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TREATMENT OF ASTHMA PATIENTS UNDER SEVERE CONDITIONS

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by an obstruction of airflow. It affects people of all ages and is characterized by repeated attacks of difficulty in breathing. Airway inflammation may cause recurrent or persistent bronchospasm, wheezing, breathlessness, tightness in the chest and coughing, particularly at night, in the early morning, or after exercise.

Airway inflammation is associated with airway hyper-reactivity and/or bronchial hyper-responsiveness, with a tendency for the airways to narrow after exposure to allergens, environmental irritants, viruses, cold air, or exercise. In some patients with chronic asthma, airflow limitation may be only partially reversible because of airway remodeling (hypertrophy and hyperplasia of smooth muscle, sub epithelial fibrosis) that occurs with chronic untreated disease.

The mainstay of therapy for acute asthma is a drug inhaled via an aerosol and this therapy is highly effective in resolving the symptoms of a large number of patients.

Status asthmaticus is an emergency in which an acute exacerbation of asthma is unresponsive to bronchodilator therapy and conventional treatment (oxygen supplementation, humidification, etc.). Status asthmaticus can vary in form from mild to severe with severe bronchospasm, airway inflammation and mucous plugging that can cause breathing difficulties, CO_2 retention, hypoxemia, and severe respiratory failure which can lead to cardiac arrest.

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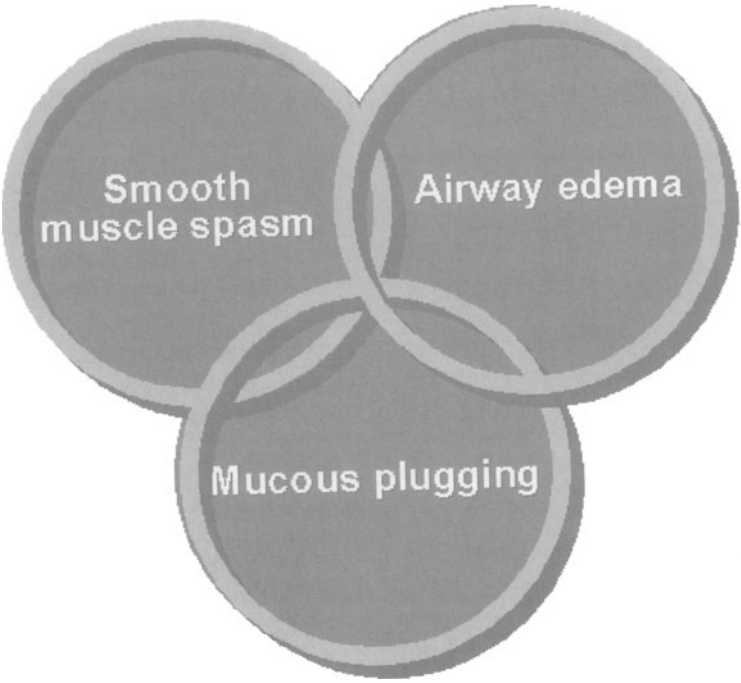

Figure 1. Characteristics of asthma as an inflammatory disease of airway.

Asthma affects up to 10% of the population of the United States of America. Worldwide its incidence is unclear, but it is estimated that there are about 20 million cases, 15% of who are children. A dramatic rise in the worldwide incidence of asthma has been described in the past 20 years. This has been accompanied by a significant rise in hospitalization and mortality. A significant increase in mortality has also been noted, especially amongst children between the ages of 0-4 and 9-16 years in recent years not only in the United States of America but also in Australia, Canada, the United Kingdom, Germany, and Switzerland. This has been attributed, in part, to pollution and industrialization. [1-4].

The complications associated with a severe asthmatic attack may include apnea, central nervous system (CNS) damage from hypoxia and toxicity from medications. The two common causes of death from asthma are hypoxic cardiac arrest and pneumothorax or pneumomediastinum. Mortality is higher in very young children and the elderly.

Patients with other preexisting conditions, such as restrictive lung disease, congestive heart failure, and chest deformities are at particular risk of death from status asthmaticus. Death may result from a single attack, when the patient does not respond to therapy, but occurs more frequently in long-term, uncontrolled asthma patients. In many cases, mortality and morbidity are related to cerebral hypoxia occurring prior to emergency department admission and/or consequent to lung barotrauma [5-9].

