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REVIEW

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Management of mechanical ventilation in acute severe asthma: practical aspects

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Abstract *Background:* Acute severe asthma induces marked alterations in respiratory mechanics, characterized by a critical limitation of expiratory flow and a heterogeneous and reversible increase in airway resistance, resulting in premature airway closure, lung, and chest wall dynamic hyperinflation and high intrinsic PEEP. *Discussion:* These abnormalities increase the work of breathing and can lead to respiratory muscle fatigue and life-threatening respiratory failure, in which case mechanical ventilation is life-saving. When instituting mechanical ventilation in this setting, a major concern is the risk of worsening lung hyperinflation (thereby provoking barotrauma) and inducing or aggravating hemodynamic instability. Guidelines for mechanical ventilation in acute severe asthma are not supported by strong clinical evidence. Controlled hypoventilation with permissive hypercapnia may reduce morbidity and mortality compared to conventional normocapnic ventilation. Profound pathological alterations in respiratory mechanics occur during acute severe asthma, which clinicians should keep in mind when caring for ventilated asthmatics. *Conclusion:* We focus on the practical management of controlled hypoventilation. Particular attention must be paid to ventilator settings, monitoring of lung hyperinflation, the role of extrinsic PEEP, and administering inhaled bronchodilators. We also underline the importance of deep sedation with respiratory drive-suppressing opioids to maintain patient-ventilator synchrony while avoiding as much as can be muscle paralysis and the ensuing risk of myopathy. Finally, the role of noninvasive positive pressure ventilation for the treatment of respiratory failure during severe asthma is discussed.

Keywords Mechanical ventilation · Acute severe asthma · Practical management

Introduction

According to consensus guidelines, acute severe asthma is defined by the occurrence of a rapid exacerbation characterized by the presence of one or more of the following features: accessory muscle activity, paradoxical pulse exceeding 25 mmHg, heart rate greater than 100 beats/minute, respiratory rate greater than 25–30 breaths/minute, limited ability to speak, peak expiratory flow rate or forced expiratory volume in 1 s less than 50% of predicted, and an arterial oxygen saturation less than 91–92% [1].

In contrast to usual practice in other forms of respiratory failure, mechanical ventilation in acute severe asthma is often delayed and is used mostly as an ultimate mean when all conventional medical treatments have failed. In patients admitted to medical intensive care units for acute severe asthma the rate of intubation varies widely between studies (2–70%, mean approx. 30% [1]). A major concern

in initiating mechanical ventilation in this setting relates to technical difficulties and to the risk of complications [2]. To understand why this is the case it is important to bear in mind the consequences of severe bronchial obstruction on respiratory mechanics. These are reviewed in the first part of this contribution. We then outline the practical aspects of mechanical ventilation in severe asthma, with particular attention paid to ventilatory mode, monitoring of lung hyperinflation, reasons for using or not using extrinsic PEEP, administration of inhaled β-adrenergic agents, and protective effects of controlled hypercapnic hypoventilation. We also cover the management of sedation, analgesia, and muscle paralysis.

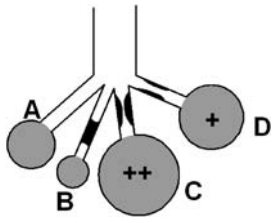

Fig. 1 Effect of varying amounts of airway osbstruction on end-expiratory alveolar volumes and pressures

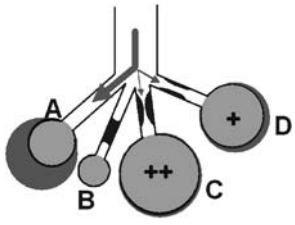

Fig. 2 Expected distribution of the tidal volume during positive-pressure mechanical ventilation in the context of inhomogeneous obstruction

Respiratory mechanics

Acute severe asthma is characterized by pulmonary hyperinflation, with an increase in functional residual capacity of up to twice the normal values in very severe cases [3]. The mechanism of this hyperinflation consists in the critical limitation of the expiratory flow [4], due mainly to two factors. First, the driving forces for expiratory flow are reduced due to an abnormally low pulmonary elastic recoil of unclear mechanism [5, 6] and to an abnormally high outward recoil of the chest wall generated by the persistent activation of the inspiratory muscles during expiration [7]. Second, resistance to airflow is strongly increased because of severely reduced airway caliber and perhaps also expiratory narrowing of the glottic aperture [8]. These particular conditions induce a prominent increase in the mechanical time constant of the respiratory system and a markedly prolonged expiration so that the following inspiration starts before static equilibrium is reached. Consequently the end-expiratory alveolar pressure remains positive, a phenomenon known as auto-PEEP or intrinsic PEEP (PEEPi) [9, 10].

