the mixed venous oxygen saturation and the withdrawal of blood samples.

Mechanical ventilation
Mechanical ventilation was performed in volume-controlled mode, set with the following initial parameters: tidal volume: 10 ml/kg, respiratory rate: 17 cycles/min, fraction of inspired oxygen 0.30, positive end-expiratory pressure (PEEP) 0 cmH2O, inspiratory rise time 35%, no plateau. A synchronized ventilator (Servo/Neubauer 945 Siemens) was connected to the respiratory circuit. An Ohmeda 5310 (Ohmeda, Louisville, Colo., USA) vol-ume monitor connected to the inspiratory tubing of the ventilator continuously measured tidal volume. Ventilation was adjusted to obtain normocapnia. All ventilatory parameters were kept constant during the subsequent phases of the experiment. Minute ventilation was checked by filling a neoprene balloon connected to the expiratory port of the ventilator for 7 mm and measuring the volume of the gas with a dry gasmeter (DTM 415, Singer, American Meter Company) after correction for the body temperature and pressure conditions. The following parameters were monitored: heart rate, arterial oxygen saturation, end tidal CO2, peak inspiratory pressure (PIP), and mean inspiratory pressure.

Lung mechanics
A disposable esophageal balloon (International Medical, Holland) was introduced via a 6 mm inner-diameter endotracheal tube (Portex) to avoid damaging the balloon. The balloon was filled with 1 cc air after manual compression of the thorax. The catheter was connected to a -140 cmH2O Validyne differential pressure transducer (Validyne Engineering, Northridge, Calif., USA). The correct placement of the esophageal balloon was determined to obtain a representative pleural pressure by a standard technique [11] and checked using the occlusion test [12]. The balloon was emptied and refilled with air before each measurement. A Fleisch no. 2 pneumotachograph (Fleisch, Lausanne, Switzerland) was connected between the esophageal tube and the ventilator. Airflow was measured by the pneumotachograph connected to a ±25 cmH2O Validyne differential pressure transducer. Volume was obtained by electrical integration of the flow signal. A T-tube was placed between the ventilator and the pneumotachograph, and connected to (g) the other port of the pressure transducer used for esophageal pressure to measure the transepithelial pressure and (h) a 140 cmH2O differential pressure transducer for the measurement of airway pressure. The pressure, flow, and volume signals were recorded on paper with a Gould electronic recorder (TA 11, Gould Instrument, Valley View, USA). The pneumotachograph was calibrated with a manometer and the pressure transducers with an alcohol manometerometer. The traces of P, V and V and their calibrations were scanned and digitized (Ur-Scan, IL, Silk Scientific, Orem, USA). Lung resistance (R) and dynamic elastance (Ed) were calculated by multiple linear
5 – Animal model of bronchospasm

Ventilation-perfusion relationships

The $V_{O}/Q$ ratio was measured according to the MIGET of Wagner et al. [11]. Six inert gases of different solubilities ($SF_{6}$, ethane, cyclopropane, halothane, ether, and acetylene) equilibrated in 0.9% NaCl were infused at a constant rate of 3 ml/min through a central venous catheter (the Swann-Ganz introducer). After an equilibration period of 30 min double 10-ml blood samples from the carotid artery and 3-ml blood samples from the pulmonary artery were taken into heparinized 20-ml glass syringes (Hamilton 50 TLL). Samples of mixed expired gas were collected from the exhaust port of the ventilator into 30-ml gas-tight syringes (Hamilton 50 TLL). At least two samples of mixed expired gas were taken at ± 2 min intervals. Inert gas concentrations were determined with a Perkins Elmer gas chromatograph equipped with an electron capture detector for SF$_6$ and a flame ionization detector for the other five gases. For each gas retention (ratio of arterial to mixed venous concentration) and excretion (ratio of mixed expired air to mixed venous concentration) were calculated. The computer program of Evans and Wagner [15] calculated the continuous distribution of blood flow and ventilation against the ventilation-perfusion ratio from these data. The width of ventilation and perfusion distribution was measured by the log standard deviation (log SD). The log SD Q and log SD V were markers of the dispersion of the distribution of perfusion and ventilation, and consequently of the overall $V_{O}/Q_{m}$ heterogeneity.

Methacholine challenge

The bronchoconstrictive agent was given continuously. An initial dose of 8 mg/kg MCh was administered during 3 min. PIP was continuously observed, and the concentration of MCh was adjusted to obtain an increase in PIP up to 40 cmH$_2$O. Once this level was attained, MCh concentration was readjusted, as needed, to stabilize the level of bronchospasm. Figure 1 presents one example of the course of PIP during the successive adjustments of MCh concentration. To evaluate the stability of the bronchospasm in terms of gas exchange, the mixed expired PO$_2$ and PO$_4$ obtained at a 2-min interval (at the moment the samples were collected for the MIGET) were compared.

Statistical methods

Values reported in the results are expressed as mean standard deviation. The paired Student’s t test was used to compare the values obtained before and during bronchospasm. A p value less than 0.05 was considered as statistically significant. Statistics were computed using Systat 8.0 software (SPSS, Chicago, Ill., USA).

Results

A total of 13 animals were used for the study. The first animal died during induction of anesthesia, probably because of acute pulmonary edema. A second animal was used to test the intravenous and aerosolized administration of MCh. The next two animals were used to refine the administration and the initial dose of MCh, and dose-response to maintain a stable level of bronchospasm. Two other animals were excluded from the study because they presented severe ventilation/perfusion inequalities before induction of the bronchospasm. Seven animals underwent the complete protocol.

Table 1 shows the impact of the induced bronchospasm on respiratory system mechanics, hemodynamics,
Table 2. Effect of the bronchospasm on inert gas parameters (V̇\textsubscript{E}/Q̇\textsubscript{L}) ventilation to perfusion ratio. QT pulmonary blood flow, VE minute ventilation, Log SD Q̇\textsubscript{L} log standard deviation of perfusion distribution, Log SD V̇̇̇ \textsubscript{E} log standard deviation of ventilation distribution, Dist R-E* heterogeneity index of \textsubscript{Q}E/\textsubscript{L} residual sum of squares. 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Bronchospasm</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>S joint (% QT)</td>
<td>3.3±0.9</td>
<td>0.3±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>0.05\textsubscript{e}/Q̇\textsubscript{L}0.01 (% QT)</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>NS</td>
</tr>
<tr>
<td>0.01\textsubscript{e}/Q̇\textsubscript{L}0.1 (% QT)</td>
<td>0.0±0.0</td>
<td>41.2±30.3</td>
<td>0.002</td>
</tr>
<tr>
<td>0.1\textsubscript{e}/Q̇\textsubscript{L}0.1 (% QT)</td>
<td>80.7±60.0</td>
<td>32.7±21.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1\textsubscript{e}/Q̇\textsubscript{L}0.001 (% QT)</td>
<td>16.2±4.8</td>
<td>25.3±9.5</td>
<td>NS</td>
</tr>
<tr>
<td>1\textsubscript{e}/Q̇\textsubscript{L}0.01 (% QT)</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (Q̇\textsubscript{L} [nm²])</td>
<td>0.54±0.17</td>
<td>0.7±0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log SD Q̇\textsubscript{L}</td>
<td>0.63±0.00</td>
<td>1.4±0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dead space (% VE)</td>
<td>57.5±6.0</td>
<td>61.5±6.7</td>
<td>NS</td>
</tr>
<tr>
<td>0.05\textsubscript{e}/Q̇\textsubscript{L}0.01 (% VE)</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>NS</td>
</tr>
<tr>
<td>0.01\textsubscript{e}/Q̇\textsubscript{L}0.1 (% VE)</td>
<td>0.0±0.0</td>
<td>1.5±0.9</td>
<td>0.003</td>
</tr>
<tr>
<td>0.1\textsubscript{e}/Q̇\textsubscript{L}0.1 (% VE)</td>
<td>31.5±1.4</td>
<td>3.9±3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1\textsubscript{e}/Q̇\textsubscript{L}0.001 (% VE)</td>
<td>10.2±0.7</td>
<td>32.7±7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1\textsubscript{e}/Q̇\textsubscript{L}0.01 (% VE)</td>
<td>0.0±0.0</td>
<td>1.0±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (VE [nm²])</td>
<td>0.84±0.30</td>
<td>1.9±0.66</td>
<td>0.002</td>
</tr>
<tr>
<td>Log SD V̇̇̇ \textsubscript{E}</td>
<td>0.4±0.00</td>
<td>1.2±0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dist R-E*</td>
<td>4.7±0.9</td>
<td>27.9±6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RSS</td>
<td>3.5±2.1</td>
<td>3.4±0.82</td>
<td>NS</td>
</tr>
</tbody>
</table>

and blood gases. As can be seen, lung resistance, dynamic resistance, and work of breathing increased markedly during bronchospasm, while PaCO\textsubscript{2} increased and PaO\textsubscript{2} decreased, in the absence of any change in ventilator settings, as stated above. The bronchospasm remained stable as shown by the plateau of PIP observed in all animals, but the gas exchanges were also stabilized when the blood and gas samples were taken for the MICET. Mixed PO\textsubscript{2} and PCO\textsubscript{2} values taken at a 2-min interval were comparable. The maximum difference between sample 1 and 2 was 1 mmHg for PO\textsubscript{2} (mean difference: 0.27 mmHg) and 0.6 mmHg for PCO\textsubscript{2} (mean difference: 0.16 mmHg).

Table 2 presents the effects of the bronchospasm on the inert gas parameters. All seven animals had a normal V̇̇̇\textsubscript{E}/Q̇\textsubscript{L} distribution before the bronchospasm but exhibited major inequalities during MCh-induced bronchoconstriction, as documented by the large increase in indices of V̇̇̇\textsubscript{E}/Q̇\textsubscript{L} dispersion (log SD Q̇\textsubscript{L}, log SD V̇̇̇ \textsubscript{E} and Dist R-E*).

Figure 2 shows the characteristic bimodal V̇̇̇\textsubscript{E}/Q̇\textsubscript{L} distribution changes in all animals during bronchospasm, in the
absence of significant increases in either shunt or dead space. The residual sum of squares, an index of goodness of fit of the inert gas data, was 3.40±0.23 during baseline and 3.44±0.82 during bronchospasm. All the data sets were less than 10.6, and 85% were less than 5.3, in agreement with the criteria of data adequacy proposed by Roca and Wagner [16]. Finally, there were no significant changes in heart rate, mean systemic blood pressure and cardiac output (Table 1).

Discussion

The present study demonstrates that in unanesthetized, paralyzed, and mechanically ventilated piglets, the administration of a cyclic aerosol of MCH results in a stable bronchospasm allowing the measurement of V/Q relationships with the MIGET. Some of the key methodological aspects of the study compared to previously published data should be addressed.

The first issue is that of MCH administration and stability of bronchospastic state. An intravenous injection of MCH was not used because it induces hemodynamic changes. In a canine model of MCH-induced bronchoconstriction Iommi et al. [17] have shown that MCH significantly lowers blood pressure and cardiac output. Two previous studies on gas exchange during induced bronchospasm with aerosolized MCH have been performed on dogs [6, 7]. At variance with our protocol, these authors aerosolized MCH during a period of 3-5 min, and therefore pigs after the end of the MCH challenge. In another study in pigs, Omini et al. [5] aerosolized MCH continuously over 3 min until a maintenance level of ventilation was reached and MCH was then stopped. However, it is known that MCH has a rapid onset and short action duration when given in a single dose. Therefore we chose to give small concentrations of MCH during a continuous aerosol, since we found that the level of bronchospasm (assessed by monitoring of the PIP) systematically decreased as soon as the aerosol was stopped. Likewise, we did not observe any cumulative effect of MCH, as with a continuous nebulization the level of continuously monitored PIP remained stable in all the animals studied. The majority of animal studies do not report the stability of their model [6, 7, 18]. In this study we considered that the steady state was obtained when the values of PIP were stable for at least 15 min.