Pathophysiology

Asthma is an inflammatory lung disorder characterized by smooth muscle spasm, airway edema and mucous plugging. Different airway cells, including mast cells, epithelial cells, macrophages, and activated T lymphocytes are involved.
T lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines. Other airway cells, such as fibroblasts, endothelial cells, and epithelial cells, contribute to the chronicity of the disease. Additional factors, such as adhesion molecules (selectins and integrins), are critical in directing the inflammatory changes in the airway. Finally, cell-derived mediators influence smooth muscle tone and produce structural changes and remodel the airway.

This inflammation causes recurrent episodes of wheezing, dyspnea, and cough. Episodes are associated with obstruction in predominantly small-to-medium airways that reverses partially or completely, either spontaneously or with treatment.

Bronchospasm, mucus plugging, and edema in the peripheral airways are characteristics of the pathology and result in a non-uniform pattern of airflow obstruction and increased airway resistance. With a decreased ability to expel air, hyperinflation occurs, which can lead to severe ventilation/perfusion mismatch and increased dead space ventilation. This results in alveolar hypoventilation and atelectasis. The increased pleural and intra-alveolar pressures that result from obstruction and hyperinflation, together with the mechanical forces of the distended alveoli, can lead to a decrease in perfusion. The combination of atelectasis and decreased perfusion leads to ventilation perfusion mismatch within lung units and the resultant hypoxemia triggers an increase in minute ventilation. Over distention helps to maintain airway patency, thereby improving expiratory flow. However, it also leads to deterioration in pulmonary mechanics and increases the work of breathing and oxygen consumption.

Hyperinflation compensates for the airflow obstruction, but this compensation is limited when the tidal volume approaches the volume of the pulmonary dead space: the result is alveolar hypoventilation. Uneven changes in airflow resistance, the resulting uneven distribution of air, and alterations in circulation from increased intra-alveolar pressure due to hyperinflation all lead to ventilation-perfusion mismatch. Hypoxic vasoconstriction also contributes to this mismatch.

In the early stages of acute asthma, hyperventilation results in respiratory alkalosis. This is due to the fact that there are relatively fewer obstructed lung units (slow compartment) than there are unobstructed lung units (fast compartment). Hyperventilation allows CO_2 removal via the fast compartment. However, as the disease progresses and more lung units become obstructed, there is an increase in the slow compartments with decreased ability for CO_2 removal, eventually resulting in hypercarbia.

When ventilation-perfusion mismatch results in hypoxia, hypercarbia is prevented by the ready diffusion of carbon dioxide across alveolar capillary membranes. Thus, asthmatic patients who are in the early stages of an acute attack have hypoxemia in the absence of carbon dioxide retention.

Hyperventilation triggered by the hypoxic drive causes a decrease in $PaCO_2$ with consequent alkalosis. With worsening obstruction and increasing ventilation-perfusion mismatch, carbon dioxide retention appears. Respiratory failure leads to respiratory acidosis. Later, the increased work of breathing, increased oxygen consumption, and increased cardiac output result in metabolic acidosis