The level of PEEPi and the degree of hyperinflation increase with the tidal volume, time constant of the respiratory system, and shortening of expiratory time. Because of the uneven distribution of bronchial obstruction both anatomical (due to secretions, edema, bronchospasm) and dynamic (due to the external compression exerted on the distal airways by intrathoracic positive pressure during expiration), the lung is extremely inhomogeneous during acute severe asthma [11]. Schematically, the asthmatic lung can be described as consisting of four parallel compartments (Fig. 1): compartment A refers to the portion of the lung without bronchial obstruction nor hyperinflation; in compartment B the airways are entirely obstructed during the whole respiratory cycle (mucous plugging); in compartment C obstruction appears only during expiration, inducing alveolar hyperinflation and high PEEPi; in compartment D partial obstruction of the airways is present throughout the respiratory cycle causing a lesser extent of alveolar hyperinflation and PEEPi than in compartment C. In such a system characterized by variable time constants most of the tidal volume delivered by positive pressure ventilation goes to compartment A, which represents lung parenchyma with almost normal mechanical characteristics (Fig. 2). Since such "mechanically normal" areas represent only a small fraction of the total asthmatic lung, these conditions resemble those created by overdistending a tiny normal lung with a large tidal volume (the "baby lung" concept [12]). Several detrimental consequences may ensue: (a) abnormal distribution of ventilation-perfusion ratio due to diversion of blood perfusion to normally ventilated lung zones, (b) increased risk of barotrauma, and (c) impedance to venous return with hemodynamic compromise, shock, and cardiocirculatory arrest [13].

Therefore, when ventilating patients with acute severe asthma, the crucial objective is to prevent any further increase in lung hyperinflation. In this respect the systematic observations made by Tuxen and Lane [14] more than 15 years ago are still valid. These authors studied eight patients suffering from acute airway obstruction, five from acute severe asthma and three from acute exacerbation of chronic obstructive pulmonary disease. All patients were intubated, ventilated using volume-controlled mode, and paralyzed. Dynamic hyperinflation was evaluated during a prolonged apnea of 60 s by measuring the exhaled volume starting from the end of inspiration. From these observations several statements can be made: (a) For any given value of minute ventilation (V_E), end-inspiratory lung distention is minimized by a combination of low tidal volume (V_T) and high respiratory rate (Fig. 3, compare adjacent columns within a group of three). (b) For any given value of V_T hyperinflation is minimized by increasing the expiratory time (T_E), which is achieved by reducing respiratory rate and therefore V_E (Fig. 3, compare groups of 3 columns with one another).

When keeping V_T, respiratory rate, and V_E constant, the T_E remains adaptable and can be increased at the

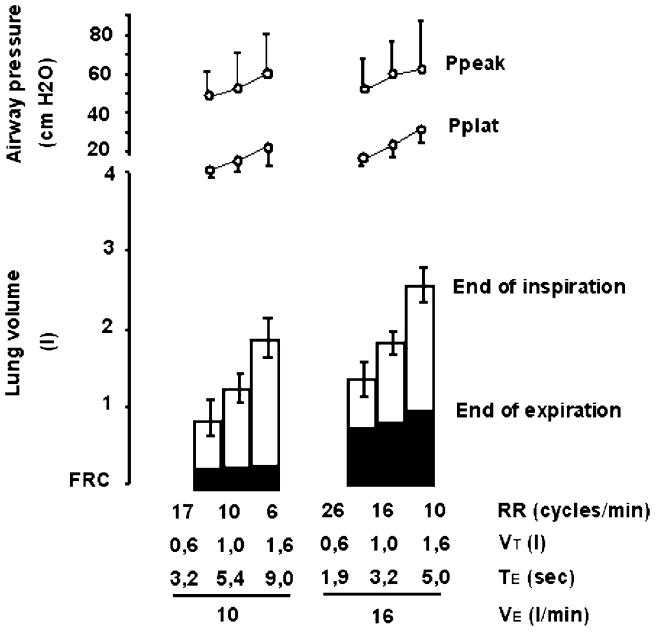

Fig. 3 Effect of respiratory rate and tidal volume variations on airway pressures and lung volumes during mechanical ventilation of acute severe asthma. *FRC* Functional residual capacity; *Ppeak* peak inspiratory pressure; *Pplat* end-inspiratory plateau pressure; *RR* respiratory rate; V_T tidal volume; T_E expiratory time; V_E minute ventilation. All conditions are for a square inspiratory flow of 100 l/min. (Data with permission from [3])