The second issue is that of the validity of MIGET measurements in the absence of demonstrated stability. For instance, in a canine model of asthma Rubinfeld et al. [7] used the inert gas method but without the steady-state gas exchange that this method is based on. The same is true of a study by Rodriguez-Rossin et al. [6] using a MCH challenge in dogs, in which the development of airway obstruction was demonstrated by increases in lung resistance in all animals, but no data are given relative to stability of these modifications. We have three arguments in favor of our approach. First, we adjusted the dose of MCH until a plateau of PIP was clearly shown. Second, the samples of mixed expiratory PO2 and PCO2 taken at 2-min intervals were equal, demonstrating that the steady state was obtained in the gas exchanges. Second, there was no increase in the residual sum of squares during bronchospasm, which is an additional argument in favor of the stability of the model and of the quality of the technique.

We did not measure the particles characteristics of the aerosol. We used a side-stream nebulizer driven by a flow of 8 l/min which gives, according to Loffurt et al. [19], a mass median aerodynamic diameter (MMAD) of 2.1 µm and fine particle fraction of 71.9%. Schneekel et al. [20] compared the response to inhaled MCH delivered by two nebulizers: one with 2 µm of MMAD and the other with larger particles: 9 µm of MMAD. They found that the changes in airway mechanics were greater with larger particles, but also that changes in arterial blood gases and gas exchange data measured by the MIGET were the same with both aerosols. We found that the baseline values of pH were higher in humans than in pigs, however, these values were within the normal range for the pigs [21].

Finally, the absence of collateral ventilation is an important difference between porcine and human lungs. Acute asthma may induce mucous plugging in the small airways, resulting in stenosis in absence of efficient collateral flow. In chronic asthma, the presence of bronchial lesions such as submucosal fibrosis may result in the development of bronchiolar stenosis and may affect the baseline ventilation-perfusion relationships between the upper and lower parts of the lung, since we did not observe increases in shunt with bronchospasm in our animals. The percentage of low V/Q units (V/Q between 0.005 and 0.1) observed during bronchospasm was nearly the same in our study (41.8%) than in patients with status asthmaticus (27.6%) [10]. However, MIGET was measured after the beginning of the treatment of the asthmatic attack, and the level of bronchospasm was probably far less than that we imposed to our animals.

The first two animals that completed the study were autopsied, the lungs were removed, and no mucous plugging or stenosis were found. This feature may be due to the fact that the experiments were limited in time, but also because we just induced a bronchoconstriction, not an asthmatic attack. With the MCH challenge we were able to reproduce one aspect of asthma, by acting on the bronchial muscles, but not the complex inflammatory processes associated with asthma. Another difference with reports in the literature that found MCH challenge to produce an intense shunt in pigs is the fact that previous published studies on ventilation-perfusion relationships were carried out with intravenous administration, in contrast to our methods.
Finally, sensitization to allergens such as ascaris and ovalbumin have previously been used by other groups to induce a long-lasting bronchospasm. These methods are used mainly when the biochemical markers of asthma are investigated. Although the allergic bronchial challenge reproduces more specific aspects of asthma, we performed the MCh challenge because the major aim of our model was its stability. We wanted to induce a stable bronchospasm for the MIGET because this method requires at steady state period of at least 15 min. Allergic bronchial provocation is less easy to control and may give less reproducible results.

Respiratory mechanics

Since the purpose of this model is to study ventilator and gas mixture strategies using, among other tools, MIGET, an important aspect is the relevance of the changes in respiratory mechanics and V̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̈
References

6- Effects of helium-oxygen ventilation in the porcine model.

Introduction

The stability of our animal model of bronchospasm being proved, the next step was to test Heliox ventilation on the porcine model.

At this time we encountered some difficulties:

- the severity of the bronchospasm and an inspiratory fraction of oxygen used of 0.3 induced a profound hypoxia and a relative hemodynamically instability developed at the end of each protocol set

- we needed to calibrate all respiratory and measurement equipments for helium mixture

These difficulties overcome, we randomly assigned pigs to receive first air or He/O₂ ventilation followed by He/O₂ or N₂/O₂ respectively. Seven piglets completed the study successfully.

This study brought us to the conclusion that while helium improved respiratory mechanics and work of breathing, hypercapnia and respiratory acidosis increased, and that close attention should be paid to monitor arterial blood gases when helium is used in mechanically ventilated acute severe asthma.
Effects of helium-oxygen on respiratory mechanics, gas exchange, and ventilation-perfusion relationships in a porcine model of stable methacholine-induced bronchospasm

Abstract Objective: To explore the consequences of helium/oxygen (He/O2) inhalation on respiratory mechanics, gas exchange, and ventilation-perfusion (VA/Q) relationships in an animal model of severe induced bronchospasm during mechanical ventilation. Design: Prospective, interventional study. Setting: Experimental animal laboratory, university hospital. Intervention: Seven pigs were anaesthetized, paralysed, and mechanically ventilated, with all ventilator settings remaining constant throughout the protocol. Acute stable bronchospasm was obtained through continuous aerosolization of methacholine. Once steady-state was achieved, the animals successively breathed air/O2 and He/O2 (FiO2 0.3) or, inversely, in random order. Measurements were taken at baseline, during bronchospasm, and after 30 min of He/O2 inhalation. Results: Bronchospasm increased lung peak inspiratory pressure (49±6.9 vs 18±1.1 cm H2O, P<0.001), lung resistance (22.7±1.5 vs 6.8±1.5 cm H2O/l/s, P<0.001), dynamic elastance (He 11.2 vs 22.8±1.4 cm H2O/l/s·cmH2O, P<0.001), and work of breathing (1.51±0.26 vs 0.47±0.08, P<0.001). Mean arterial pH decreased (7.47±0.06 vs 7.32±0.06, P<0.001), PaCO2 increased, and PaO2 decreased. Multiple inert gas elimination showed an absence of shunt, substantial increases in perfusion to low VA/Q regions, and disportion of VA/Q distribution. He/O2 reduced lung resistance and work of breathing, and worsened hypercapnia and respiratory acidosis.

Conclusions: In this model, while He/O2 improved respiratory mechanics and reduced work of breathing, hypercapnia and respiratory acidosis increased. Close attention should be paid to monitoring arterial blood gases when He/O2 is used in mechanically ventilated acute severe asthma.

Keywords: Asthma; Methacholine; Respiratory mechanics; Ventilation/perfusion; MIGET; Helium
helium/oxygen (HeO₂) reduces the resistance to flow in the airways [7], and has been shown to improve peak inspiratory flow, dyspnea, and pulmonary hyperinflation in intubated patients with ASA [8, 9], to increase arterial pH and decrease PaCO₂ in intubated and mechanically ventilated patients [10, 11], and to improve respiratory mechanics in a mechanically ventilated animal model [12]. Thus, HeO₂ inhalation could be included in the management strategy of such patients. However, this approach raises some concerns. Indeed, the low density of helium can interfere with the pneumotachograph used by most ventilators to measure inspiratory flow and compute delivered tidal volume (VT), as these devices are normally calibrated for air/O₂ [13]. In turn, this can lead to improper tidal volume and PIP administration [13]. Furthermore, a worsening of hypoxemia with helium has been documented in obstructive airway disease [14, 12].

The purpose of this study was to explore the effects of HeO₂ inhalation on respiratory mechanics, gas exchange, and ventilation-perfusion relationships in a recently validated model of stable methacholine-induced bronchoconstriction mimicking ASA in intubated and mechanically ventilated pigs [16].

Materials and methods

Animals

The study was conducted in the Laboratory of Experimental Surgery, SL-Lar Hospital, in Brno. The study protocol was approved by the ethics committee for animal experiments of the Catholic University of Laramie, Brno. Eight young pigs aged 9–11 months were used, and at the end of the experiment were killed using a solution of pentobarbital, meperidine, and ketamine (Thiopental, Nembutal, Nembutal, Belgium).

Anaesthesia and equipment

The animals were anaesthetised with intramuscular ketamine hydrochloride (2 mg kg⁻¹), and thiopental sodium (7.5 mg kg⁻¹), followed by intravenous propofol as a constant infusion rate of 2 mg kg⁻¹ h⁻¹. Animals were placed in the supine position, intubated (3.5 mm internal diameter cuffed tracheal tube), and mechanically ventilated with a Servo 300 ventilator (Siemens, Berlin, Germany). Muscle paralysis throughout the experiment was achieved with vecuronium bromide (0.1 mg kg⁻¹ h⁻¹). Inspiratory and expiratory blood gas sampling were obtained with a peripheral arterial catheter. A continuous cardiac output and mixed venous oxygen saturation pulmonary artery catheter (CO-0100, Lumen; Baxter Edwards, Laboratorium, Irvine, Calif., USA) was inserted to allow measurements of cardiac output, blood temperature, mixed venous oxygen saturation (SvO₂), and the withdrawal of blood samples.

Mechanical ventilation and basic monitoring

Mechanical ventilation was performed in volume-controlled mode, adjusted to obtain asynchrony with a fraction of inspired oxygen (FIO₂) of 0.3, no PEEP, and an inspiratory time of 33% with an inspiratory pause. All respiratory parameters and PIP were kept constant during the subsequent experimental phases. Heart rate, SaO₂, and tidal CO₂ peak inspiratory pressure (PIP), and mean intrapleural pressure were monitored.

Respiratory system mechanics

An esophageal balloon (Intersurgical Medical Products, Kieve, The Netherlands) filled with 3.3 ml air was connected to a ±10 cm H₂O differential pressure transducer (ValiData Engineering, Northridge, Calif., USA). The balloon was positioned to obtain a reproducible intrapleural pressure tracing according to standard techniques [17] and checked using the occlusion test [18]. Airflow (VT) was measured by a Procon N2 pneumotachograph (Forney, Lancaster, Switzerland). Volume (V) was obtained by electrical integration of the flow signal. The pneumotachograph was calibrated by placing it in series with a dry gasometer (Fleisch and Cowan CDS, Manchester, UK), and noting the two gas volumes, i.e., air/O₂ 20, 30, and HeO₂ 30, 30 through this setup. A T cube was placed between the ventilator and the pneumotachograph, and connected to both the other port of the pneumotachograph for monitoring pressure, to measure transpulmonary pressure, and to a second 140 cm H₂O differential pressure transducer, for the measurement of airway pressure. Pressure, VT, and V signals were recorded on paper with a TA-11 electronic recorder (Gould Instruments, Valley View, Ohio, USA), then scanned and digitalized (De Soto-LS, SIV Scientific Instruments, Vil. USA). Lung resistance (RL) and dynamic compliance (DL) were calculated by multiple linear analysis [19] fitting of the equation of motion:

\[ \text{Pip} = [\text{E} - \text{V} - \text{R} - V'] \text{V} + k \]

where Pip is the transpulmonary pressure and k is a constant. Tracheal lobe resistance was not subtracted from Dl.

Dynamic inductance (PEDP, PEDP') was measured according to the method of Paszl et al., which assumes that the increase in airway pressure preceding expiratory inspiratory reflects the equivalent of pressure needed to sustain inflation: PEDP' = PEDP.

Work of breathing was measured by graphical analysis of the esophageal pressure curve [21] and normalized for the tidal volume. Fifteen respiratory cycles were analyzed during each step of the protocol.

