Anaesthetic management in asthma

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ABSTRACT

Anaesthetic management in asthmatic patients has been focused on avoiding bronchoconstriction and inducing bronchodilation. However, the definition of asthma has changed over the past decade. Asthma has been defined as a clinical syndrome characterized by an inflammatory process that extends beyond the central airways to the distal airways and lung parenchyma. With this concept in mind, and knowing that asthma is a common disorder with increasing prevalence rates and severity worldwide, a rational choice of anaesthetic agents and procedures is mandatory. Thus, we pursued an update on the pharmacologic and technical anaesthetic approach for the asthmatic patient. When feasible, regional anaesthesia should be preferred because it reduces airway irritation and postoperative complications. If general anaesthesia is unavoidable, a laryngeal mask airway is safer than endotracheal intubation. Lidocaine inhalation, alone or combined with albuterol, minimizes histamine-induced bronchoconstriction. Propofol and ketamine inhibit bronchoconstriction, decreasing the risk of bronchospasm during anaesthesia induction. Propofol yields central airway dilation and is more reliable than etomidate or thiopental. Halothane, enflurane, and isoflurane are potent bronchodilators and can be helpful even in status asthmaticus. Sevoflurane has shown controversial results in asthmatic patients. Vecuronium, rocuronium, cisatracurium, and pancuronium do not induce bronchospasm, while atracurium and mivacurium can dose-dependently release histamine and should be cautiously administered in those patients. Further knowledge about the sites of action of anaesthetic agents in the lung, allied with our understanding of asthma pathophysiology, will establish the best anaesthetic approach for people with asthma.

Key words: Asthma - Anaesthesia - Anaesthetics - Bronchial spasm - Bronchial hypereactivity.

Asthma is a major public health issue with high and increasing prevalence rates [1] and a concomitant increase in morbidity and mortality.[2] Studies have shown that the lifetime prevalence of asthma among adults is 11%,[3] and it is even higher among children.[4] These data contribute to make challenging adverse events due to asthma a widespread situation in anaesthesiological practice.

Therefore, in order to avoid increasing the risk of perioperative complications, a good understanding of asthma pathophysiology, an adequate preoperative evaluation, and optimisation of the patient's condition, allied with the best pharmacological and technical approach, are imperative.

The pathophysiological hallmark of asthma is a reduction in airway diameter due to the contraction of smooth muscle, vascular congestion, oedema of the bronchial wall, and tenacious secretions.[5] The chronic inflammatory process leads to tissue injury and subsequent reorganization. The term "airway remodelling" is widely used to refer to the development of those structural changes,[6, 7] such as: epithelial shedding, subepithelial fibrosis, increased numbers and volume of mucous cells in the epithelium, airway smooth muscle hyperplasia and hypertrophy, and increased vascularization of the airway wall.[8] These changes in the extracellular matrix, smooth muscle, and mucous glands

have the capacity to influence airway function and reactivity in asthmatic patients manifested by a decline in forced expiratory volume in 1 s (FEV_1) and bronchial hyper-responsiveness.[9]

Bronchospasm and mucous plugging obstruct both inspiratory and expiratory airflow. Resistance to expiratory airflow results in positive alveolar pressures at the end of expiration, which causes air-trapping and hyperinflation of the lungs and thorax, increased work of breathing, and alterations in respiratory muscle function. Airflow obstruction is not uniform, and the mismatching of ventilation to perfusion occurs, leading to changes in arterial blood gases.[10, 11]

The definition of asthma has changed over the past decade. Asthma has been defined as a clinical syndrome characterized by an inflammatory process that extends beyond the central airways to the distal airways and the lung parenchyma. Small airways have recently been recognized as a site of airflow obstruction and hyper-responsiveness.[12-14]

In view of these new pathophysiological findings, we attempted this review to outline available data and the criteria for the anaesthetic management in asthmatic patients.