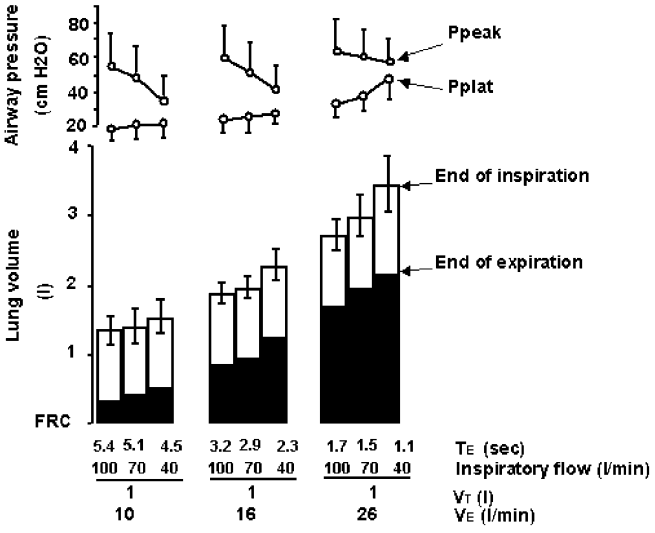

Fig. 4 Effect of inspiratory flow variations on airway pressures and lung volumes during mechanical ventilation in acute severe asthma. *FRC* Functional residual capacity; *Ppeak* peak inspiratory pressure; *Pplat* end-inspiratory plateau pressure; *RR* respiratory rate; V_T tidal volume; T_E expiratory time; V_E minute ventilation. All conditions are for a square inspiratory flow of 100 l/min. (Data with permission from [3])

expense of the inspiratory time (T_I). In conditions of high levels of V_E (16 and 26 l/min), increasing inspiratory flow and thus reducing T_I allows a decrease in lung hyperinflation (Fig. 4, compare the adjacent columns within a group of three). However, with a lower V_E (10 l/min) and a T_E somewhat above 4 s, the impact on hyperinflation (as reflected by end-inspiratory plateau pressure, Pplat) of further lengthening T_E at the expense of T_I becomes negligible. The relative futility of increasing T_E beyond 4 s in ventilated asthmatics receiving 10 l/min V_E or less has been recently emphasized by Leatherman and colleagues [15], who pointed out the very low end-expiratory airflows prevalent in such conditions (Fig. 5).

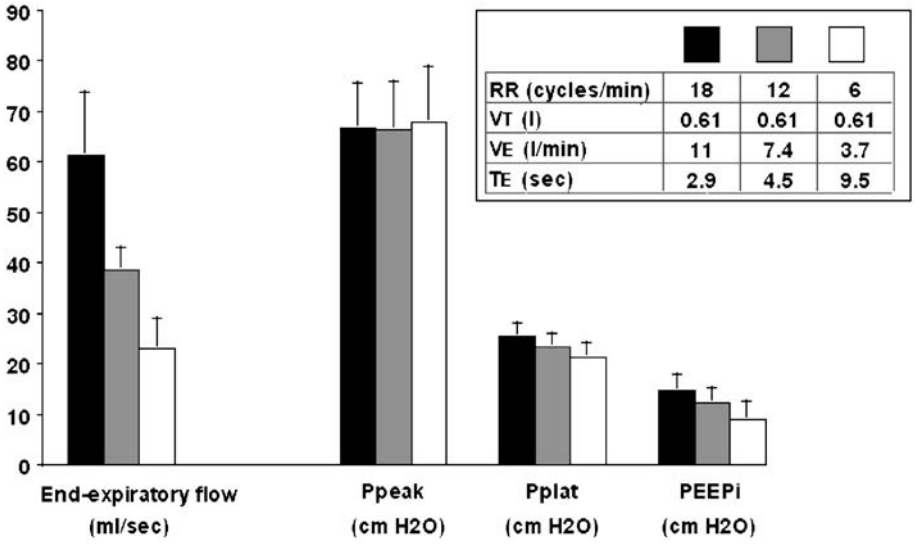

Fig. 5 End-expiratory flow, peak inspiratory pressure (*Ppeak*), end-inspiratory plateau pressure (*Pplat*) and auto-PEEP (*PEEPi*) in asthmatic patients ventilated with close to or less than 10 l/min minute ventilation (V_E). V_E was progressively reduced and expiratory time (T_E) progressively increased by lowering cycling frequency (*RR*) at constant V_T and inspiratory time, using a square inspiratory flow waveform. Note the trivial effect on dynamic hyperinflation (as reflected by Pplat) of halving V_E (from 7.4 to 3.7 l/min) and thus more than doubling TE (from 4.5 to 9.5 s) which is related to the very low end-expiratory flow rates in these conditions (< 40 ml/s). (Adapted from [5])