Ventilation-perfusion (V/Q) relationship

The measurements of the distribution of the V/Q ratios were performed according to the multiple inert gas elimination technique (MIGET) [22]. Six inert gases of different solubilities (oxygen, helium, argon, carbon dioxide, methane, nitrous oxide) were equilibrated in 0.9% NaCl solution infused at a constant rate of 3 ml h⁻¹ through a central venous catheter (the Swan-Ganz lung catheter). After an equilibration period of 30 min, double 10 ml blood samples from the peripheral artery and 5 ml blood samples from the pulmonary artery were taken into heparinated 5 ml glass syringes. Samples of mixed expired gas were collected from the exhaust port of the ventilator into 5 ml glass syringes (Razba, Prague, Czech Republic). Inert gas concentrations were determined with a gas chromatograph (Perkin Elmer, Shelton, Conn., USA) equipped with an electron capture detector for N₂ and a flame ionization detector for the other five gases. For each gas, retention (rad of arterial to mixed venous concentration) and extraction (ratio of mixed expired air to mixed venous concentration) were calculated. The continuous distribution of blood flow and ventilation against the V/Q ratios from these data were calculated by the computer program of Evans and Wagner [23].
Table 1 Ventilatory parameters and hemodynamics. Results are expressed as mean ± SD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Bronchospasm</th>
<th>Bronchospasm</th>
<th>Bronchospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ht (cm H2O)</td>
<td>6.7±1.3</td>
<td>22.7±0.2*</td>
<td>16.3±2.5**</td>
<td>1.5±0.2***</td>
</tr>
<tr>
<td>Et (cm H2O)</td>
<td>72.8±1.1</td>
<td>78.3±1.2***</td>
<td>71.1±1.3***</td>
<td>1.8±0.2***</td>
</tr>
<tr>
<td>CI (L/min 1.73m2)</td>
<td>3.1±0.5</td>
<td>4.9±0.5**</td>
<td>2.4±0.1*</td>
<td>1.0±0.1***</td>
</tr>
<tr>
<td>WOB (J/L)</td>
<td>0.4±0.08</td>
<td>3.5±0.5***</td>
<td>1.3±0.1***</td>
<td>1.3±0.1***</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>9.0±0.0</td>
<td>9.0±0.0</td>
<td>9.0±0.0</td>
<td>9.0±0.0</td>
</tr>
<tr>
<td>PIP (cm H2O)</td>
<td>16±1</td>
<td>40±2**</td>
<td>10±1</td>
<td>10±1</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.1±1.3</td>
<td>3.5±0.1**</td>
<td>3.5±0.1**</td>
<td>3.5±0.1**</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>96±19</td>
<td>96±19</td>
<td>96±19</td>
<td>96±19</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>125±12</td>
<td>125±12</td>
<td>125±12</td>
<td>125±12</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>22±10</td>
<td>33±12*</td>
<td>33±12*</td>
<td>33±12*</td>
</tr>
</tbody>
</table>

*p<0.05 versus baseline; **p<0.001 versus baseline; ***p<0.001 versus bronchospasm air/O2

Metacholine challenge

The details of the metacholine challenge have been described and validated in a previous study [16]. In brief, a continuously monitored (Beech-Nalizer, Willow, Series 8500) was connected to the ventilator's inspiratory circuit. Peak inspiratory pressure was continuously observed, metacholine was aerosolized, and its concentration was adjusted to obtain an increase in PIP of up to 30 cm H2O. Subsequently, the concentration was increased to obtain a level of broncho-
spasm sufficient to increase PIP of 5% over 15 min. Results from our previous validation study [16] showed that, once achieved, steady-state lasted for approximately 60 min without the need for further adjustments in metacholine concentration.

Measurement protocol

A complete set of all measurements described above were performed at the following time points:

1. Immediately prior to initiating the metacholine aerosolization (air/O2, baseline).
2. After induction of the bronchospasm, once steady-state was achieved (air/O2, baseline).
3. In random order:
   - After 30 min of air/O2 breathing followed by 30 min of 100% O2 breathing.
   - After 30 min of 100% O2 breathing followed by 30 min of air/O2 breathing.

Since no statistically significant difference was noted between air/O2 measurements during bronchospasm, results are reported as air/O2 baseline, air/O2 bronchospasm, and 100% O2 bronchospasm.

Statistical methods

Values reported in the results are expressed as mean ± SD. A one-way analysis of variance (ANOVA) for repeated measures was used to compare the values obtained at each of the three protocol conditions. A p value <0.05 was considered significant. Statistics were computed using StatSoft 8.0 software (SPSS, Chicago, IL, USA).

Results

Nine piglets (body weight 5.4±1.6 kg) were used in the study. One animal was excluded due to the presence of severe hypoxemia at baseline suggesting pre-existing lung disease, and another was lost during induction of anesthesia. The seven other animals completed the study successfully. Bronchospasm led to a marked increase in peak inspiratory pressure, lung resistance, and dynamic elastance. Lung resistance was lowered by 100% O2 (Table 1). Minute ventilation remained unchanged during all three phases, while work of breathing increased substan-
6 – Helium on the model

Fig. 2. Multiple inert gas elimination technique (MIGET). Ventilation (white area) and perfusion (black area) distribution in two representative animals in the three conditions studied: S (Shunt), Ds deadspace.

Discussion

The main findings of the present study are that: (1) acute bronchospasm led to a considerable increase in peak inspiratory pressure, lung resistance, and dynamic elastance, as well as hypoxemia due to decreased mean perfusion index and increased distribution of perfusion dispersion, and respiratory acidosis due to hypercapnia resulting from increased deadspace, and (2) He/O₂, while reducing lung resistance and work of breathing, worsened the dispersion of perfusion distribution, as well as hypercapnia and respiratory acidosis.

Let us first discuss the limitations of the study. First, the stability of such a model must be questioned. In a previous study, we demonstrated that continuously aerosolized doses of methacholine, such as administered in the present study, could lead to a stable and prolonged bronchospastic state, allowing repeated measurements over time, including MIGET [16], without the adverse hemodynamic effects of intravenous administration [24]. Furthermore, the modifications of respiratory mechanics, blood gases, and V/Q indices observed in our previous and present studies were similar, underlining the good reproducibility of the model. Second, the validity of the
model in reproducing the conditions of mechanically ventilated ASA should be addressed. The changes we observed were comparable to those documented in other studies, with respect to arterial blood gases and VAQ abnormalities [25, 26, 27] as well as respiratory mechanics [28]. Third, due to the complexity of the manipulations and explorations, the number of animals was small, limiting the possibility of a type II error. Finally, HeO₂ can interfere with various aspects of ventilator function, which can lead to changes in minute ventilation and administered FIO₂ [13]. However, reliable and stable HeO₂ administration with the machine used in these experiments has been demonstrated, providing the appropriate correction factors are used [13].

The alterations of respiratory mechanics witnessed in the present study, i.e., increase in lung resistance and dynamic elastance during bronchoscopy, are typical of observations made in two animal models [12, 28] as well as studies in humans [29, 30]. In a porcine model of mechanical-induced bronchoscopy, Ornini et al. showed that HeO₂, inhaled reduced resistance and elastance [12], whereas only resistance was improved in our study. Airway resistance is expected to decrease during HeO₂ inhalation due to two mechanisms. First, the lower density of the mixture reduces Reynold’s number, thereby increasing the likelihood of laminar flow conditions, in which the relationship between driving pressure and flow is linear as opposed to nonlinear in turbulent flow conditions [7, 31]. Second, in areas where turbulent flow conditions prevail, the driving pressure required to obtain a given flow is reduced as density is decreased [7, 31]. Hence, both factors combine to reduce airway resistance to flow, a commonly observed manifestation of HeO₂ inhalation, both in normal subjects [32] and obstructive lung disease [33]. Increased elastance in asthma is thought to result from dynamic hyperinflation due to incomplete end-expiratory lung emptying [5, 6]. Our results show a nonsignificant trend towards elastance reduction. These findings could be explained by other factors contributing to increased elastance, such as chest wall or abdominal modifications, to insufficient time of HeO₂ administration for complete lung emptying to occur, or to a type II error. Regarding the former, it appears that it was not detected during the experiments, but specific measurements of intra-abdominal pressure or partitioning of respiratory mechanics were not performed, thus not allowing to rule out this hypothesis completely. The duration of 30 min of HeO₂ inhalation is consistent with the study by Ornini et al., in which elastance was significantly reduced by helium, although the model was designed differently from ours [12]. Unfortunately, though even though PEFR was not significantly reduced, no measurement of end-expiratory volume was performed, thus precluding a definite answer as to the possibility of incomplete lung emptying in our model.

Hypoxemia and hypercapnia are well-known manifestations of ASA, and are in line with findings of other investigators [10, 11]. In the study by Glick et al., intubated and mechanically ventilated patients with sinus arrhythmia exhibiting hypercapnia with respiratory acidosis markedly improved both pH and PaCO₂ after 20 min of HeO₂ inhalation [11]. In the present study, however, HeO₂, leading to worsen both these parameters. One possible explanation rests in the high deadspace documented in the MIGET exploration, both at baseline and in the two experimental conditions. Such a high baseline deadspace was also present in our validation study [16], and is mainly the result both from anatomical and instrumental deadspace. For HeO₂ to correct hypercapnia, the latter should mostly result from two causes (1) alveolar hypoventilation due to a fall in tidal volume resulting from severe bronchoscopy, the pressure l
on the ventilator being reached before the preset tidal volume is delivered [11], and (2) deadspace resulting from high levels of hyperinflation [14]. In both these instances, HeO₂, by decreasing airway resistance and hyperinflation [35], should increase alveolar ventilation and reduce deadspace, which should in turn decrease PaCO₂. Regarding the first point, ventilator parameters were not modified, and minute ventilation remained unchanged during all three phases of the protocol (Table 1). As for deadspace, no modification was noted with HeO₂ (Table 2). However, there was a marked increase in the dispersion of V/Q ratios (Dop R-E), during bronchoscopy, which remained elevated during HeO₂ inhalation (Table 2). Thus, it seems that the absence of improvement of PaCO₂ with HeO₂ probably resulted from failure of the latter to correct this major increase in Dop R-E (Table 2). The reasons for this absence of improvement are not obvious at this time.

The absence of change of PaO₂ with HeO₂ was probably the result of several factors. Hypoxemia in patients with ASA has been shown to result from an abnormally elevated dispersion of pulmonary blood flow distribution with an increase in perfusion to low V/Q units, in the absence of shunt [36, 37]. In our study, the dispersion of the perfusion distribution was markedly increased by bronchoscopy, and was further worsened by HeO₂ (Table 2), which should have worsened PaO₂. Furthermore, even though statistically nonsignificant, there was a trend towards an increase in shunt with HeO₂, which should also have lowered PaO₂. The cause for this remains speculative, but some derecruitment with HeO₂ could have occurred, a hypothesis we are presently investigating in the same model. Nonetheless, the effects of gas density on convective and diffusive gas transport in the lungs are quite complex [38], and conflicting results have emerged regarding HeO₂. HeO₂ has been shown to increase PaO₂ and reduce the alveolar-arterial PO₂ differences (DA-αO₂) in animal studies [39], while the opposite was documented in COPD patients [14, 15]. In two studies in COPD, one during noninvasive ventilation [40], the other in intubated, paralyzed, and mechanically ventilated COPD patients [35], no effect on PaO₂ was observed. Finally, in a recent study in intubated and mechanically ventilated patients with ASA, HeO₂ reduced DA-αO₂ and increased PaO₂ [41]. Thus, the difficulty of extrapolating from animal data notwithstanding, it seems that HeO₂ does not markedly deteriorate arterial oxygenation in this situation, due to the probable interaction of opposing mechanisms.

In conclusion, the results of this study show that, in a stable animal model of methacholine-induced bronchoscopy, HeO₂ exerts favorable effects on airway resistance and work of breathing, but fails to improve EESF, arterial blood gases, and V/Q relationships. Further studies should be conducted in this model to determine the mechanisms underlying these effects, and to explore whether they can be extrapolated to the clinical setting. Indeed, in intubated and mechanically ventilated patients with acute severe asthma, avoidance of lung damage by reducing inhaled pressures with HeO₂ still remains an attractive option, whose favorable effects could outweigh what appears to be a moderate price to pay in terms of gas exchange.

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References

7 – Helium and Salbutamol
7- Helium, Salbutamol 
and assisted ventilation

Introduction

The first step of this study consisted in creation of an other new model of induced bronchospasm in the pig i.e. a model of bronchospastic pig in which the asthma crisis is provoked by an intra venous administration of methacholine. The reason of this change in methacholine administration was that we wanted to let the pigs in spontaneous breathing. We know that any change in minute ventilation would have modified the dose administered by aerosol, which should not be the case during continuous IV administration.

These two ways of methacholine administration resulted in comparable effects on lung mechanics but in different alterations of the ventilation-perfusion relationships (intravenous methacholine induced a significant increase in shunt whereas no change was found with aerosolised methacholine). The pattern of ventilation-perfusion alterations induced by aerosolized methacholine was more comparable to bronchospasm observed in humans. Despite this, both ways of methacholine administration resulted in a comparable increase in lung resistance and elastance, and we chose the intravenous way for methacholine administration in our study because we wanted the insurance that any change in lung mechanics could not be due to variability of delivery of the bronchoconstrictor agent. For the same reason we decided to give Salbutamol intravenously.