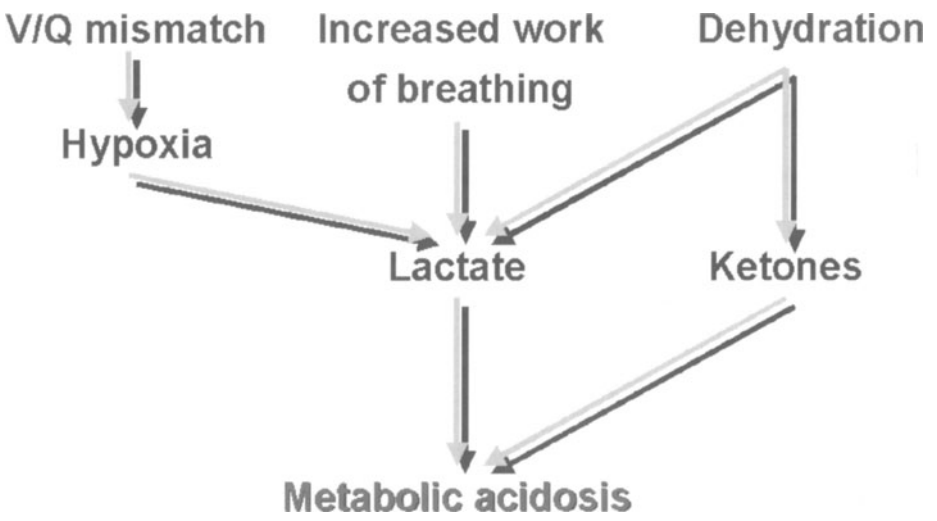

Figure 2. Origin of metabolic acidosis.

Lung hyperinflation and thoracic hyper-expansion cause reduced respiratory muscle efficiency and the flattened diaphragm is forced to contract with shortened muscle fibers.

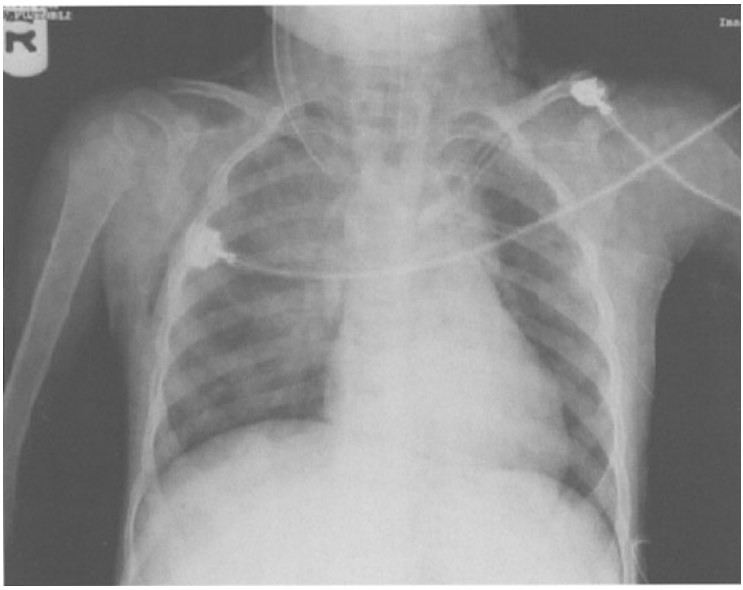

Figure 3. Chest x-ray of severe asthma in adolescent boy. Lungs are over inflated and hyper transparent, diaphragm and ribs are flattened, heart is reduced in volume due to external compression.

Airway rupture as subcutaneous emphysema, pneumodiastinum and pneumothorax can complicate the pathology.

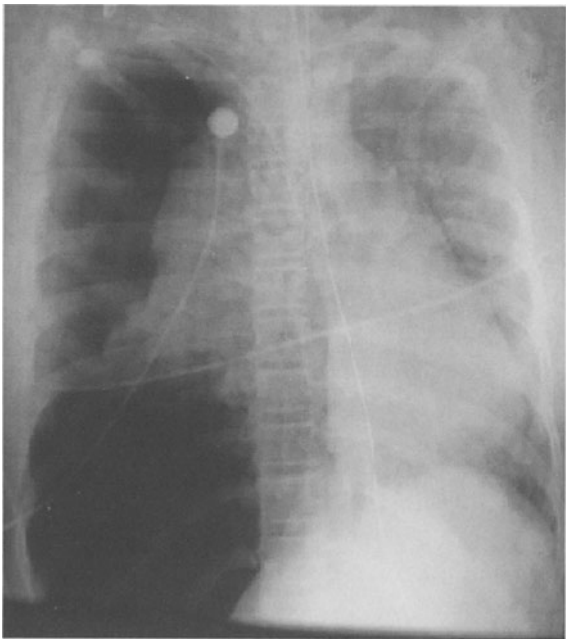

Figure 4. Dramatic right pneumothorax complicating asthma attack.