Methods

A computerized search of the English-language literature of PUBMED between 1995 and 2005 was conducted using the terms airway obstruction, asthma, bronchial hyper-reactivity, anaesthesia, and anaesthetics. Various combinations of the terms were used to maximize the results. Bibliographies of original research, commentaries, textbooks, and symposia were reviewed for additional relevant references. These publications were abstracted and compiled into tabular form under types of study design. Two-hundred twenty-two articles were selected for critical review. Of the articles excluded, most were reports that described anaphylactic reactions, bronchial hyper-responsiveness, and bronchospasm in nonasthmatic patients.

Anaesthetic management strategy

Preoperative evaluation

The anaesthesiologist's responsibility starts at the preoperative phase with the evaluation of the patient's pulmonary function. Warner *et al.*[15] observed that the frequency of perioperative bronchospasm and laryngospasm was surprisingly low in asthmatic patients. They identified 3 factors correlated with perioperative bronchospasm: the use of antibronchospastic medications; recent symptomatic exacerbation; and recent visit to a medical facility for treatment of asthma. Therefore, they reached the following conclusions: 1) persons with asthma but no symptoms are at low risk for severe morbidity from anaesthesia; 2) persons with asthma are, however, at a low but increased risk for severe morbidity; and 3) adverse outcomes from bronchospasm occur in patients with no previous history of asthma.[16]

In view of this, the approach to the asthmatic patient should include a detailed history of the patient's experience with reactive airway disease, searching for the following: 1) a recent upper respiratory infection; 2) allergies; 3) possible precipitating factors for asthma; 4) use of medications, including drugs that could precipitate the attack, as well as those used to prevent an attack; and 5) the occurrence of dyspnoea at night or in the early morning hours. Furthermore, to better understand a patient's bronchial reactivity, it is important to know whether he or she can tolerate cold air, dust, or smoke and if he or she has ever undergone tracheal intubation under general anaesthesia.[17] Documentation of an episode of status asthmaticus requiring intubation portends of a difficult perioperative course.[10]

Drugs are commonly associated with the induction of acute episodes of asthma, and it is important to recognize drug-induced bronchial narrowing because its presence is often associated with great morbidity. Even the selective β_1-adrenergic antagonists regularly obstruct the airways in individuals with asthma and should be avoided.[5]

The triad of bronchial asthma, nasal polyposis, and intolerance to aspirin or aspirin-like chemicals is designated aspirin-induced asthma (AIA) or Samter's syndrome. In these patients, marked cross-sensitivity with nonsteroidal anti-inflammatory drugs may precipitate severe bronchospasm and adverse reactions. Hence, it is important to refer these patients to allergy clinics to evaluate possible analgesic cross reactivity and intolerance to anaesthetic agents.[18]

Physical examination of the lungs may be normal or reveal wheezing and/or other adventitial sounds. Preoperative wheezing is predictive of a difficult perioperative course. Indeed, if a severe asthmatic history and auscultatory wheezing are encountered during the initial screening, a consultation with the pulmonologist may be recommended. In severe cases of asthma, laboratory studies such as arterial blood gases and pulmonary function tests should be indicated in order to analyse the degree of respiratory impairment.[19] Preoperative spirometry is a simple means of assessing the presence and severity of airway obstruction as well as the degree of reversibility in response to bronchodilator therapy. An increase of 15% in FEV_1 is considered clinically significant.[20]

In asthmatic patients, chest roentgenogram even in acute asthma attacks often shows normal findings.[17]

Preoperative management of asthma

In patients with reversible airway obstruction and bronchial reactivity, preoperative treatment with β_2-adrenergic agonists and corticosteroids should be considered. β_2-adrenergic agonists have been shown to attenuate the reflex bronchoconstriction following endotracheal intubation. Even with this intervention, significant bronchoconstriction and wheezing occurs following intubation.[17, 21, 22]