Ventilatory techniques

Indications for intubation

The decision to intubate is based essentially on clinical judgement. Progressive exhaustion and patient fatigue despite maximal therapy together with altered level of consciousness are indications for intubation. In the absence of respiratory arrest maintaining adequate oxygenation (and oxygen transport) with supplemental oxygen is seldom a problem even in very severe asthma and is a relatively uncommon reason for intubation. If the patient is cooperative, hypercapnia and fatigue do not necessarily mandate intubation because noninvasive ventilation may be an option (see below).

Recommendations for ventilator management

The primary focus must be on avoiding excessive airway pressure and minimizing lung hyperinflation. To achieve this goal it is often necessary to hypoventilate the patient and thus to tolerate hypercapnia. This strategy, initially proposed by Darioli and Perret [16] in 1984, is termed "controlled hypoventilation" or "permissive hypercapnia" [17]. It differs from the conventional ventilation as practiced two decades ago which, by trying at all costs to restore a normal $PaCO_2$, imposed on the lung a mechanical stress potentially more dangerous to the patient than is respiratory acidosis.

Table 1 summarizes the proposed initial settings of the ventilator. From the data presented above (Figs. 3, 4, 5), the way to minimize hyperinflation essentially consists in keeping V_E down (i.e., $\leq$ 10 l/min in the average adult patient) and T_E up ($\geq$ 4 s). Once a ventilatory pattern consistent with these goals has been achieved, there is probably little to be gained by further fiddling with machine settings. This statement is exemplified by the trivial effect on PEEPi and Pplat of halving V_E (from 7.4 to 3.7 l/min) and more than doubling T_E (from 4.5 to 9.5 s) shown in Fig. 5 [5]. At any given value of V_T and respiratory rate, increasing inspiratory flow allows T_I to be reduced and thus T_E to be increased. In this respect values of 60–80 l/min (Table 1) are optimal, while only marginal gains are to be expected from higher inspiratory flow rates (e.g., T_E is generally augmented by $\leq$ 1 s if inspiratory flow rate is increased from 60–80 to 100–120 l/min, which is largely insufficient to significantly impact on hyperinflation).

Some specific issues related to the ventilatory management of severely asthmatic patients are discussed below.

Table 1 Initial ventilator settings in intubated asthmatic patients

Ventilatory parameters	Settings
Mode	Volume-controlled ventilation
Minute ventilation	<10 l/min
Tidal volume	6–10 ml/kg ideal body weight
Respiratory rate	10–14 cycles/min
Plateau pressure	<30 cmH_2O
Inspiratory flow rate	60–80 l/min
Inspiratory flow waveform	Decelerating waveform
Expiratory time	4–5 s
PEEP	0 cmH_2O
FIO_2	To an SaO_2 of >90%

Ventilatory mode

Controlled ventilation is normally required following intubation because of the deep sedation (with or without muscle paralysis, see below) that is necessary to avoid patient-ventilator asynchrony and to manage controlled hypoventilation. No consensus exists in terms of what mode of ventilation should be used later. Volume-controlled ventilation is currently usually preferred, pressure-control being discouraged for the following reasons. First, in conditions of fluctuating high airway resistance and PEEPi, pressure-control entails the risk of variable tidal volume with sometimes unacceptably low alveolar ventilation. With this mode, furthermore, severe reventilation alkalosis may develop if airway obstruction subsides rapidly. Volume-control obviates these disadvantages but mandates careful monitoring of inflation pressures (see below).

The optimal inspiratory flow waveform to be used in asthmatics on volume-controlled ventilation is not entirely clear. At identical levels of V_T, T_I and Pplat a square wave results in a higher peak inspiratory pressure (Ppeak) than does a decelerating wave (i.e., flow-resistive pressure, or Ppeak-Pplat, is greater with the former flow pattern). This consideration has limited clinical relevance because due to its important resistive component Ppeak does not reflect alveolar distension pressure in most of the lung [18]. Nevertheless, a lower Ppeak may mean less overdistention of alveoli distal to the least obstructed airways, as such the most exposed to high pressure in the central airways (unit A in Fig. 2). A more practical and important reason to minimize Ppeak and thus to prefer the decelerating over the square waveform is that delivery of the full V_T as set on the ventilator is less easily interrupted by opening of the pop-off safety valve, making up for a steadier V_E.