The greatly increased intra-thoracic pressure connected with lung over-inflation impedes venous return, thus decreasing right and left ventricular pre-load. Children breathing spontaneously with severe asthma have negative intra-pleural pressure (as low as -35 cmH_2O) during the entire respiratory cycle that can lead to left ventricular load. Negative intra-pleural pressure causes increased left ventricular after-load, resulting in risk of pulmonary edema. Hypoxic pulmonary vasoconstriction and lung hyperinflation lead to increased right ventricular afterload with right ventricular load. Tachycardia and hypotension related to reduction of cardiac output ensues and can lead to cardiac arrest.

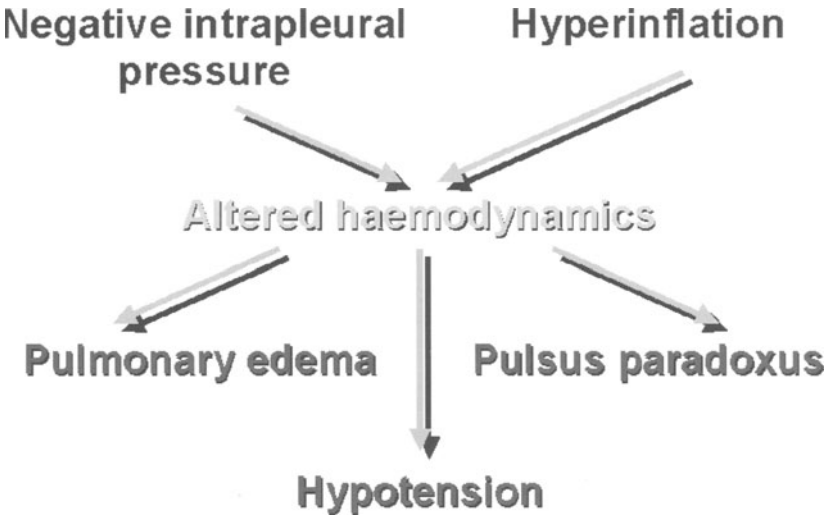

Figure 5. Cardiopulmonary interaction in asthmatic patients.

In the past decade, evidence has emerged for surfactant as a factor in the regulation of airway calibers and a modulator of allergic inflammation. Airway obstruction in asthma is commonly connected with smooth muscle constriction, mucosal edema and mucus presence in the small airway, may be due to a lack of pulmonary surfactant [10-12].

Indication for intubation and mechanical ventilation

Tracheal intubation and mechanical ventilation is frequently the last therapeutic option after the failure of standard therapy, i.e., β2–antagonists, aminophylline, steroids, epinephrine [13, 14]. The immediate indicators for initiating mechanical ventilation are respiratory arrest (apnea) and cardiac arrest [5, 15].

There is a hesitation to intubate the asthmatic patient. This is related to:

- the presence of the tube in the trachea can aggravate bronchospam;
- positive pressure ventilation increases risk of barotrauma and hypotension;
- over 50% of the morbidity and mortality during severe asthmatic attack occurs during or immediately after intubation.

Tracheal intubation must be applied promptly once it is deemed necessary. A delay in intubation and mechanical ventilation can increase morbidity and mortality.

In less severe conditions, arterial blood gas does not appear to be a good indicator of the need for mechanical ventilation because of delay in appearance of marked signs of worsening of ventilation. Apnea due to exhaustion which requires assisted

ventilation often appears before gas exchange impairment. Arterial blood gases are often indicative of the efficacy of treatment [16]. In the initial phase of an asthma attack, $paCO_2$ can be reduced < 40 mmHg, but when status asthmaticus progresses $paCO_2$ rises, reflecting the severity of bronchospasm and difficulty of CO_2 elimination [17, 18].

PaO_2 falls precociously in an asthma attack because of a misdistribution of ventilation to alveolar perfusion. Oxygen supplementation is necessary to maintain normal PaO_2 but a fraction of inspired oxygen (FiO_2) > 0.60 is rarely needed to obtain SpO_2 >90 %. Oxygen supplementation may obscure the patient's need for ventilation for a long time.

According to arterial blood gases , mechanical ventilation is generally initiated when PaO_2 is < 60 mm Hg using oxygen concentration over 60-70% and/or $PaCO_2$ is > 50 -55 mmHg and rising more than 5 mmHg/hour.