Combined treatment with corticosteroids and a β_2-adrenergic agonist can improve preoperative lung function and decrease the incidence of wheezing following endotracheal intubation.[21, 23] Concerns about negative effects of perioperative treatment with corticosteroids in terms of wound healing and infection were not supported by studies in asthmatic patients receiving prophylactic treatment with corticosteroids perioperatively, and there is evidence that asthmatic patients who are treated with corticosteroids can undergo surgical procedures with a low incidence of complications.[24] Thus, preoperative treatment with combined corticosteroids [methylprednisolone (40 mg/day orally)] and salbutamol minimizes intubation-evoked bronchoconstriction in patients with reversible airway obstruction or with a history of severe bronchial hyper-reactivity.[17, 21]

According to Enright,[11] preoperative management in asthmatics should include the following measures:

1. bronchospasm should be treated with inhaled β_2-agonists;
2. if a patient is at risk for complications, preoperative treatment with 40-60 mg of prednisone/day or hydrocortisone 100 mg every 8 h intravenously is suggested. Anyone with a preoperative FEV_1<80% of predicted should receive steroids;
3. infections should be eradicated using antibiotics;
4. fluid and electrolyte imbalances should be corrected, given that high dose β_2-agonists can cause hypokalemia, hyperglycemia, and hypomagnesemia. In addition to that imbalance, there may be a decreased response to β_2-agonists and predisposition to cardiac arrhythmias;
5. prophylactic cromolyn treatment to prevent degranulation of mast cells and release of mediators should be continued;
6. chest physiotherapy improves sputum clearance and bronchial drainage;
7. other conditions such as *cor pulmonale* should be treated;
8. the patient should stop smoking in order to reduce carboxyhemoglobin levels.

Choice of anaesthetic technique

Bronchial hyper-reactivity associated with asthma is an important risk factor for perioperative bronchospasm. The occurrence of this potentially life-threatening condition in anaesthesia practice varies from 0.17% to 4.2%.[20]

During general anaesthesia, with or without tracheal intubation, there is a reduction of tone in either the palatal or pharyngeal muscles accompanied by a lung volume reduction and an augmentation of the layer of liquid on the airway wall. These factors predispose to unstable airway conditions, airflow obstruction, and considerably greater airway resistance.[25]

Airway instrumentation causes reflex bronchoconstriction mediated by the parasympathetic nervous system.[17, 26] In addition, evidence suggests that mechanical stimulation of the airways may activate the peripheral terminals of C-fibre afferents. These nerve fibres release substance P and neurokinin A, which can cause an increase in

vascular permeability, bronchial smooth muscle constriction, and local vasodilatation.[27] The anaesthesiologists' goal should be to minimize the risk of inciting bronchospasm and to avoid triggering *stimuli*.

The effect of endotracheal intubation, even in symptom-free asthmatics, was demonstrated by Groeben *et al.*[28] in a randomized double-blind fashion study of 10 volunteers with mild asthma who underwent endotracheal intubation under local anaesthesia. They performed lung function tests before and after intubation and observed over a 50% reduction in FEV_1 after the procedure. However, after prophylactic administration of a β_2-adrenergic agonist and topical lidocaine, the reduction in FEV_1 was lower (20%).

In summary, it is preferable to avoid airway instrumentation in asthmatic patients, and regional anaesthesia should always be considered for this purpose, as well as for reducing postoperative complications.[17]

Pregnancy can adversely affect the course of asthma, increasing perioperative risk in these patients. For this reason, regional anaesthesia is the technique of choice for pregnant asthmatics and parturients, especially if prostaglandins and their derivates are administered for abortion or operative delivery.[20, 29]

When regional anaesthesia is not feasible and general anaesthesia is required, prophylactic antiobstructive treatment, volatile anaesthetics, propofol, opioids, and an adequate choice of muscle relaxants minimize the anaesthetic risk.[17] In addition to this, the use of face masks and laryngeal mask airways have been reported to cause less airway irritation. Kim and Bishop [30] randomized 52 nonasthmatic patients to receive an endotracheal tube or a laryngeal mask airway under general anaesthesia; they observed that respiratory system resistance (Rrs) was lower in patients receiving laryngeal mask airways than in those submitted to endotracheal intubation. This result supports the idea that use of a laryngeal mask might be a more reliable alternative than endotracheal intubation.