Nine piglets completed the study successfully. The study brought us to the conclusion that He/O₂ failed to improve gas exchange and Vₐ/Q relationships. However, due to its favorable effects on respiratory mechanic and inspiratory muscle workload, He/O₂ might represent an attractive option
in patients with acute severe asthma ventilated in pressure support, as it could prevent the occurrence of diaphragmatic fatigue.
EFFECTS OF HE/O₂ AND SALBUTAMOL ON VA/Q RELATIONSHIPS IN ASTHMATIC MODEL IN PRESSURE SUPPORT MODE

Watremez Ch.¹, Liistro G², Roeseler J³, De Kock M.¹ Clerbaux Th.², Detry B², Reynaert M.², Gianello P.⁴, and Jolliet Ph.⁵

Dept of Anesthesiology¹, Pneumology Unit², Intensive Care Dept³, Experimental Surgery⁴ Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium and Intensive Care ⁵, University Hospital, Geneva, Switzerland.

Corresponding author: Watremez Ch.

Department of Anesthesiology
Cliniques Universitaires Saint Luc
Avenue Hippocrate, 10
1200 BRUSSELS
christine.watremez@uclouvain.be
Abstract

Objective: To explore the consequences of helium/oxygen inhalation in association with a β2-agonist bronchodilator on respiratory mechanics, gas exchange, and ventilation-perfusion relationships in an animal model of severe induced bronchospasm during assisted spontaneous breathing.

Design: Prospective, interventional study.

Setting: Experimental animal laboratory, university hospital.

Interventions: 9 anesthetized piglets were studied. When acute stable bronchospasm was obtained through continuous i.v. infusion of methacholine, the animals were ventilated in a pressure support mode at FIO2 0.4. An infusion of a β2-agonist bronchodilator was started and the animals successively breathed 60/40 air/O2 and He/O2, or inversely, in random order. Ventilatory parameters were maintained constant during the subsequent phases of the study. Cardio-pulmonary physiologic data were obtained, including measurement of VA/Q relationships with the multiple inert gas elimination technique (MIGET).

RESULTS: Administration of salbutamol increased minute ventilation, improved PaO2, but did not change PaCO2 because of an increase in shunt (38.2 ± 23.6 versus 22.2 ± 18.3 %, p<0.01). He/O2 while decreasing airway resistance (9.7 ± 4.6 versus 16.8 ± 4.4 cm H2O l-1 s, p<0.001) and work of breathing (1.924 ± 0.481 versus 2.243 ± 0.473 J/l, p<0.01), worsened hypoxemia and did not change the VA/Q relationships, as compared with air/O2. The trans-diaphragmatic pressure decreased with He/O2 suggesting a decrease in inspiratory muscle effort.

CONCLUSION: Ventilation with He/O2 during salbutamol infusion, did not change significantly the VA/Q relationships as compared with air/O2, despite it substantially decrease airway resistance. Further studies should attempt to define the optimal strategy for the combined use of these two agents.

Introduction

Status asthmaticus is a difficult to manage cause of acute respiratory failure (1). The combination of CO₂ retention, acidosis, and hypoxemia may herald the sudden occurrence of respiratory arrest or cardiac arrhythmias. The attack is usually of several hours duration and respiratory muscle fatigue from excessive workload is a frequent complication, sometimes leading to endotracheal intubation. Volume controlled mechanical ventilation often proves extremely difficult, and the high airway pressures required to generate an adequate minute volume can potentially damage the lungs (1; 35).

Helium-oxygen (He/O₂) has a significantly lower density than air/O₂ and, in theory, should reduce the work of breathing. Therefore in acute severe asthma, He/O₂ while not a cure for the underlying disease should reduce airway resistance and high inflation pressures and thereby diminish the risk of lung damage. Furthermore, in patients who can be ventilated with a spontaneous-assisted mode such as pressure support (PS), He/O₂ could reduce the magnitude of inspiratory effort and work of breathing (29).

After more than 30 years of use, inhaled salbutamol is well established as a “first choice” treatment in reversible obstructive airways disease. Studies in healthy volunteers have shown that salbutamol causes large airways dilatation by reducing bronchomotor tone (17; 24). But despite this bronchodilation, the i.v. administration of beta-adrenergic agents to patients with airway obstruction often results in a transient decrease in PaO₂ (20; 15).

Given the high likelihood that asthmatic patients receiving He/O₂ would also concomitantly receive salbutamol, the aim of this study was to evaluate the effects of air/O₂ and He/O₂ breathing on inspiratory muscle workload, respiratory mechanics, gas exchange, and Vₐ/Q relationships in an animal model
of severe methacholine (MCh)-induced bronchospasm during pressure assisted spontaneous breathing in association with intravenous salbutamol.

Materials and methods

Animals

Nine piglets were used and at the end of each experiment were euthanized using a solution of embutramide, mebuzoniumiodide, and tetracaine (T61, Intervet, Mechelen, Belgium). The study was conducted in the Laboratory of Experimental Surgery, St Luc Hospital, Brussels. The ethics committee of our university approved the protocol.

Anesthesia

The animals were anaesthetized with intramuscular xylazine hydrochloride, 2 mg/kg, and tiletamin/zolazepam (Zoletil, Vibrac, Belgium), 7.5 mg/kg, followed by and intravenous infusion of propofol at 2 mg/kg/h. Animals were placed in the supine position, intubated with a 6.5 mm internal diameter cuffed endotracheal tube and mechanically ventilated with a Servo 900C ventilator (Siemens Elema, Solna, Sweden). Muscle paralysis was obtained with i.v. pancuronium bromide, 0.1 mg/kg followed by 0.2 mg/kg/h until a stable bronchospasm was obtained and then stopped to permit a return to spontaneous ventilation. Invasive blood pressure measurement and arterial blood gas sampling were obtain via a carotid artery catheter. A CCO-SvO₂-Swan-Ganz catheter (Edwards Lifesciences, Germany) was placed to allow measurements of cardiac output, blood temperature, mixed venous oxygen saturation, and the withdrawal of blood samples.

Mechanical ventilation

Mechanical ventilation was performed in volume-controlled mode, initially with 8 ml/kg tidal volume then adjusted for normocapnia at FIO₂ of 0.3 and no PEEP,
until a stable bronchospasm was obtained reflected by the PIP level which was twice his baseline value. When the neuromuscular blocking agent was discontinued, the pigs were ventilated in pressure support mode with a PEEP of 5 cm H₂O. The level of PS was set to match that of peak inspiratory pressure (PIP) during volume-controlled mode minus PEEP. FIO₂ was increased to 40 % to reduce the risk of hypoxemia, thereby ensuring optimal conditions to complete the study. Ventilatory parameters were kept constant during the subsequent phases of the study. The minute ventilation was checked by filling a neoprene balloon connected to the expiratory port of the ventilator for 2 minutes.

Respiratory system mechanics
Two esophageal balloons (International Medical Products, Kleve, The Netherlands) filled with 1 cc air, connected to a ± 140 cm H₂O differential pressure transducer (Validyne Engineering, North Ridge, Calif., USA), were placed one in the stomach and the other in the esophagus (11) and checked using the occlusion test (3). Transdiaphragmatic pressure (Pdi) is defined as the difference between pleural pressure (Ppl) or esophageal pressure (Pes) and abdominal pressure or gastric pressure. Airflow was measured by a Fleisch n°2 pneumotachograph (Fleisch, Lausanne, Switzerland) connected between the endotracheal tube and the ventilator. Volume was obtained by electrical integration of the flow signal. A T-tube was placed between the pneumotachograph and the ventilator, and connected to both the other port of the pressure transducer used for Pes to measure the trans pulmonary pressure (Ptp), and to a second 140 cm H₂O differential pressure transducer for the measurement of airway pressure (Paw). The pressure, flow, and volume curves were recorded on paper with a Gould TA 11 electrostatic recorder (Gould Instruments, Valley View, USA), then scanned and digitalized (Un-Scan-It, Silk
Scientific, Orem, USA). Lung resistance (Rl) and dynamic elastance (Ed) were calculated by multiple linear analysis fitting to the equation of motion:

$$P_{TP} = Ed \cdot V + Rl \cdot V' + k$$

where $V$ is the volume, $V'$ the flow and $k$ a constant. Tracheal tube resistance was not subtracted from Rl. The work of breathing was measured by graphical analysis of the Ptp-volume curve and normalized for the tidal volume (16). A calibration was made before each measurement set.

Ventilation-perfusion (VA/Q) relationship
The measurements of the distribution of the VA/Q ratios were performed according to the multiple inert gas elimination technique (MIGET), described by Wagner and al. (30). Six inert gases of different solubility (SF6, ethane, cyclopropane, halothane, ether and acetone) equilibrated in 0.9% NaCl were infused at a constant rate of 3 ml/min through a central venous catheter. After an equilibration period of 30 min, dual 10 ml blood samples from the carotid artery and 5 ml from the pulmonary artery were taken into heparinized glass syringes. Samples of mixed gas were collected from the exhaust port of the ventilator into 50 ml gas-tight syringes (Hamilton 50 TLL). Inert gas concentrations were determined with a Perkin Elmer gas chromatograph equipped with an electron capture detector for SF6 and a flame ionisation detector for the other five gases. For each gas retention (ratio of arterial to mixed venous concentration) and excretion (ratio of mixed expired air to mixed venous concentration) were calculated. The continuous distribution of blood flow and ventilation against the VA/Q ratios from these data were calculated by the computer program of Evans and Wagner (9).
Methacholine challenge
The bronchoconstrictive agent was administered by continuous intravenous infusion, at an initial dose of 2 μg/kg/min. PIP was continuously monitored, and the infusion rate of MCh was adjusted to obtain an increase in PIP up to ± 40 cm H₂O (twice the baseline value). When the target level of bronchospasm, reflected by the PIP, was obtained, infusion of MCh was maintained at the same rate during the subsequent experimental phases.

Measurement protocol
One complete set of all measurements (Fig 1 and Fig 2) described above was performed at the following time points:

1. Immediately prior to initiating the methacholine administration at FIO₂ 0.3 (Air/O₂ baseline)
2. After induction of the bronchospasm, stabilisation, and return to PS mode of ventilation at FIO₂ 0.4 (Air/O₂ bronchospasm)
3. After i.v. administration of salbutamol (Ventolin®, Glaxo Smith Kline, Genval, Belgium) 1 μg/kg/min during 10 minutes followed by 0.2 μg/kg/min continuously during the subsequent experimental phases, and in random order:
   a. After 30 min of air/O₂ breathing followed by 30 min of He/O₂ breathing (4)
   b. After 30 min of He/O₂ breathing followed by 30 min of air/O₂ breathing (4)
The results are reported as air/O₂ baseline, air/O₂ bronchospasm, air/O₂ salbutamol, and He/O₂ salbutamol.
Fig. 1: Time course of the study protocol with the 4 measurements sets.

Fig. 2: Measurement protocol, example in one pig. *: Start infusion of MCh at 2 μg/kg/min with increments of 1 μg/kg/min every 5 minutes. **: Target level of PIP is obtained, stabilization of MCh infusion at 20 μg/kg/min. ***: Start PS mode of ventilation. Lower arrows: each measurement step with
1 Air/O₂ baseline
2 Air/O₂ bronchospearm followed by, in this case, helium ventilation
3 He/O₂ salbutamol followed by air/O₂ ventilation
4 Air/O₂ salbutamol
Statistical methods

Values reported in the results are expressed as mean ± standard deviation. A one-way analysis of variance (ANOVA) for repeated measures was used to compare the values obtained at each of the four protocol conditions. A p value less than 0.05 was considered significant. Statistics were computed using Systat 8.0 software (SPSS, Chicago, Ill., USA).