The decision to intubate and mechanically ventilate a patient with severe status asthmaticus should preferably be based on the following clinical criteria rather than on gas analysis alone [19, 20]:

Exhaustion and apnea;

Significant hypoxemia poorly or not responsive to supplemental oxygen therapy alone;

Severe respiratory muscle fatigue and increased effort to breath;

Continued rise in PCO_2 despite therapy with marked decrease in airflow;

Markedly decreased air entry into the lungs and limited thoracic expansion;

Presence of pulsus paradoxus (> 20-40 mmHg) consequent to inspiratory decline in systolic blood pressure;

Altered sensorium and diminished level of consciousness, e.g., agitation, confusion, lethargy and coma;

Presence of high-risk factors.

Pulsus paradoxus is the clinical correlate of cardiopulmonary interaction during severe asthma. It is defined as the exaggeration of the normal inspiratory drop in systolic blood pressure: normally < 5 mmHg, but > 10 mmHg in pulsus paradoxus.

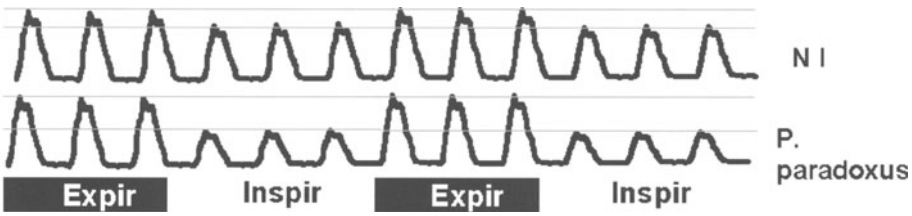

Figure 6. Pulsus paradoxus: Superior part of the graph is normal condition. Inferior part shows situation during asthma attack.

Tracheal intubation

Oral and nasal-tracheal intubation during inhaled anesthesia is a safe method that allows spontaneous breathing to be maintained. Halogenated anesthetics (e.g. isoflurane, enflurane, sevoflurane and halothane) can be used to obtain a suitable level of anesthesia to perform intubation with reduced risks (laryngospasm, vagal stimulation, vomiting). Hypotension and cardiac dysrhythmias can be observed in hypoxemic and hypovolemic patients during the maneuver.

An easy intubation can be performed using a short or middle duration neuromuscular blocking agent (succinylcholine, rocuronium, vecuronium), which allows a rapid return to spontaneous breathing in cases where it is impossible to intubate. When the patient is paralyzed and ventilation is impossible, the risk of severe hypoxia (neurological damage) and the patient dying is increased [21]. Bradicardia is frequent after succinylcholine in children and can be prevented by atropine. Neuromuscolar blocking agents which liberate histamine (e.g. pancuronium) are not indicated in asthmaticus status.

Manipulation of the airway can worsen the bronchospasm and provoke laryngospasm that can be prevented by topical application of local anesthetics at glottis level. Paralysis with curare drugs suppresses the tonic part of hyperinflation (accessory muscle paralysis) and may aggravate the obstructive syndrome leading to unventilatable thorax.

Bag-and-mask ventilation can be difficult or even impossible after muscle paralysis in acute asthma patient because of severe lung hyperinflation. Gastric distension connected with ineffective manual lung ventilation can increase the risk of aspiration of gastric content.

Immediately after intubation overzealous manual ventilation that can lead to emphysema and pneumothorax must be avoided. If manual ventilation is prolonged and dry gases are used endotracheal tube obstruction can appear due to consolidation of abundant secretion. Tube obstruction is more frequent at pediatric age using tube of reduced internal diameter. After intubation and uncontrolled mechanical ventilation (tidal volume) a rapid reduction of $paCO_2$ can result in hypotension and circulatory failure.

Mechanical ventilation strategies

The goals of mechanical ventilation include: [4, 15, 19]
reduction of dynamic lung hyperinflation, using a low tidal volume and high respiratory frequency, with an extended expiratory time;

permissive hypercapnia, as consequence of reduced tidal volume;
avoiding intrinsic positive end-expiratory pressure (auto PEEP) connected with bronchoconstriction and dynamic hyperinflation;
removal of secretion and restoration of airway patency.