Monitoring of hyperinflation

Tuxen and colleagues [14] have proposed to monitor dynamic hyperinflation by measuring the volume exhaled from end-inspiration to static functional residual capacity in the course of a 60 s apnea (V_{EI}). In 22 patients mechanically ventilated for acute severe asthma V_{EI} values above 20 ml/kg were associated with an increased risk of hypotension and barotrauma [19]. Based on these data

the authors tested in eight patients a ventilatory strategy able to maintain V_{EI} at 20 ml/kg or less and thus to reduce the complications related to mechanical ventilation while avoiding excessive hypoventilation [20]. However, the need for complete muscle relaxation, with its corollary of potential complications (see below), does not justify the use of V_{EI} as a practical clinical tool. In addition, the theoretical advantage of V_{EI} over other clinical variables as a predictor of the risk of barotrauma is supported only by few observations [18]. Of note, the measurement of PEEPi by the end-expiratory occlusion technique sometimes yields unexpectedly low values, presumably reflecting airway closure [21]. In practical terms Pplat remains the recommended variable for the monitoring of lung hyperinflation during mechanical ventilation in general [22] and in asthmatic patients in particular [15]. It must be underscored that an end-inspiratory pause of several seconds is required for an accurate measurement of Pplat, due to the prolonged equilibration time of the extremely heterogeneous asthmatic lung. Also, the recorded value is only valid in absence of leaks in the system (endotracheal tube cuff, valve activated for end-inspiratory occlusion). The clinical threshold value of Pplat has been fixed at 30 cmH_2O. This is based, first, on the general guidelines concerning mechanical ventilation [22] and, second, on data reported by Leatherman [18]; in this series of 90 patients ventilated for acute severe asthma the mean Pplat was 26 cmH_2O with a rate of barotraumas of 4%. As noted above, Ppeak, in contrast to Pplat, is not useful for assessing lung hyperinflation in asthmatic patients because depends strongly on airway resistance and inspiratory flow setting (Fig. 4). In conclusion, the measurement of Pplat (care being taken to use an end-inspiratory pause of sufficient duration) probably constitutes the best assessment of both hyperinflation and the risk of barotrauma in patients on mechanical ventilation for severe asthma.

The role of extrinsic PEEP

Tuxen [23] measured the effect of progressive PEEPe on lung volumes and pressures in six patients with severe airway obstruction. The gradual increase in PEEPe from 5 to 15 cmH_2O induced a proportional and significant increase in end-inspiratory volume and of functional residual capacity, paralleled by an elevation in Pplat. In addition, an elevation in both esophageal and central venous pressures with a concomitant reduction in cardiac output and blood pressure was observed. These data are consistent with observations by McFadden and colleagues [24] indicating that at the height of an asthmatic attack the predominant site of increased resistance to airflow is located in the central, noncollapsible airways, and that the transmural pressure of peripheral, collapsible bronchi and bronchioles therefore remains positive throughout expiration. In these conditions passive exhalation is not flow limited (i.e., there is no "waterfall effect"), and the applied PEEPe extends all the way up to the alveoli. Thus during controlled ventilation in asthma there is no benefit from PEEPe regarding work of breathing since patients are passive. Furthermore, because these patients may not have expiratory flow limitation (unlike those with chronic obstructive pulmonary disease), the institution of PEEPe may only increase end-expiratory lung volume [9, 25].

In contrast, low levels of PEEPe may be useful at the resolution phase when inspiratory muscle activity resumes and the patient triggers the ventilator. At this stage the resistance of central airways normalizes first while protracted obstruction may persist in the periphery of the lung [24], creating conditions for expiratory flow limitation, as occurs during exacerbation of chronic obstructive pulmonary disease [26]. Therefore when patients are triggering and especially during weaning PEEPe may decrease muscle effort required to trigger the ventilator. Keeping in mind that the existence of the waterfall effect is not guaranteed, and also that flow-limited and flow-unlimited pathways may coexist in these conditions, a prudent trial of low level PEEPe (≤ 8 cmH_2O) can be advocated, with titration for patient comfort under close monitoring of airway and blood pressures [25]. Frequent reassessment is essential because the adequate level of PEEPe is subject to change as lung mechanics and ventilatory requirements evolve.

In conclusion, PEEPe normally has no indication in acute severe asthma during controlled ventilation. In contrast, as soon as a mode of ventilation is selected that allows the patient to spontaneously trigger the ventilator, PEEPe can be applied and must be titrated gradually to a level lower than PEEPi, based on patient comfort.