Results

Nine piglets (body weight 77.8 ± 4.4 kg) were used in the study, and all of them completed the study successfully. Results of the MIGET analysis are summarized in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Ano2</th>
<th>Helium</th>
<th>Helium and Salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.40 ± 0.03</td>
<td>7.26 ± 0.06</td>
<td>7.27 ± 0.06</td>
<td>7.29 ± 0.09</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>147 ± 73</td>
<td>62 ± 14</td>
<td>64 ± 14</td>
<td>56 ± 14</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>37 ± 4</td>
<td>49 ± 12</td>
<td>44 ± 9</td>
<td>43 ± 15</td>
</tr>
<tr>
<td>Perfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR % GTR</td>
<td>12 ± 1.6</td>
<td>22.2 ± 10.3</td>
<td>30.2 ± 23.6</td>
<td>36.2 ± 19.6</td>
</tr>
<tr>
<td>0.1 WQ GTR (GTR)</td>
<td>0.0 ± 0.0</td>
<td>4.5 ± 1.2</td>
<td>1.0 ± 2.5</td>
<td>3.4 ± 2.1</td>
</tr>
<tr>
<td>Mean % GTR (mL)</td>
<td>56.2 ± 8.0</td>
<td>58.7 ± 6.9</td>
<td>58.2 ± 6.0</td>
<td>58.7 ± 6.0</td>
</tr>
<tr>
<td>Log(DQ)</td>
<td>3.42 ± 0.16</td>
<td>1.05 ± 0.03</td>
<td>1.00 ± 0.10</td>
<td>1.53 ± 0.05</td>
</tr>
<tr>
<td>Ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead space % Vt</td>
<td>50.2 ± 13.5</td>
<td>53.1 ± 10.5</td>
<td>38.2 ± 12.4</td>
<td>51.2 ± 6.4</td>
</tr>
<tr>
<td>Mean % Vt (mL)</td>
<td>37.6 ± 23</td>
<td>173 ± 92</td>
<td>286 ± 174</td>
<td>220 ± 84</td>
</tr>
<tr>
<td>Log(GT)</td>
<td>3.46 ± 0.27</td>
<td>0.77 ± 0.21</td>
<td>0.78 ± 0.24</td>
<td>0.71 ± 0.12</td>
</tr>
<tr>
<td>Cap R B</td>
<td>3.6 ± 3.6</td>
<td>266 ± 74</td>
<td>347 ± 113</td>
<td>36.0 ± 13.8</td>
</tr>
<tr>
<td>RSV</td>
<td>6.2 ± 1.6</td>
<td>56 ± 44</td>
<td>70 ± 29</td>
<td>45 ± 21</td>
</tr>
</tbody>
</table>

Table 1: Arterial blood gases and MIGET results. Results are expressed as mean ± SD. (Disp R-E Index of dispersion of ventilation/perfusion ratio, corrected for dead space; QT pulmonary blood flow; FE minute ventilation, Log SDQ log standard deviation of perfusion distribution, Log SDV log standard deviation of ventilation distribution, RSS residual sum of squares)
Bronchospasm led to a marked increase in PIP, RI, Ed and work of breathing (Fig. 3); Arterial pH decreased and PaCO₂ increased. Hemodynamic data (Table 2) showed increased heart rate and pulmonary arterial pressure, and a reduction in mean arterial pressure. The main perfusion abnormalities were an increase in the log SDQ and development of a shunt with hypoxemia during bronchospasm.

Ventilation data show an increase in the mean V and log SDV.

![Graph showing pressure-volume curve](image)

Fig. 3 Example of evolution of the pressure-volume curve in one animal showing the changes in work of breathing during the different steps of our protocol.

Administration of salbutamol increased minute ventilation, PaCO₂ being improved. Respiratory mechanics were not modified. The increased heart rate and reduction in mean arterial pressure worsened with salbutamol. The shunt was further increased with salbutamol associated with an increase of the mean...
Q. Ventilation data show a decrease of dead space associated with an increase of mean V.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Air/O₂ bronchospasm</th>
<th>Air/O₂ salbutamol</th>
<th>He/O₂ salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rl (cm H₂O/l/s)</td>
<td>6.4 ± 3.7</td>
<td>15.1 ± 6.0</td>
<td>16.8 ± 4.4</td>
<td>9.7 ± 6.6</td>
</tr>
<tr>
<td>Ed (cm H₂O/l/s)</td>
<td>15.6 ± 6.7</td>
<td>40.8 ± 16.8</td>
<td>38.3 ± 15.8</td>
<td>30.1 ± 14.1</td>
</tr>
<tr>
<td>Cd (1 cm H₂O/l)</td>
<td>0.076 ± 0.038</td>
<td>0.026 ± 0.015</td>
<td>0.033 ± 0.020</td>
<td>0.043 ± 0.022</td>
</tr>
<tr>
<td>WOB (J/l)</td>
<td>0.596 ± 0.226</td>
<td>2.063 ± 0.382</td>
<td>2.243 ± 0.473</td>
<td>1.524 ± 0.481</td>
</tr>
<tr>
<td>Pdi (cm H₂O)</td>
<td>4.96 ± 2.18</td>
<td>8.32 ± 5.23</td>
<td>9.38 ± 4.55</td>
<td>6.75 ± 1.5</td>
</tr>
<tr>
<td>VE (l/min)</td>
<td>7.0 ± 1.4</td>
<td>10.0 ± 4.6</td>
<td>14.0 ± 4.0</td>
<td>14.8 ± 6.0</td>
</tr>
<tr>
<td>PIP (cm H₂O)</td>
<td>18.4 ± 4</td>
<td>36.0 ± 5.05</td>
<td>36.0 ± 4</td>
<td>36.0 ± 5</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.9 ± 2.1</td>
<td>7.0 ± 1.6</td>
<td>8.5 ± 1.8</td>
<td>8.4 ± 2.0</td>
</tr>
<tr>
<td>HR (beats.min⁻¹)</td>
<td>85 ± 22</td>
<td>104 ± 24</td>
<td>130 ± 18</td>
<td>127 ± 24</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>116 ± 12</td>
<td>92.10 ± 16</td>
<td>81.9 ± 9</td>
<td>60 ± 17</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>31 ± 4</td>
<td>41 ± 29</td>
<td>39 ± 6</td>
<td>43 ± 10</td>
</tr>
</tbody>
</table>

Table 2 Venital and hemodynamic parameters. Results are expressed as mean ± SD. (Rl Lung resistance, Ed dynamic elastance, Cd dynamic compliance, WOB work of breathing, Pdi transdiaphragmatic pressure, VE minute ventilation, PIP peak inspiratory pressure, CO cardiac output, HR heart rate, MAP mean arterial pressure, PAP mean pulmonary arterial pressure)

\( ^{3} p<0.05 \) versus baseline, \( ^{4} p<0.01 \) versus baseline, \( ^{5} p<0.001 \) versus baseline, \( ^{*} p<0.05 \) versus air/O₂ bronchospasm, \( ^{**} p<0.01 \) versus air/O₂ bronchospasm, \( ^{***} p<0.001 \) versus air/O₂ bronchospasm, \( ^{p} p<0.05 \) versus air/O₂ salbutamol, \( ^{**} p<0.01 \) versus air/O₂ salbutamol, \( ^{***} p<0.001 \) versus air/O₂ salbutamol.

He/O₂ lowered Rl, Pdi and work of breathing (Table 2). Minute ventilation was not improved with He/O₂. The perfusion data were not modified by He/O₂ but bronchospasm-induced hypoxemia worsened (Table 1). Ventilation data show an increase of dead space associated with a decrease of mean V.

Tracings of one representative animal are shown in Fig. 4.
Fig. 4 Multiple inert gas elimination technique (MIGET). Ventilation (*white dots*) and perfusion (*black dots*) distribution in one representative animal in the four conditions studied. *DS* dead space.

Discrimination

The main findings of the present study are that: (1) acute bronchospasm led to a considerable increase in peak inspiratory pressure, lung resistance, and dynamic elastance, as well as hypoxemia due to the development of a shunt and increased distribution of perfusion dispersion, and respiratory acidosis due to hypercapnia resulting from increased mean and dispersion of ventilation, (2) salbutamol given intravenously, at doses described by Downes (8), did not.
decrease lung resistance but significantly impaired ventilation-perfusion relationships, but while reducing hypercapnia and dead space, it worsened the shunt and the dispersion of perfusion distribution and did not improve hypoxemia. (3) He/O_2, added to salbutamol, while reducing lung resistance and dynamic elastance, worsened hypoxemia and dead space, and decreased the inspiratory muscle workload by a decrease in Pdi and in work of breathing.

Let us first discuss the limitations of the study. First, due to the complexity of the manipulations, the number of animals is small and it can be difficult to extrapolate the results to the clinical setting. Second, our results do not allow differentiation between the effects of He/O_2 and those of salbutamol, given that we did not perform ventilation with He/O_2 alone. However, as salbutamol is usually the first-line treatment in status asthmaticus, we considered that adding He/O_2 to this drug more closely reflected clinical practice in most severe cases. Furthermore, the effects of He/O_2 alone in this model have already been documented (33).

The changes we observed during induced bronchospasm were comparable to a previous study, with respect to arterial blood gases and V_A/Q abnormalities as well as respiratory mechanics (23). During IV methacholine administration, these authors also observed a shunt, contrary to provoked bronchospasm in human. The presence of a significant shunt during bronchospasm in pigs is probably due to the lack of collateral ventilation, at variance with human. It is well known that acidemia tends to antagonize the bronchodilator effects of sympathomimetic agents (14). In our study no animal had, at any time, a pH less than 7.2.

Salbutamol was recommended to be used as the standard i.v. beta-agonist (4), with a protocol similar to that devised by Downes et al. (8) for IV isoproterenol i.e. 1 µg/kg/min over 10 minutes followed by a continuous infusion of 0.2 µg/kg/min. We used the same protocol, and have documented a
relative hemodynamic stability despite the intravenous administration of methacholine (5).

During bronchospasm, salbutamol administration did not change lung resistance and compliance. This lack of change is at variance with a previous study on dogs (25). In this latter study, the authors also used intravenous methacholine administration to induce bronchospasm but the dogs were paralyzed, the $\beta_2$ agonist was terbutaline and it was administrated by aerosol. We decided against administering salbutamol by aerosol because our animals breathed spontaneously during the bronchospasm, and any change in minute ventilation would have modified the dose of salbutamol, which should not be the case during continuous IV administration.

Hypoxemia is frequent in patients with acute severe asthma and is the result of predominant bimodal blood flow pattern of the $V_A/Q$ distributions without true shunt or increased dead space (26; 27). In our study, the dispersion of the perfusion distribution was markedly increased by bronchospasm, worsened by infusion of salbutamol and further increased, but not significantly, by He/O$_2$ (Table 1). Furthermore, there was an increase in shunt with administration of the beta-2 stimulating drug. All these effects would have decreased PaO$_2$. In fact, the extra pulmonary factors that modulate the decrease in PaO$_2$ (28; 31) were effective in our animals receiving a beta-adrenergic stimulation: the cardiac output rose and minute ventilation increased, and there was a decrease in perfusion to low $V_A/Q$ units (Table 1). Moreover, log SDQ, which is considered as one of the best descriptors of $V_A/Q$ inequality (20), tended to decrease, albeit non significantly. The log SDQ was inversely correlated to PaO$_2$ in two studies including patients with chronic moderate to severe asthma (32;2).

The vasodilatation produced by stimulation of peripheral beta$_2$-receptors may decrease diastolic blood pressure and increase cardiac output. In our study,
systolic blood pressure decreased and heart rate increased (Table 2), and as a result cardiac output increased significantly. This might probably participate, with the reduction in pulmonary vascular tone, in the increase of shunt with the consequence that it was not possible to determine the separate roles of pulmonary vasodilatation and increased cardiac output. Our results are similar to those found in dogs by Rodriguez-Roisin et al. (25). The rise in cardiac output observed could also explain the absence of worsened hypoxemia, which would have been expected from increased dispersion of \( V_{A}/Q \) distribution.