At present no ventilation mode has been proved to be superior in status asthmaticus. Adults and children have been ventilated both in volume controlled and in pressure controlled ventilation. Volume controlled ventilation appears to be more effective because this mode guarantees stable tidal volume despite variations in airway resistance. A reduction of inspiratory pressure can be obtained by using low tidal volume and high respiratory rate, maintaining adequate minute volume necessary to obtain normal gas exchanges. Pressure controlled ventilation has been used for a long time to reduce barotrauma connected with peak inspiratory pressure in newborns and infants. This method has been under review in recent years primarily because volume (volutrauma) rather than pressure (barotrauma) has been shown to determine the damage of the lung. This method does not guarantee stable tidal volume as it is influenced by the resistance of the airways and can lead to hyper- or hypo-ventilation.

Ventilator settings
In an emergency it is essential to control hypoxia and lung dynamic hyperinflation.High inflating pressures are usually required to ventilate the lungs because of increased airway resistance. When the emergency phase is resolved, recruitment of lung areas and maintaining the patency of bronchioles and alveoli become indispensable to reducing lung barotrauma and improving lung pathology. When bronchospasm has been reduced and the mucous largely aspirated, the pressure needed to open the airways during the inspiratory time must be reduced. Bronchioles and alveoli recruited have to be maintained continuously open in order to reduce shear forces which hinder opening of alveoli. Mucous and secretion removal are facilitated when bronchial obstruction is resolved [21-24].

For many years, "permissive hypercapnia" [25-28] or "controlled hypoventilation" has been considered a suitable way of providing adequate oxygenation and ventilation while minimizing high airway pressures and barotrauma. It involves the administration of as high an inspired oxygen fraction (FiO_2) as is necessary to maintain normal PaO_2, acceptance of hypercapnia (maximum 90 mmHg, without rapid rise) and treatment of respiratory acidosis (pH > 7.20 minimum level accepted) with intravenous sodium bicarbonate. Ventilator rate is maintained at no more than 12/minute, with a slow inspiratory flow rate and a long expiratory time (1:3 or 1:4 inspiration-expiration [I-E] ratio) to facilitate complete emptying of lung during expiration. With low ventilatory rates and prolonged expiratory time, breathing can be very uncomfortable for the patient and syncronisation with the ventilator difficult to obtain. Deep sedation is necessary and neuromuscular blocking agents are often required.

Permissive hypercapnia can expose the patient to:
intracranial hemorrhage;
worsening of pre-existent intracranial hypertension in the presence of cerebral vasodilation and edema;
myocardial depression;
pulmonary vasoconstriction;
cardiac arrhythmia connected with hypokalemia.

It is important to monitoring of flow-volume loops to ascertain whether adequate time has been provided for expiration to avoid breath stacking, which will occur if the next breath is delivered before expiration is completed. It is also important to monitor exhaled tidal volume and auto-PEEP.

This ventilator strategy is not uniformly successful in critically ill asthma patients. Reasons for this include the difficulty of synchronizing ventilation, of eliminating secretion, of weaning the patient from the ventilator and the frequent appearance of complications such as pneumonia and atelectasis which are the result of the consolidation of secretions and inability to cough

A new ventilatory mode [21, 29] which involves ventilator settings being adapted in order to maintain $PaCO_2$ near to normal limits using a low tidal volume (8-10 ml/kg) and high respiratory rate (> 20-40% of expected for the patient's characteristics age) according to preset minute volume, and an I:E ratio 1:2 is gaining consensus . A PEEP level of
5 cm H_2O is applied at the beginning of ventilation if the cardiovascular system is stable and when hypovolemia is resolved. The PEEP level is progressively increased in accordance with the re-opening of bronchioles and when the bronchospasm is reduced. This technique reduces the risk of hypercapnia to a minimum, resolves the cerebral edema frequently present in these patients, and reduces the need for deep sedation and the use of neuromuscular blocking agents, with beneficial effect on mobilization and aspiration of broncho-alveolar mucous.

Epinephrine (intramuscular or intravenous), salbutamol (intravenous) and inhaled anesthetics are recommended when patients are difficult to ventilate [30].