Premedication

Adequate sedation of the patient should be achieved in order to avoid perioperative complications. For this purpose, benzodiazepines are safe and do not alter bronchial tone.[17] In this context, Kil *et al.*[31] noticed that oral midazolam (0.5 mg/kg) did not change oxygen saturation, respiratory rate, and pulse rate in children with mild to moderate asthma undergoing dental treatment. Hence, midazolam at a dose of 0.5 mg/kg is a safe and effective means for sedation of patients with mild to moderate asthma.

Inhalational anaesthetics

Inhalational agents possess bronchodilatory effects, decrease airway responsiveness, and attenuate histamine-induced bronchospasm.[10] The mechanism is thought to be β-adrenergic receptor stimulation leading to increased intracellular cyclic-AMP. This has a direct bronchial muscle relaxing effect. Increased cAMP may bind free calcium within bronchial myoplasm and cause relaxation by negative feedback. It may impede antigen-antibody mediated enzyme production and the release of histamine from leukocytes as well.[11]

For all these reasons, volatile agents such as halothane and isoflurane have been recommended for general anaesthetic techniques in patients with obstructive airway diseases for many years, and they are even helpful to treat status asthmaticus. An exception should be made for desflurane, which can lead to increased secretions, coughing, laryngospasm, and bronchospasm.[32]

Thus far, studies using sevoflurane have shown controversial results. Rooke *et al.*[33] compared the bronchodilating efficacy of sevoflurane, isoflurane, and halothane after tracheal intubation in patients without asthma. In their study, halothane was not significantly better than isoflurane at reducing Rrs. Nonetheless, sevoflurane decreased Rrs more than either halothane or isoflurane.

Habre *et al.*[34] studied lung function in children with and without asthma receiving anaesthesia with sevoflurane and concluded that, in children with mild to moderate asthma, endotracheal intubation during sevoflurane anaesthesia was associated with an increase in Rrs that was not seen in nonasthmatic children. In spite of this, no apparent clinical adverse event was observed, and according to the Scalfaro *et al.* study,[35] a pre-anaesthetic treatment with inhaled salbutamol administered before sevoflurane anaesthesia can prevent that increase of Rrs.

Correa *et al.*[36] analysed the respiratory mechanics and lung histology in normal rats anaesthetised with sevoflurane. They observed that sevoflurane anaesthesia did not act at the airway level but at the lung periphery, stiffening lung tissues and increasing mechanical inhomogeneities. In addition, Takala *et al.*[37] evaluated pulmonary inflammatory mediators in bronchoalveolar lavage fluid after sevoflurane anaesthesia in pigs and reported that sevoflurane increased pulmonary leukotriene C_4, NO_3-, and NO_2- production, suggesting an inflammatory response.

Intravenous anaesthetics

Ketamine is an *i.v.* general anaesthetic that is considered an attractive choice because of its sympathomimetic bronchodilatory properties and its effectiveness at preventing and reversing wheezing in patients with asthma who require anaesthesia and intubation.[38] Ketamine relaxes the bronchiolar musculature and prevents the bronchoconstriction induced by histamine, decreasing the risk of bronchospasm during the induction of anaesthesia. These effects derive from a direct action on bronchial muscle as well as a potentiation of catecholamines. Nonetheless, ketamine increases bronchial secretions and it is usual to administer an anticholinergic agent such as atropine or glycopyrrolate in conjunction. Hallucinations are the most unpleasant side effect of ketamine and can be minimized with concomitant sedation with benzodiazepines.[10] However, its effectiveness has not been demonstrated in a controlled trial.[39, 40] Although previous studies analysed the effects of ketamine on central airways, Alves-Neto *et al.*[41] observed in rats without pre-existing airway constriction that ketamine acted not at the airway level but at the lung periphery, increasing mechanical inhomogeneities, which may result from dilation of distal airways and alveolar collapse.