The principal mechanism by which \( \text{He}/O_{2} \) worsened hypoxemia is the increase in perfusion to low \( V_{A}/Q \) units. This could be explained by some derecruitment with \( \text{He}/O_{2} \) exacerbate by the physical properties of the gas. The MIGET also documented the presence of a high level of dead space (Table 1) even in baseline conditions. Such a high baseline dead space was also present in our previous studies on pigs (33; 34) and was mainly ascribed to both anatomical and instrumental dead space. While bronchospasm did not increase the dead space, salbutamol decreased the level of this pre-existent dead space, which returns to its baseline values after \( \text{He}/O_{2} \) administration. The virtual absence of areas of high ventilation-perfusion ratio, including dead space, is consistent with previous studies in adult asthma. High \( V_{A}/Q \) regions have been demonstrated only in children with low FEV\(_1\) after exercise-induced asthma (10). Both gas trapping and lung hyperinflation would induce the development of areas of high \( V_{A}/Q \) ratio.

Bulow and al. showed an increase of volume of trapped gas in the lung during provoked asthma in human and a decrease of this trapped gas after salbutamol (7). Salbutamol causes large airways dilatation by reducing bronchomotor tone, and produces an improvement in small airways function (22). The decrease of dead space observed in our study can be attributed in part to the bronchodilator effect of salbutamol, and then to the decrease of hyperinflation and trapped gas, but also to the pulmonary vasodilatator effect.
This decrease of dead space associated with the increased minute ventilation (Table 2) resulted in a significant improvement of PaCO₂. However, the decrease of PaCO₂ with administration of salbutamol was probably counterbalanced by an increase in the dispersion of Vₐ/Q ratios (Disp R-E) (Table 1). This increase of Disp R-E remains elevated during He/O₂ inhalation and, as seen in our previous study (33), this phenomenon explain the failure of He/O₂ to improve the PaCO₂ despite a decrease of elastance and lung resistance. The decreased dynamic elastance is the result of a reduction of dynamic hyperinflation commonly seen in asthma and due to incomplete end-expiratory lung emptying. The decrease in airway resistance is the result of two mechanisms of He/O₂ inhalation. The lower density of the mixture, first, increases the likelihood of laminar flow conditions, and second, reduces the driving pressure required to obtain a given flow in areas where turbulent flow conditions prevail (21). As expected during He/O₂ inhalation, we observed a decrease in lung resistance. This decrease was reported in other studies in porcine model of methacholine-induced bronchospasm (18), in normal subjects (19), and obstructive lung disease (13).

Finally, Pdi is an index often used to represent the activity of the entire diaphragm. The baseline values of Pdi in our study were low first because the use of propofol decreased contractility of the diaphragm (12), and second because of the PS mode of ventilation reducing diaphragmatic effort (6). However, we observed a significant decrease in Pdi and work of breathing during He/O₂ inhalation. This decrease occurred with no modification in ventilation parameters and confirms previous results showing that He/O₂ inhalation decreases inspiratory muscle workload (3).

In conclusion, the results of this study show that in this model of severe bronchospasm:
1. IV salbutamol while reducing hypercapnia and dead space worsened the shunt and the dispersion of perfusion distribution and neither improved nor worsened hypoxemia. Parameters of respiratory mechanics were unchanged in this early stage of treatment by salbutamol.

2. He/O₂ failed to improve gas exchange and Vₐ/Q relationships. However, due to its favorable effects on respiratory mechanic and inspiratory muscle workload, He/O₂ might represent an attractive option in patients with acute severe asthma ventilated in pressure support, as it could prevent the occurrence of diaphragmatic fatigue. Further studies should now attempt to define the optimal strategy for the combined use of these two agents.

Conflict of interest statement: none of the authors have a conflict of interest to declare in relation to this work.

Footnote: This study was supported in part by grant n° 3.4.506.02.F from the Fonds National de la Recherche Scientifique.

Reference List


8- Comparative effects of helium-oxygen and external positive end-expiratory pressure in mechanically ventilated patients with COPD.

Introduction

In this study we wanted to apply the use of helium ventilation in the clinical setting. The best way would be to apply helium ventilation to acute asthma attack but in emergency conditions it is difficult to take time for measurement of the ventilation-perfusion relationships by the MIGET.

So we applied the helium ventilation in the chronic obstructive pulmonary disease (COPD), in which helium properties could be advantageous for reducing dynamic hyperinflation and airway resistance. The study included ten patients and helium ventilation was compared with application of an external positive end-expiratory pressure (PEEP).

The study brought us to the conclusion that helium ventilation and application of an external PEEP comparably reduced intrinsic PEEP and trapped gas volume. He/O\textsubscript{2} decreased airway resistance and intrathoracic pressures at a small cost in arterial oxygenation.
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

Abstract

Objective: To compare the effects of He\textsubscript{2}O\textsubscript{2} and external PEEP (PEEP\textsubscript{e}) on intrinsic PEEP (PEEP\textsubscript{i}), respiratory mechanics, gas exchange, and ventilation/perfusion (V\textsubscript{A}/Q) in mechanically ventilated COPD patients.

Design and setting: Prospective, interventional study in the intensive care unit of a university hospital.

Intervention: Ten intubated, sedated, paralyzed, mechanically ventilated COPD patients studied in the following conditions: (a) baseline settings made by clinician in charge, air\textsubscript{2}O\textsubscript{2}, ZEEP; (b) He\textsubscript{2}O\textsubscript{2}, ZEEP; (c) air\textsubscript{2}O\textsubscript{2}, PEEP\textsubscript{e} 80% of PEEP\textsubscript{i}; (d) He\textsubscript{2}O\textsubscript{2}, PEEP\textsubscript{e} 80% of PEEP\textsubscript{i} by the multiple inert gas elimination technique (MIGHT). Outcome measures: PEEP\textsubscript{i}, PEEP\textsubscript{e}, and trapped gas volume were comparably reduced by He\textsubscript{2}O\textsubscript{2} (4.2±4 vs. 7.7±4 cmH\textsubscript{2}O and 98±82 vs. 217±124 ml, respectively) and PEEP\textsubscript{e} (4.4±1.3 vs. 7.8±3.6 cmH\textsubscript{2}O and 120±107 vs. 216±115 ml, respectively). He\textsubscript{2}O\textsubscript{2} reduced inspiratory and expiratory respiratory system resistance (15.2±4.4 vs. 20.7±6.9 and 19±9 vs. 28.8±30 cmH\textsubscript{2}O s\textsuperscript{-1}, respectively) and plateau pressure (12±4 vs. 17±6 cmH\textsubscript{2}O). PEEP\textsubscript{e} increased airway pressures, including total PEEP and elastance. Pao\textsubscript{2}/FiO\textsubscript{2} was slightly reduced by He\textsubscript{2}O\textsubscript{2} (225±83 vs. 240±82) without significant V\textsubscript{A}/Q change. Conclusions: He\textsubscript{2}O\textsubscript{2} and PEEP\textsubscript{e} comparably reduced PEEP\textsubscript{i} and trapped gas volume. However, He\textsubscript{2}O\textsubscript{2} decreased airway resistance and intrathoracic pressures, at a small cost in arterial oxygenation. He\textsubscript{2}O\textsubscript{2} could offer an attractive option in COPD patients with PEEP\textsubscript{e} dynamic hyperinflation.

Keywords: Chronic obstructive pulmonary disease; Helium; Heliox; Ventilation/perfusion; Multiple inert gas elimination technique

Introduction

In mechanically ventilated patients with chronic obstructive pulmonary disease (COPD), incomplete exhalation of inspired tidal volume (VT) due to elevated airway resistance and decreased lung elastic recoil can lead to an increase in end-expiratory lung volume, termed “dynamic hyperinflation” [1, 2] or “intrinsic” positive end-expiratory pressure (PEEP\textsubscript{i}) [3, 4]. The numerous deleterious effects of PEEP\textsubscript{i} on respiratory mechanics, gas exchange, hemodynamics, oxygen transport, and work of breathing [3, 4, 5] can be attenuated by measures aimed at reducing dynamic hyperinflation, such as reduction in VT and respiratory rate [6], bronchodilators [7], and applying external PEEP (PEEP\textsubscript{e}) [8]. However, the latter is difficult to titrate [4] and may by itself be detrimental by increasing lung volumes and intrathoracic pressures [9, 10], and worsening of hemodynamics [9, 11]. Alternatively, replacing the inhaled air-oxygen mixture by helium-oxygen, which reduces resistance to flow in the airways [12]
due to its low density, has been shown to decrease PEEPi and trapped gas volume [13]. However, He/O2 also raises concerns, among which are interference with ventilator function [14] and worsening of hypoxemia, the latter having been documented in spontaneously breathing COPD patients [15, 16]. The purpose of this study was then to compare the effects of He/O2 and PEEP/COPD on respiratory mechanics, gas exchange, and ventilation/perfusion (V/Q) in mechanically ventilated COPD patients.

Methods

Patients

The study was conducted in the Intensive Care Unit, St. Luc Hospital, Brussels. Imbursed patients consecutively admitted to the ICU were included if they met diagnostic criteria of COPD [17] and had been mechanically ventilated for no longer than 48 h. Patients were excluded if pneumothorax was present or the inspired O2 fraction (FiO2) was 0.6 or higher. The study included 10 patients (aged 45.9 years) after a mean of 26±5.8 of mechanical ventilation. Individual baseline characteristics, main ventilator settings, PEEP measurement and arterial blood gases of the patients are summarized in Table 1. The study protocol was approved by the ethics committee of the Catholic University of Louvain, Brussels. Consent was obtained from all the inpatients.

Table 1: Patients’ baseline characteristics (PEEP: intrinsic positive end-expiratory pressure, RR: respiratory rate, VT: tidal volume, V50: volume of gas trapped in the lungs at end-expiration)

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age (years)</th>
<th>RR (min⁻¹)</th>
<th>VT (ml)</th>
<th>V50 (ml)</th>
<th>PEEP (cmH2O)</th>
<th>FiO2</th>
<th>PaO2/PaCO2</th>
<th>PaCO2 (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>13</td>
<td>590</td>
<td>110</td>
<td>7</td>
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<td>313</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>16</td>
<td>365</td>
<td>150</td>
<td>16</td>
<td>0.38</td>
<td>200</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>16</td>
<td>494</td>
<td>490</td>
<td>12</td>
<td>0.30</td>
<td>190</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
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<td>12</td>
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<td>0.31</td>
<td>255</td>
<td>42</td>
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<td>73</td>
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<td>9</td>
<td>68</td>
<td>12</td>
<td>560</td>
<td>210</td>
<td>0</td>
<td>0.40</td>
<td>175</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>85</td>
<td>16</td>
<td>430</td>
<td>390</td>
<td>0</td>
<td>0.33</td>
<td>191</td>
<td>69</td>
</tr>
<tr>
<td>Mean</td>
<td>64</td>
<td>14.5</td>
<td>442</td>
<td>217</td>
<td>7.7</td>
<td>0.35</td>
<td>353</td>
<td>31</td>
</tr>
<tr>
<td>SD</td>
<td>9</td>
<td>3</td>
<td>100</td>
<td>125</td>
<td>4.1</td>
<td>0.07</td>
<td>82</td>
<td>0</td>
</tr>
</tbody>
</table>

During the entire protocol, the FiO2, and ventilator settings modeled by the clinician in charge of the patient before inclusion were kept constant. Maximum pressure limit was set at 40 cmH2O. Inspiratory flow rate was 60 l/min, square wave pattern. No PEEP was set on the ventilator except during the last step of the study at which time an PEEP of 80% of PEEPi measured at air/O2 zero end-expiratory pressure (ZEEP) was applied (see below).

Respiratory rate, airway pressure, flow, and respiratory exchange ratio (RER) were recorded from the ventilator. Respiratory system static compliance (Cst) and inspiratory (RI) and expiratory (Re) resistances were computed by the automatic measuring alouds of the ventilator before a brief end-inspiratory pause. PEEPi was measured by an end-expiratory occlusion [3], also performed automatically on the Servo 300. This end-expiratory occlusion technique actually measures total PEEP in static conditions. Therefore when no PEEPi is applied, the result is equivalent to the value of PEEPi, whereas when PEEPi is applied, PEEPi is equal to the value of total PEEP (PEEPtot) obtained by end-expiratory occlusion minus that of PEEPi set on the ventilator [4, 19]. For each set of measurements the end-expiratory occlusion was performed three times at 1-min intervals and PEEPi reported as the mean of the three readings. End-expiratory gas trapped volume (V50) was determined by the end-inspiratory key occlusion technique [8]. Briefly, the patient was disconnected from the ventilator at end-inspiration, and the total exhaled volume measured with the spirometer, until expiratory flow was no longer detectable. Total exhaled volume represents total end-inspiratory volume (V50) above functional residual capacity. V50 was at end-expiration was then computed as: V50 = V50 – V50 measured VT. Measured VT was determined as the most of the last five breaths before the maneuver [6].