Administration of beta-adrenergic agents

As a first-line treatment of bronchoconstriction β-adrenergic agents are preferably given as repeated inhaled doses rather than as continuous intravenous infusion due to the faster onset of action and the lesser incidence of adverse side effects with the former mode of administration [27, 28]. Aerosolized salbutamol can be delivered via metered-dose inhalers (MDI) or nebulizers. MDI, if possible with the adjunction of a spacer device, are preferred to nebulizers because of easier manipulation, more readily reproducible dose, quicker achievement of maximal bronchodilatation and a lesser risk of bacterial contamination [29, 30, 31, 32].

Humidification of inspired air

Humidification should be achieved with a heated cascade humidifier, not with heat and moisture exchangers. The latter devices are undesirable for two reasons: First, they add

to expiratory airway resistance, which would hardly be of any help to reduce hyperinflation. Second, being inserted between the endotracheal tube and the Y-piece of ventilator tubing, they increase dead space and therefore contribute unnecessarily to hypercapnia (see below).

Weaning

When exactly to start the weaning process is a matter of clinical judgement. In our practice, once dynamic hyperinflation has abated sufficiently (as assessed by a substantial resolution of wheezing on chest auscultation and a PEEPi below 5 cmH_2O), a trial of pressure-support ventilation is initiated, followed if well tolerated by a standard weaning procedure [20, 33, 34, 35]. In contrast with chronic obstructive pulmonary disease [36], weaning is normally rapidly achieved in patients with acute severe asthma [37]. Weaning difficulty in absence of persistent severe airway obstruction must raise the suspicion of myopathy induced by previous administration of neuromuscular blocking agents and corticosteroids (see below).

Complications and mortality

In the first sizable series of severely asthmatic patients managed with controlled hypoventilation for acute severe asthma, published by Darioli and Perret [16] in 1984, complications and mortality rates were considerably lower than reported in previous studies which used conventional mechanical ventilation. These favorable results of controlled hypoventilation have been confirmed repeatedly [19, 37, 38, 39, 40, 41, 42, 43].

The most frequently reported complication of mechanical ventilation in patients with acute severe asthma is hemodynamic instability manifested as hypotension, usually occurring at the initiation of ventilation and related to the decrease in systemic venous return caused by worsening of hyperinflation. This mechanism is easily verified by temporarily disconnecting the patient from the ventilator (60 s, under close monitoring of SpO_2) and documenting an immediate increase in blood pressure. In such conditions ventilation should be resumed with lower tidal volume and respiratory rate and adequate volume expansion should rapidly follow. It is important to note that when the decrease in blood pressure is unresponsive to ventilator disconnection, tension pneumothorax must be suspected.

Barotrauma is the second most frequently reported complication. Controlled hypoventilation does not confer complete protection in this context [19]. Although usually not reported as a direct cause of mortality when rapidly diagnosed and adequately treated, barotrauma can still be life-threatening [43]. The mortality of patients mechanically ventilated for acute severe asthma has been less than 10% in all studies published since 1990 except in two [37, 43]. A frequently reported cause of death is postanoxic brain injury secondary to prehospital cardiac arrest.

Effects of CO_2 retention

Except in patients with raised intracranial pressure or severe myocardial depression the respiratory acidosis induced by permissive hypercapnia is generally well tolerated and does not need to be treated. This topic has been exhaustively reviewed and is not discussed in detail here [17]. In all ventilated asthmatics, in order to reduce hypercapnia, we recommend maximally reducing CO_2 production by the use of sedation, analgesia, and antipyretics. If these measures are deemed insufficient, muscle relaxants may be considered. A clinical challenge is presented by acute severe asthma culminating in cardiorespiratory arrest with potential postanoxic injury, which faces the clinician with the therapeutic dilemma of brain protection vs. ventilator-induced lung injury. Blood alkalinization, although not supported by strong clinical data, may be considered in this context. Briefly, one may use a slow infusion of sodium bicarbonate. However, too rapid alkali administration in the context of suppressed ventilatory drive may transiently raise the arterial PCO_2, thus worsening intracellular and cerebrospinal acidosis. In addition, with severe respiratory acidosis very large amounts of sodium bicarbonate may be required to substantially raise blood pH, potentially leading to volume overload. Other buffers, such as *tris*-hydroxymethyl aminomethane (tromethamine, Carbicarb), do not have these disadvantages, but clinical experience with these agents is quite limited [44].