When the emergency phase is resolved, it is necessary to focus on recruiting a large part of the lung areas to ventilation using a ventilatory model that opens the lung and keeps it open during the entire respiratory phase. This goal can be achieved by using an end inspiratory pause > 10% in order to favor gas redistribution in the alveoli at the end of inspiration and a PEEP level increased progressively over the inflation point of pressure volume curve (until 10 cm H_2O) according to hyperinflation and hemodynamics. This approach appears to be effective in resolving severe cases and reduces the duration of artificial ventilation with consequent barotrauma and volutrauma [31, 32].

Weaning from ventilator can begin when bronchoconstriction has been reduced and dynamic hyperinflation has decreased. The PEEP level must be reduced progressively to 5 cm H_2O, in order to avoid alveolar collapse. A short period of pressure support ventilation and volume support ventilation alternating with mechanical ventilation appears to be the best weaning method because it does not create fatigue, does not increase the effort to breath or consume oxygen. T-tube trial should be avoided in order to reduce the tendency to alveolar collapse and increase the possibility to create stiffing secretions when the patient is ventilated through endotracheal tube in air ambient. Extubation maintaining the catheter in continuous aspiration should be avoided in order to reduce the risk of a collapse of alveoli and bronchioles especially in very young children.

PEEP

Controversies remain around the role of PEEP and its use in status asthmaticus. PEEP has generally been considered to be contraindicated in asthmatics because of hyperinflation of the lung. In acute asthma, however, "hyperinflation" may not result from air-trapping so much as from the voluntary or reflex attempts of the patient to maximize the diameter of the small airways during expiration by maintaining a large functional residual capacity (FRC). Those who do not support its use point out that PEEP should not be applied during mechanical ventilation (0 - 3 cm H_2O maximum) in order to decrease the risk of auto-PEEP and any reduction of venous return and cardiac output. On the other hand, those who support its use stress the advantages to be derived from decreasing the effort to breath if the extrinsic PEEP is not higher than the intrinsic PEEP (< 10 cm H_2O), preventing the airway collapsing during expiration and maintaining bronchioles and alveoli open. They also point out that it facilitates the recruitment of non-ventilated areas and mucous elimination. [33-36]. Assisted and spontaneous ventilatory support are not indicated in the first phase of treatment, especially if the patient is comatose or deeply sedated.

Recently, non-invasive positive pressure ventilation (NIPPV) such as continuous positive airway pressure (CPAP) or bi-modal positive airway pressure (BiPAP) with a facemask have been used to support of status asthmaticus. NIPPV has been shown to "splint" the airways, allowing better exhalation and emptying to take place. These methods need more confirmation from clinical data. At present clinical data is insufficient to propose the use of these methods in routine clinical practice.

Complications from mechanical ventilation

The asthmatic patient is at great risk from barotrauma during mechanical ventilation because of the high pressure required and the uneven distribution of ventilation. Barotrauma is severe if the patient is not completely synchronized with the ventilator, in the presence of a sudden cough or if a very tight cuffed tube is used. Interstitial emphysema is frequent and cannot have clinical evidence. Monolateral or bilateral pneumothorax is the most feared complication. Sudden deterioration of either respiratory or cardiovascular function should suggest this complication. It can

be life-threatening and requires rapid chest drainage. Pneumo-mediastinum can appear either on its own or along with pneumothorax. If it is small it can escape detection, be barely visible on a chest X-ray and not lead to important cardiocirculatory alterations. When present, however, the prognosis is severe due to the reduction in cardiac output. Treatment is difficult and reappearance after apparent resolution is frequent. Pneumoperitoneum is a rare complication and is present when air migrates from the thorax to the abdominal cavity. It is generally treated by the application of a thoracic drainage that can be used to deal with the pneumothorax that usually accompanies it [22, 37].In addition, mechanical ventilation can be responsible for:
Hemodynamic variations. After intubation hypotension is linked to hyperinflation, hypovolemia and sedation [22]. The treatment consists of replacing intravascular volume. In addition mechanical ventilation can decrease venous return, increase tissue hypoxia, and lead to the development of cardiac arrhythmia and edema.

Mucous plugs. Incorrect or inadequate humidification/heating of ventilated gases may result in worsening of bronchospasm and may lead to the formation of dense secretions that cannot be easily drained. Such a situation may increase airway obstruction, create atelectasis, favor the appearance of pneumonia and worsen gas exchange.