Heart rate and mean systemic arterial pressure were continuously monitored by standard three-lead monitoring electrodes and an indwelling arterial catheter, respectively. Arterial oxygen saturation was continuously monitored by pulse oximetry.

Ventilation-perfusion relationships by the multiple inert gas elimination technique

The distribution of the V/Q values was assessed by the multiple inert gas elimination technique (MIGET) [20]. Briefly, six inert gases of varying solubility (SF6, ethane, cyclopropane, halothane, ether, and acetone) were equilibrated in 0.9% NaCl and were infused at a constant rate of 3 mL/min through the central venous line. After a 30-min equilibration period 00 mL blood
8 – Helium and COPD

Fig. 1 Intrinsic PEEP and trapped gas volume. Individual values of trapped gas volume ($V_{\text{trapped}}$) and limited PEEP (PEEPi) under all conditions listed. Air/O$_2$, ZEEP 1 initial settings made by clinician. no PEEP. He/O$_2$, ZEEP after 30 min of He/O$_2$ inhalation, no PEEP; air/O$_2$, ZEEP 2 after 30 min of air/O$_2$ inhalation, no PEEP; air/O$_2$, PEEP 0% after 30 min of air/O$_2$ inhalation, PEEP 80% of PEEP measured at air/O$_2$, ZEEP 2

Cardiac output and oxygen transport

If a pulmonary artery catheter was in place, cardiac output was determined by thermodilution. In the absence of such a catheter, cardiac output was estimated by the Fick method, using central venous rather than mixed venous blood samples. Oxygen transport (DO$_2$) was computed according to standard equations. Oxygen consumption (VO$_2$) was determined from the inspired-expired O$_2$ concentrations.

Measurement protocol

A complete set of all measurements was performed at the following time points: (a) upon starting the protocol, no PEEP (air/O$_2$, ZEEP); (b) after 30 min of He/O$_2$ inhalation, no PEEP (He/O$_2$, ZEEP); (c) after 30 min of air/O$_2$ inhalation, no PEEP (air/O$_2$, ZEEP 2); (d) after 30 min of air/O$_2$ inhalation, PEEP set as 80% of PEEP measured at air/O$_2$, ZEEP 2 (air/O$_2$, PEEP).

Statistical methods

Values are reported as mean ± standard deviation. One-way analysis of variance for repeated measures was used to compare the values obtained at each of the four conditions. Significance between time points was determined by Fisher’s protected least significance test. A $p$ value less than 0.05 was considered significant.
Table 2 Ventilatory parameters (Endurance distance of the respiratory system, PEEP, inspiratory positive end-expiratory pressure, PIP peak inspiratory pressure, PEEP, mean airway pressure, fpeak, plateau pressure, Rsys inspiratory respiratory system resistance, Rexp expiratory respiratory system resistance, F_tpeak trapped lung volume at end-expiration)

<table>
<thead>
<tr>
<th></th>
<th>Air/O2, ZEEP</th>
<th>He/O2 ZEEP</th>
<th>Air/O2, ZEEP2</th>
<th>Air/O2, PEEPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>14±2.5</td>
<td>14±2.4</td>
<td>14±2</td>
<td>14±2.6</td>
</tr>
<tr>
<td>VTR (ml)</td>
<td>44±2.100</td>
<td>41±0.154</td>
<td>43±2.130</td>
<td>44±0.100</td>
</tr>
<tr>
<td>PIP (cmH2O)</td>
<td>24±0</td>
<td>23.5±6.8</td>
<td>23.4±0</td>
<td>24±6.9</td>
</tr>
<tr>
<td>mean (cmH2O)</td>
<td>7.5±3</td>
<td>6.4±3</td>
<td>8.1±3.4</td>
<td>11.3±4**</td>
</tr>
<tr>
<td>PEEP (cmH2O)</td>
<td>17±6</td>
<td>17.4±7</td>
<td>16.4±6</td>
<td>19.7±11**</td>
</tr>
<tr>
<td>Res (cmH2O l⁻¹ s⁻¹)</td>
<td>23.8±8</td>
<td>23.3±9</td>
<td>23.5±10</td>
<td>25±5.0</td>
</tr>
<tr>
<td>Rn (cmH2O l⁻¹ s⁻¹)</td>
<td>20.7±6.9</td>
<td>21.2±5.8</td>
<td>18±4.4</td>
<td>18±4.4</td>
</tr>
<tr>
<td>PEEPs (cmH2O)</td>
<td>7.7±6</td>
<td>4.2±2.4**</td>
<td>7.3±5.8</td>
<td>4.5±11**</td>
</tr>
<tr>
<td>V_tpeak (ml)</td>
<td>21±1.22</td>
<td>9.8±2.2</td>
<td>20±1.15</td>
<td>13±1.0**</td>
</tr>
</tbody>
</table>

*p<0.001 vs. air/O2, ZEEP 1, ZEEP 2 and air/O2, PEEPs; **p<0.01 vs. air/O2, ZEEP 1, ZEEP 2 and He/O2, ZEEP; ***p<0.05 vs. air/O2, ZEEP 2, ****p<0.01 vs. air/O2, ZEEP 1 and ZEEP 2 (analysis of variance)

Fig. 2 Total and external PEEP. Individual measured levels of total PEEP (PEEPtot) determined by the end-expiratory occlusion technique during He/O2 inhalation (A, left) and external PEEP (PEEPtot) application (B, right). A Magnitude of PEEPtot (i.e., inspiratory, PEEP, since no PEEPs were applied) during air/O2 (white bars) and He/O2 (black bars) inhalation. B Magnitude of PEEPtot with air/O2 and ZEEP (white bars) and He/O2 and PEEPs application, partitioned into PEEP (black bars) and PEEPs (hatched bars) components.

Results
Ventilatory parameters PEEP and respiratory mechanics

As shown in Table 2, He/O2 led to a significant reduction in peak (PIP) and plateau (Pmean) pressures, Ers, and both Rn and Rsys. Conversely, PEEPs significantly increased mean airway pressure and Pmean while there was a trend towards a rise in PIP and Ers. Rn and Rsys were not significantly affected by PEEPs. V_tpeak, and PEEPs were both compatibly reduced by He/O2 and PEEPs (Table 2), this response being present in all patients, as shown in Fig. 1.
Table 3 Hemodynamics, arterial blood gases and oxygen transport. 

<table>
<thead>
<tr>
<th></th>
<th>AirO2, ZEEP 1</th>
<th>HeO2, ZEEP</th>
<th>AirO2, ZEEP 2</th>
<th>AirO2, PEEP</th>
<th>PEEP vs. AirO2-ZEEP 1 (analysis of variance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b/min)</td>
<td>83±19</td>
<td>82±18</td>
<td>84±17</td>
<td>84±19</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76±11</td>
<td>79±9</td>
<td>81±12</td>
<td>81±14</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6.5±0.37</td>
<td>6.5±0.07</td>
<td>6.5±0.03</td>
<td>6.5±0.03</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.38±0.06</td>
<td>7.37±0.05</td>
<td>7.37±0.03</td>
<td>7.37±0.06</td>
<td></td>
</tr>
<tr>
<td>Ppa (mmHg)</td>
<td>81±21</td>
<td>74±4*</td>
<td>80±19</td>
<td>74±4*</td>
<td></td>
</tr>
<tr>
<td>PacO2 (mmHg)</td>
<td>37±15</td>
<td>37±15</td>
<td>37±15</td>
<td>37±15</td>
<td></td>
</tr>
<tr>
<td>Da, dl (mmHg)</td>
<td>96±19</td>
<td>90±28</td>
<td>90±28</td>
<td>90±28</td>
<td></td>
</tr>
<tr>
<td>PacO2 (mmHg)</td>
<td>51±4</td>
<td>51±11</td>
<td>51±11</td>
<td>51±11</td>
<td></td>
</tr>
<tr>
<td>DO2 (ml/min)</td>
<td>85±129</td>
<td>85±123</td>
<td>85±123</td>
<td>85±123</td>
<td></td>
</tr>
<tr>
<td>VO2 (ml/min)</td>
<td>170±72</td>
<td>176±83</td>
<td>162±56</td>
<td>166±65</td>
<td></td>
</tr>
<tr>
<td>PaO2/PH2</td>
<td>0.21±0.09</td>
<td>0.22±0.10</td>
<td>0.21±0.10</td>
<td>0.21±0.11</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 Results of multiple inert gas elimination technique (MIGET) R-E* index of dispersion of ventilation/perfusion ratios, corrected for deadspace, RSV residual sum of squares, V/Q; percentage of pulmonary blood flow; V/Q ventilation to perfusion ratio, % VE percentage of minute ventilation, Log SD Q log standard deviation of perfusion, Log SD V log standard deviation of ventilation distribution.

<table>
<thead>
<tr>
<th></th>
<th>AirO2, ZEEP 1</th>
<th>HeO2, ZEEP</th>
<th>AirO2, ZEEP 2</th>
<th>AirO2, PEEP</th>
<th>PEEP vs. AirO2-ZEEP 1 (analysis of variance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stunt (% QT)</td>
<td>6.8±10</td>
<td>7.5±12.2</td>
<td>5.9±10.3</td>
<td>7.7±13.6</td>
<td></td>
</tr>
<tr>
<td>0.005&lt;_Q&lt;0.01 (% QT)</td>
<td>4.4±1.1</td>
<td>4.1±1.7</td>
<td>4.1±1.3</td>
<td>2.7±2.5</td>
<td></td>
</tr>
<tr>
<td>0.01&lt;_Q&lt;0.02 (% QT)</td>
<td>15.3±0.6</td>
<td>23.7±17.2</td>
<td>23.7±14.9</td>
<td>17.2±14.1</td>
<td></td>
</tr>
<tr>
<td>0.1&lt;_Q&lt;0.1 (% QT)</td>
<td>62.1±28</td>
<td>56.6±18.7</td>
<td>57.1±18.2</td>
<td>61.3±17.8</td>
<td></td>
</tr>
<tr>
<td>0.1&lt;_Q&lt;0.15 (% QT)</td>
<td>10.4±28</td>
<td>8.3±2.1</td>
<td>8.3±0.2</td>
<td>11.1±9.8</td>
<td></td>
</tr>
<tr>
<td>0.1&lt;_Q&lt;0.15 (% QT)</td>
<td>10.4±28</td>
<td>8.3±2.1</td>
<td>8.3±0.2</td>
<td>11.1±9.8</td>
<td></td>
</tr>
<tr>
<td>Mean Q (l/min)</td>
<td>0.07±0.09</td>
<td>0.13±0.01</td>
<td>0.00±0.09</td>
<td>0.02±0.06</td>
<td></td>
</tr>
<tr>
<td>Log SD Q</td>
<td>1.34±0.33</td>
<td>1.44±0.33</td>
<td>1.42±0.31</td>
<td>1.31±0.28</td>
<td></td>
</tr>
</tbody>
</table>

However, PEEPometry differed markedly between these two conditions (Fig. 2). With HeO2, as expected, since PEEP was also decreased in all patients and no PEEP was applied, PEEPometry was also decreased in all patients. With PEEP, even though PEEP was decreased in all patients, PEEPometry decreased only in two patients (5 and 7), while the other remained unchanged in three patients (1, 6, and 9), and increased in five patients (2, 3, 4, 8, and 10), as shown in Fig. 2.

Arterial blood gases and V/Q relationships

No significant modification in arterial pH or arterial blood gases was observed during the study, with the exception of a decrease in arterial oxygenation during HeO2 inhalation (Table 3). MIGET analysis (Table 4) showed a small stunted baseline, with most of the perfusion directed to areas of intermediate or normal V/Q. A high deadspace fraction was present at baseline, the remaining ventilation being distributed mainly to areas of intermediate or normal V/Q. HeO2 exerted little change on V/Q relationships. No significant V/Q modification was observed with PEEP. MIGET tracings from a typical patient are shown in Fig. 3. V/Q heterogeneity, quantified by the Duson R-E* index, was not significantly modified by either HeO2 or PEEP (Table 4). Mean overall residual sum of squares was 3.02±1.84, and was less than 5.5% of data sets, within the range of high technical quality measurements [23].