Sedation and muscle paralysis

Controlled hypoventilation requires deep sedation. Benzodiazepines can be safely used [19, 40]. Alternatively, propofol may be preferred because of its bronchodilating action [41, 45] but must be instituted with great caution due to the risk of hypotension, particularly in hypovolemic patients [46]. Ketamine may also be considered. In addition to anesthetic, sedative and analgesic effects, it exerts a bronchodilating action via several pathways (adrenergic stimulation, cholinergic and histaminic blockade) [47]. In refractory acute severe asthma its use in anesthetic [48] or infra-anesthetic [49, 50] doses has been associated with reduced bronchospasm and favorable outcome. However, this agent can stimulate tracheobronchial secretion and increase intracranial pressure [47]. In view of the latter effect ketamine should be withheld in presence of established or suspected anoxic encephalopathy.

When trying to enforce controlled hypoventilation, the addition of opioids to either benzodiazepines or propofol

may help suppress the ventilatory drive, at times enabling paralysis to be avoided. The natural opioid morphine can cause allergic reactions and bronchoconstriction [51] and thus should be avoided in acute severe asthma. Synthetic opioids should be used instead, either fentanyl or remifentanyl. The latter drug potently suppresses the ventilatory drive [52] and has a rapid onset of action.

Despite the use of deep sedation patient-ventilator asynchrony can be a problem that requires muscle paralysis, particularly in the presence of acute hypercapnia. Substantial data support a high frequency of complications induced by neuromuscular-blocking agents (NMBA) in mechanically ventilated asthmatics. In particular, diffuse paresis of voluntary muscles has been noted on cessation of NMBA administration, lasting from a few hours to months, sometimes involving the respiratory muscles and thus delaying ventilator weaning [53, 54, 55, 56]. This was recently confirmed by a French retrospective study which showed a higher frequency of postextubation muscle weakness among mechanically ventilated asthmatics treated with NMBA for more than 12 h in comparison to similar patients who received sedation alone [57]. Because the great majority of cases occur following combined treatment with NMBA and corticosteroids, a deleterious interaction of these two classes of drugs has been proposed [58]. Further commonly accepted risk factors are the duration of muscle relaxation [59, 60] and the cumulative dose of NMBA [61]. Electromyography (EMG) typically shows acute myopathy confirmed by elevated levels of creatine-phosphokinase and thick filament necrosis noted on muscle biopsy [59, 60, 61]. In a study by Leatherman and colleagues [59] all patients (18 of 20, paralyzed for >24 h) who developed clinically significant muscle weakness had acute myopathy when EMG was performed. Considering the high probability that muscle weakness developing following mechanical ventilation for acute severe asthma is due to acute myopathy (rather than polyneuropathy, which has never been well documented in status asthmaticus), diagnostic confirmation with an EMG is not urgent and may be restricted to protracted cases. According to current recommendations by the American Society of Critical Care Medicine, NMBA should be given as intermittent intravenous boluses rather than as a continuous infusion [54] to reduce the dose and duration of administration [62]. To further serve this goal the decision to repeat an NMBA bolus should only be made when patient-ventilator asynchrony (a) reappears and (b) cannot be suppressed by increasing the opioid dose. With this strategy of NMBA administration we advocate that neuromuscular monitoring with "train of four" nerve stimulation becomes irrelevant and dispensable, independently of the fact that its usefulness has been questioned in the ICU setting [63, 64].

Therapeutic options in refractory acute severe asthma

The main measures to relieve bronchial obstruction remain the administration of inhaled β_2-agonists and intravenous corticosteroids. However, in refractory cases, some additional therapies might be tried, although not supported by strong evidence. In these refractory cases severe airway obstruction combined with controlled hypoventilation may limit the effective delivery of inhaled bronchodilators. The intravenous administration of these agents should then be considered.

The administration of magnesium sulfate to nonintubated asthmatic patients in an emergency department either by aerosol (250 mmol/l) [65] or intravenously (2 g in 30 min) [66] has recently been shown to have powerful bronchodilating effects when used as an adjunct to aerosolized β_2-agonists. In five intubated asthmatics Sydow and colleagues [67] found that high-dose (10–20 g in 60 min) intravenous magnesium sulfate resulted in a significant decrease in peak airway pressure and inspiratory flow. Of note, these high doses were associated with a threefold increase in serum magnesium levels and with significant hypotension, requiring vasopressor treatment in two patients. Based on these studies and given the relatively low cost of this therapy we believe that intravenous magnesium sulfate therapy should be used in refractory acute severe asthma. In our experience the following dose and schedule of administration is usually safe: repeated doses of 2 g every 30 min, maximum cumulative dose 10 g, under strict monitoring of serum magnesium levels.