Brown and Wagner [38] examined the local airway effects of ketamine and propofol on attenuating direct and reflex-induced airway constriction. They developed a nonasthmatic animal model in which they administered ketamine and propofol directly to the airways *via* the bronchial artery and concluded that the major mechanism of bronchoprotection of ketamine and propofol is determined by an inhibition of neurally-induced bronchoconstriction.

Propofol, a widely used short-acting *i.v.* anaesthetic, has been associated with less bronchoconstriction during anaesthetic induction than other anaesthetic agents.[42] *In vitro* data suggest that propofol has a direct airway smooth muscle relaxant action.[43] Pizov *et al.*[44] in a randomized controlled clinical trial evaluated the incidence of wheezing in asymptomatic asthmatic and nonasthmatic patients receiving *i.v.* anaesthetic agents for induction of anaesthesia. They observed that both asthmatic and nonasthmatic patients who received a thiobarbiturate for induction had a greater incidence of wheezing than did patients receiving propofol. Similarly, Eames *et al.*[45] assessed Rrs in a nonasthmatic patient population with a high incidence of smoking and compared thiopental, etomidate, and propofol. They observed that tracheal intubation with propofol anaesthesia produced a lower Rrs than when thiopental or a relatively high dose of etomidate was used. To compare the effects of propofol anaesthesia in children with and without asthma, Habre *et al.*[46] induced anaesthesia with propofol, fentanyl, and atracurium and maintained with an infusion of propofol and 50% nitrous oxide in oxygen. Final results showed that respiratory mechanics were not altered by propofol anaesthesia in children both with and without asthma. In this context, Peratoner *et al.*[47] analysed the effects of propofol on respiratory mechanics in normal rats and correlated these parameters with lung histology, to define the sites of action of propofol. They observed that propofol acts at the airway level, decreasing respiratory system and lung impedances as a result of central airway dilation.

On the basis of the aforementioned, propofol is considered safe for patients with asthma who require timely intubation. Nevertheless, Nishiyama and Hanaoka [48] reported 2 cases of bronchoconstriction following propofol induction. Both patients had allergic problems, and it was postulated that it was the particular formulation of propofol which contained yolk lecithin and soybean oil that caused the problem. Accordingly, propofol should be used with caution in patients with allergic disease or drug-induced asthma.

Opioids

Although opioids could release histamine, they are considered safe for patients with increased bronchial reactivity. Fentanyl and its analogues are frequently used in the induction of anaesthesia, and they can lead to thorax rigidity that can be misinterpreted as bronchospasm. With slow injection, this effect is hardly observed.

Moreover, the suppression of the cough reflex and the deepening of anaesthesia level achieved after opioid administration can be helpful in asthmatic patients.[17]

Muscle relaxants

Depending on which type of muscarinic receptor is stimulated, increased or decreased bronchial tone and reactivity can be expected. It has been shown that muscle relaxants which affect M_2 receptors more than M_3 receptors (gallamin, pipecuronium, rapacuronium) can cause and enhance bronchoconstriction.[49] Otherwise, muscle relaxants which seem to bind M_3 receptors more or at least the same way as M_2 receptors do not induce bronchospasm. Among those, vecuronium, rocuronium, cisatracurium, and pancuronium are considered safe.[11]

In addition to these direct effects on muscarinic receptors, atracurium and mivacurium dose-dependently release histamine and have been identified as triggers of bronchoconstriction and should be used carefully in asthmatic patients.[17]

Furthermore, the reversal of muscle relaxation at the end of surgery should be avoided since neostigmine and physostigmine cause bradycardia, increased secretion, and bronchial hyper-reactivity. For this purpose, doses of muscle relaxants should be timed so as to be worn off at the end of surgery.[11]