Homodynamics and oxygen transport

No significant changes in arterial blood pressure, heart rate, DO2 or VO2 were noted during the various phases of the study (Table 3).
Complications
No complication occurred during any of the protocol phases.

Discussion
The main findings of this study in a group of sedated, paralyzed, and mechanically ventilated COPD patients with moderate levels of PEEPi are that HeO\textsubscript{2} reduced PEEPi and V\textsubscript{ramp}, airway pressures and resistances, and elastance at a small cost in arterial oxygenation. Conversely, PEEPi set at 80% of measured PEEPi, reduced PEEPi and V\textsubscript{ramp}, but increased airway pressures and in most patients PEEP\textsubscript{opt}. Neither approach significantly affected V\textsubscript{r}/Q distribution.

Effects of HeO\textsubscript{2}
The observed effects of HeO\textsubscript{2} on PEEPi and respiratory mechanics are consistent with those documented in a previous study in intubated, sedated, paralyzed patients undergoing controlled mechanical ventilation, with comparable levels of PEEPi, in which HeO\textsubscript{2} led to a marked decrease in V\textsubscript{ramp} and PEEPi in 22/23 patients [13]. The concordant results from the two studies, with effects observed in almost every patient, provides further evidence that HeO\textsubscript{2} due to its low density and resultant reduction in airway resistance, effectively attenuates dynamic hyperinflation/PEEP\textsubscript{i} in this setting. It should be noted nonetheless that HeO\textsubscript{2} has no impact on the cause of obstructive disease and airflow limitation. Thus its effects disappear once its administration is discontinued, as shown by the rapid return to baseline values of PEEPi and V\textsubscript{ramp} in both our studies when HeO\textsubscript{2} inhalation was stopped. Consequently the use of HeO\textsubscript{2} should not deter ICU physicians from aiming to decrease airway obstruction with bronchodilating drugs, and avoiding excessive respiratory rate and VT settings on the ventilator [4]. Among concerns regarding the use of HeO\textsubscript{2} in
COPD patients is a possible worsening of arterial oxygenation, documented in studies performed in spontaneously breathing uncompromised patients [15, 16]. In one study HeO₂ breathing entailed a decrease in PaO₂, hypothesized to result from an increase in the heterogeneity of V/Q distribution [16]. Another study documented an increase in the alveoloarterial O₂ gradient during HeO₂ inhalation [15]. MIGET analysis was consistent with a diffusion impairment for O₂, attributed by the authors to a proximal displacement of the transition from convective to diffusive gas transfer processes [15, 24]. Finally, a slight decrease in PaO₂ with HeO₂ compared to airO₂ was also noted in a study by Christopher and Hiltala [25], in mechanically ventilated dogs, without significant change in MIGET results, and also attributed by the authors to displacement of the convective/diffusive front in the Airways [15, 24, 25]. However, whether these results can be extrapolated to uncompromised and mechanically ventilated patients is unclear since in a previous study on patients undergoing mechanical ventilation we found no impact of HeO₂ on arterial oxygenation [13]. It should also be noted that a decrease in alveolar ventilation, suggested by the slight rise in PaCO₂ with HeO₂, could have contributed to the decrease in PaO₂.

Our MIGET results are in line with these observations. Overall, the baseline pattern of a small fraction of shunt and perfusion to low V/Q regions, perfusion predominating in regions of V/Q=1, and high deadspace (Table 4) is consistent with both the so-called "H" pattern described by Wagner et al. [26] in stable spontaneously breathing patients with severe COPD and the profile found in two studies in COPD patients during controlled mechanical ventilation [8, 27]. In our study no significant change was observed with HeO₂, thus excluding a major effect of HeO₂ on shunt, low V/Q or worsening of V/Q inequality. The convective/diffusive front theory mentioned above could explain these results [24], the small magnitude of worsening hypoxemia being in line with that observed in other studies [15, 25]. Indeed, the magnitude of worsening of hypoxemia was small (8%) and is probably of negligible clinical importance in patients receiving a mean FiO₂ of 0.35. Why these findings differed from those of our preceding study [13] in a comparable patient population and setting is not immediately clear. However, in the earlier study patients were ventilated for 45 min with HeO₂ compared to the 30 min in the present study, possibly allowing any time-dependent short-term V/Q heterogeneity to subside. Furthermore, there was a trend towards a decrease in PaO₂ in the former study with HeO₂, by 6%, although the difference was not statistically significant [13]. Of importance, and in the same line of thought, no worsening of hypoxemia was noted during noninvasive pressure support with HeO₂ in uncompromised COPD patients in two recent studies [18, 28]. Finally, a recent study on the impact of various inspiratory flow waveforms in mechanically ventilated COPD patients demonstrated that square wave inspiratory flow as used in the present study was less favorable on gas exchange than decelerating flow [29]. This factor might have contributed to our results. To summarize, it seems that a reduction in PaO₂ during HeO₂ inhalation in this setting is either absent or of very small magnitude and probably represents a minor price to pay for the major beneficial effects on dynamic hyperinflation and respiratory mechanics.

Regarding PaCO₂, the absence of change with HeO₂ was somewhat surprising, given that two studies using noninvasive ventilation documented a reduction in PaCO₂ with HeO₂, possibly due to improved CO₂ diffusion [18, 28]. However, the results are in accord with those of our previous study in intubated and mechanically ventilated patients [13] and are in line with the absence of change in the V/Q results, in particular deadspace (Table 4).

Effects of PEEP

In patients with PEEP undergoing spontaneous-assisted mechanical ventilation, applying PEEP has been shown to reduce the inspiratory threshold load, ease triggering of the ventilator, and reduce work of breathing [30, 31]. However, any benefit of PEEP during controlled ventilation is much less obvious [4], as underlined in a recent publication [19] and as demonstrated in various studies [8, 11, 32]. In a study using the MIGET in COPD patients during controlled ventilation, Rossi et al. [8] showed that when PEEP is at 50% of measured PEEP was applied, no change in respiratory mechanics was noted, while PaO₂ increased as a result of a rise in the mean value of the distribution of perfusion. However, when PEEP equivalent to 100% of PEEP was applied, airway pressures rose, and no further improvement in gas exchange was noted [8]. It should also be mentioned that no change in oxygen transport was noted with the application of PEEP, while reducing PEEP through controlled hyperventilation increased cardiac output and oxygen transport [8]. This could have resulted from a reduction of the adverse hemodynamic effects of PEEP and could also be observed when PEEPs is decreased by HeO₂. However, we made no such observation in our patients, probably because there appeared to be little hemodynamic impact from PEEP, as observed in a prior study [13]. Biaugetti et al. [11] showed that applying a PEEP equal to measured PEEP led to an increase in end-expiratory volume, a rise in intrathoracic pressures, and no improvement in arterial blood gases, while a decrease in cardiac output was noted with a PEEP exceeding PEEP. Fernandez et al. [32] observed that the increase in end-expiratory volume when setting PEEP equal to PEEP was directly proportional to respiratory system compliance, and hence that its magnitude was difficult to predict in routine clinical condi-
tions. The reasons for this lie in the fact that in the presence of expiratory flow limitation added increments of PEEP progressively increase total PEEP and lung volume, until a critical value of PEEP is reached, above which total PEEP and lung volume both increase [33, 34]. When the latter occurs, increased respiratory system elastance, decreased cardiac output and worsening of gas exchange occur [34].

These various issues have led to the recommendation of either refraining from using PEEP in the presence of PEEP during controlled mechanical ventilation [19], or to not exceed values of 25-35% of measured PEEP, while carefully monitoring the consequences of its application [4]. In our study the goal was to apply a PEEP equivalent to 40% of PEEP. However, it is difficult to ascertain that this goal was always attained, since although we used the PEEP measured during the third step (air/O2, ZEEP 2), it is well known that PEEP can change fairly quickly [35]. Thus it is possible that PEEP levels equal to or exceeding PEEP were applied in some patients, as our results suggest. Indeed, as shown in Fig. 2, in most patients PEEP was replaced by PEEP, but total PEEP was mainly unchanged or even increased. This observation is in line with the studies cited above demonstrating that, in the absence of expiratory flow limitation, or if excessive PEEP levels are used even if such a limitation is present, worsening dynamic hyperinflation and its complications can occur. A seminal study by Tuxen [9] has illustrated how severe the latter can be. Interestingly, in the latter study, as overall lung volume and total PEEP increased when high levels of PEEP were applied, \( V_{equated} \) decreased, most likely due to the rise in elastance and a decrease in airway resistance associated with the higher lung volume [9]. A similar observation was made in our patients (Fig. 1), probably for identical reasons. Regardless of gas exchange, the blood gas and MIGET results showed no effect of PEEP, which is in apparent contradiction with the improvement in \( P_{aO_2} \) due to a higher mean value of the perfusion distribution observed by Rossi et al. [36]. However, these favorable effects occurred at a lower PEEP (50% of PEEP), and disappeared when PEEP was equal to PEEP, which again suggests excessive PEEP levels in at least some of our patients. These observations underline the difficulty of correctly titrating PEEP in this context. Having said this, low levels of PEEP (≤ 50% of PEEP) may still be of benefit, by preventing alveolar derecruitment, as shown by the study by Rossi et al. [8].

In conclusion, the present study shows that in COPD patients undergoing controlled mechanical ventilation, with PEEP, \( P_{aO_2} \) can be a valuable approach to reducing dynamic hyperinflation/PEEP, while only slightly impairing arterial oxygenation due to a reduction in the mean value of perfusion distribution. Conversely, PEEPs can prove difficult to titrate and can induce worsening of dynamic hyperinflation, the latter probably offsetting any benefit of PEEPs on arterial oxygenation. Hence in patients with severe and symptomatic dynamic hyperinflation, as can occur during the first few days of mechanical ventilation, \( P_{aO_2} \) could prove to be a valuable approach, provided the various technical issues associated with its use are known by ICU physicians.

References

Conclusion
Conclusion

In summary, it is theoretically fairly well explained how helium breathing may reduce airway resistance and so ameliorates severely compromised respiratory functions. In contrast, there is still only poor evidence that it may be useful for treating patients with acute respiratory disorders, although most clinicians agree that in severe upper airway obstruction helium can be a life-saving measure. According to the theory, acute asthma or acute COPD exacerbations may be indications for helium therapy. We showed that Heliox has favorable effects on respiratory mechanics and inspiratory muscle workload. Hence, it could prevent the occurrence of diaphragmatic fatigue.

It is obvious that increasing oxygen concentration requires the helium fraction to be correspondingly reduced. Since the effects of helium on respiratory mechanics are strongly related to its fractional concentration, its potential benefits decrease when high inspired oxygen concentration is required. For that reason the usefulness of helium is limited to moderate disorders without hypoxia. A prominent feature of our studies is the fact that He/O₂ failed to improve gas exchange and Vₐ/Q relationships. Therefore, a close attention should be paid to monitor arterial blood gases when helium is used. Heliox reduces the work of breathing at the cost of a small decrease in PaO₂. However, one must keep in mind that several beta-agonists also produce a significant drop in the PaO₂ of patients during acute asthmatic attacks. However, the alleviation of dyspnea exceeds the disadvantages of the mild additional hypoxemia. Further studies are needed to explore the eventual benefits of Heliox in acute asthma in terms of dyspnea alleviation and an important clinical outcome as the need for invasive ventilation.
Conclusion

Considering the relatively high cost of helium and the fact that its use in clinical practice is familiar only to a very small number of physicians, this dubious benefit raises the question of the clinical role of inhaled helium in the future.

Nevertheless, at least some recent isolated observations remain promising and these should encourage us to keep helium in mind as a further therapeutic tool, potentially able to resolve even life-threatening conditions. Therefore, its main role consists in allowing the gain of time for conventional therapeutic agents or strategies to work appropriately.
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