Breathing of helium-oxygen mixtures (HeO_2) facilitates ventilation by reducing resistance to turbulent gas flow [68]. In nonintubated asthmatic patients HeO_2 breathing increases peak expiratory flow rate and improves dyspnea scores [69, 70]. Three studies, one retrospective and two prospective, were carried out in a total of 23 ventilated asthmatics and reported beneficial effects of HeO_2 breathing (60–70% He, 30–40% O_2) on oxygenation, airway resistance, and acute respiratory acidosis [71, 72, 73]. According to a meta-analysis, the beneficial effects of this therapy seem most pronounced in the severest cases and tend to wane after 1 h of administration [74]. It is important to keep in mind that the FIO_2 and particularly the tidal volume actually delivered to the patient may substantially differ from their set values. Correction factors were hence developed that can be applied to most ICU ventilators when using HeO_2 [75]. Careful reading of the report by Tassaux et al. [75] is mandatory for anyone considering the use of HeO_2 in ventilated patients.

Finally, there are isolated reports on possible beneficial bronchodilating effects of inhaled halogenated anes-

thetics [76, 77]. However, their use in ventilated asthmatics is logistically extremely cumbersome.

Noninvasive positive pressure ventilation

For the treatment of acute respiratory failure one may consider noninvasive positive pressure ventilation (NIPPV) as an option in asthmatic patients at risk for endotracheal intubation due to progressive exhaustion. Two prospective studies including a total of 47 such patients who on admission were either normocapnic [78] or hypercapnic [79] showed that a short trial of NIPPV improves respiratory distress. Although NIPPV can be effective in severe asthma, it should not unnecessarily delay endotracheal intubation. Therefore from a practical standpoint identification of which patients would most benefit of NIPPV is crucial. Absolute contraindications for the use of NIPPV in asthma are the same as in other conditions [80], including emergency intubation for cardiorespiratory resuscitation, hemodynamic and electrocardiographic instability, life-threatening hypoxemia, and an altered state of consciousness. The presence of severe respiratory acidosis on hospital admission, while not being per se a contraindication to NIPPV, should alert the clinician to the high risk of endotracheal intubation. In fact, among severe asthmatics admitted to the ICU for acute respiratory failure it has been shown that patients treated with NIPPV had less severe respiratory acidosis (mean $PaCO_2$ 53 ± 13 mmHg; mean pH 7.28 ± 0.008) than those who eventually underwent endotracheal intubation (mean $PaCO_2$ 89 ± 29 mmHg; mean pH 7.05 ± 0.21) [81].

NIPPV can be started with low levels of inspiratory pressure support (5–7 cmH_2O) and PEEP (3–5 cmH20, see previous discussion). Pressure support should be progressively increased (by 2 cmH_2O every 15 min), the goal being to reduce respiratory rate below 25 breaths/minute, while keeping peak inspiratory pressure below 25 cmH_2O. Aerosolized bronchodilators are easily administered through the ventilator circuit [82].

Conclusion

As we have seen, guidelines for mechanical ventilation in acute severe asthma are not supported by strong data in the sense of evidence-based medicine. Indeed, it is striking that the works which have most influenced present practice in this area were all observational in nature and were carried out on a limited number of patients [14, 15, 16, 19]. It seems unlikely that a higher level of evidence will emerge in the near future, due to both the relative rarity of intubation and the general agreement regarding specific techniques of ventilatory support in the acutely ill asthmatic. Such consensus is based on firm pathophysiological understanding which nothing in the available data comes to contradict.

In summary, mechanical ventilation is indicated in asthmatic patients unresponsive to aggressive medical treatment and in those admitted at an advanced stage of the disease (i.e., altered level of consciousness, total fatigue, severe respiratory distress). Such patients always have extreme lung hyperinflation due to airway obstruction and to the loss of lung elastic recoil. In these conditions striving for normocapnia may be dangerous, first, worsening lung hyperinflation with the risk of causing barotrauma and, second, by inducing cardiovascular collapse. The aim of controlled hypoventilation with permissive hypercapnia is to reduce these potentially life-threatening side effects, by using a pattern of low minute ventilation (≤ 10 l/min), tidal volume (6–10 ml/kg ideal body weight), and respiratory rate (10–14 cycles/min), taking care that expiratory time be sufficient (≥ 4 s). Controlled hypoventilation requires deep sedation, and, at least initially, muscle paralysis. The prolonged use of neuromuscular blockers should be avoided to limit the risk of ensuing myopathy. In the absence of concomitant postanoxic injury, the short-term prognosis of ventilated asthmatics is good.

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