Atelectasis. Micro, segmental or lobar atelectasis may be present at the beginning of treatment or can appear during treatment. It is related to non-idoneous ventilatory mode, use of unsuitable PEEP or with bronchial secretions that are difficult to remove, e.g. inefficacy of humidification and insufficient warming of ventilated gases, deep sedation and/or muscular paralysis and non-mobility of patient (prone positioning and postural drainage).

Nosocomial infection. Nosocomial infections such as pneumonia and sinusitis are frequently seen in artificially ventilated patients. These infections develop more frequently in cases of inadequate nursing or when the patient is deeply sedated.

Unventilatable thorax. *Paralysis with curare drugs suppresses the tonic part of hyperinflation (accessory muscle paralysis) and may cause the thorax to become unventilatable due to an aggravation of the obstructive syndrome. Transitory solutions to break this vicious circle (i.e. reducing hyperinflation) are the use of progressive high PEEP levels (> 10 cm H_2O) and alternative techniques such as halogenated gases. The use of FiO_2 1 for several minutes can help during hypoxia but increases atelectasis tendency from reabsorption. High oxygen concentration used for prolonged time can favor surfactant inactivation.*

Alternative ventilation techniques

Various techniques have been attempted when bronchoconstriction worsens and seriously affects ventilation and oxygenation.

Ketamine. A dissociative anesthetic with strong analgesic effect and direct bronchodilating action. Its use can be proposed for intubation (2mg/kg i.v.) as well as in continuous infusion (0.5 -2 mg/kg/hr). It induces bronchorrea and can provoke emergency reaction [38-40].

Halogenated gases. Inhalation anesthetics have been used in severe status asthmaticus for direct relaxant effects on airway smooth muscle. Isoflurane, sevoflurane or halothane added to a ventilator gas flow of 0.5-2 % can improve bronchoconstriction due to bronchodilatory effect of the gas itself, as well as its sedative effects. Use is generally recommended only for patients with severe status asthmaticus who are intubated and unresponsive to conventional therapy [41-43].

Magnesium. Magnesium produces bronchodilation by competing with calcium at its binding sites. Although no controlled studies have been conducted with children, one study of adults indicated no difference in admission rates and duration of ED stay between patients treated with magnesium and those treated with a placebo [44].

Heliox. Some studies have shown that a mixture of helium/oxygen (60 - 40 %) reduces PCO_2 significantly, improves pH, decreases the work of breathing by decreasing inspiratory and expiratory resistance, and improves clinical symptoms. Because of the physical properties of helium, adding it to inhaled oxygen streamlines an otherwise turbulent airflow. The only limitation to helium use is the amount of supplemental oxygen required by the patient to maintain satisfactory oxygen saturation. Its use is limited for patients who have higher oxygen requirements. The efficacy of heliox has not been confirmed in a randomized controlled trial. Benefits were reported in an observation study. At present it has a role in refractory asthma or in specific circumstances [45-48].

Nitric oxide. Nitric oxide has recently been tried successfully in a child with refractory asthma. The future role of this therapy remains to be determined [49].

Surfactant. The possible involvement of pulmonary surfactant in the patho-physiology of respiratory diseases with predominant disturbance in the conducting airways, such as asthma and bronchiolitis, has only recently been addressed and treated [11, 50-54]. Airway obstruction with increased airway resistance in asthma may partially be due to the poor functioning of pulmonary surfactant. Analysis of phospholipid molecular species from BAL and plasma in asthmatic patients suggested that changes in the phosphatidylcholine composition was due to infiltration of plasma lipoproteins, but not to phospholipid catabolism [55]. Thus, the most likely reason for surfactant inactivation was connected with proteins invading

airways as they reached a 10-fold increase in concentration. There is extensive proof that proteins inhibit surfactant function [56,57]. In animal models it has been shown that the prophylactic treatment of sensitized animals with intratracheal instillation of surfactant reduces the deterioration in lung function [58], and reduces airway resistance [12].

ECMO (Extra corporeal membrane oxygenation via veno-arterial or veno-venous by-pass). The method has been proposed [59] in order to obtain lung rest. The high cost of therapy and not controlled positive results limit its use in clinical practice.

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