Local anaesthetics

Local anaesthetics of the amide type that attenuate and even block afferent and efferent nerve conduction of autonomic nerve fibres and autonomic reflexes, such as the coughing or bronchoconstriction reflex, can be suppressed with plasma concentrations of lidocaine below the toxic threshold of 5 mg/mL.[50] In asthmatic volunteers, *i.v.* lidocaine doses of 1-2 mg/kg of body weight significantly attenuated histamine-induced bronchoconstriction and can be used to attenuate the response to airway irritations like endotracheal suction or intubation. Groeben *et al.*[51] demonstrated that, in awake humans, both *i.v.* lidocaine and inhaled albuterol significantly increased the histamine threshold when given alone. They recommended preoperative treatment with inhaled albuterol and *i.v.* lidocaine to prevent reflex bronchospasm with tracheal intubation. Alternatively, Maslow *et al.*[22] studied 60 asthmatic patients and found that inhaled albuterol attenuated the airway response to tracheal intubation in asthmatic patients, while i.v. lidocaine did not.

Inhalation of lidocaine can attenuate the response to airway irritation with plasma concentrations lower than those following systemic administration.[17] Nevertheless, the attenuation of bronchial reactivity is preceded by a mild airway irritation [52, 53] that can be avoided with pretreatment with a β_2-adrenergic agonist or minimized by using lidocaine inhalation in a dose of 2 mg/kg as a 4% solution for topical anaesthesia.[50] This is the regimen that attenuates bronchial hyper-reactivity with the least airway irritation.[54] In addition, Hunt *et al.*[55] recruited 50 subjects with mild to moderate asthma to receive either an inhaled placebo or inhaled lidocaine 4% for 8 weeks. Their results showed that nebulized lidocaine was an effective therapy in those patients.

Moreover, local anaesthetics, absorbed from the epidural space to the blood, attenuate bronchial hyper-reactivity to chemical *stimuli*. Shono *et al.*[56] reported a case of a man with bronchial asthma under continuous epidural anaesthesia with 2% lidocaine in which wheezing gradually diminished after the epidural injection and completely disappeared over 155 min during continuous epidural injection of lidocaine. Wheezing reappeared 55 min after termination of the continuous epidural injection of lidocaine. This corroborates the hypothesis that regional anaesthesia in asthmatic patients, alone or in combination with general anaesthesia, is advantageous.

Treatment of intraoperative bronchospasm

If intraoperative wheezing should develop, non-bronchospastic causes of wheezing (mechanical obstruction of the endotracheal tube, endo-

bronchial intubation, pulmonary aspiration, pulmonary embolism, pulmonary oedema, tension pneumothorax, and negative pressure inspiration) must be ruled out.[19] The first step is to deepen the level of anaesthesia *via* the *i.v.* or inhalational route or both. Administration of 100% oxygen should be instituted to prevent hypoxemia.

β_2-agonists via metered dose inhaler should be administered through the airway. It is important to consider the fact that delivery of aerosolized agents during mechanical ventilation is not adequate, being estimated that as little as 1% to 3% of a dose of nebulized medication actually reaches the lungs of a patient on positive pressure ventilation. The amount of aerosol reaching the lungs could be improved by means of an increase in respiratory time, a reduction of respiratory rate, an increase in the volume of nebulizer fill, and positioning of the nebulizer between the Y-piece and catheter mount or on the inspiratory limb of the ventilator circuit Y-piece when jet nebulizers are used.[27]

Epinephrine, either subcutaneously or intravenously, can help in severely bronchospastic patients. Corticosteroids can be utilized, but their onset of action takes place within 4 to 8 h of administration.[27]

Leukotriene receptor antagonists and mast cell inhibitors have no use in acute bronchospasm. Intravenous aminophylline can be started, but side effects such as tachycardia and hypertension may limit its usefulness. As a result, methylxantines are no longer recommended for acute exacerbations.

A smooth, slow emergence minimizes the risk of bronchospasm. Deep extubation can be attempted if no airway difficulties were encountered during induction. If deep extubation is contraindicated, the patient may be taken to the postanesthesia care unit intubated and opioids administered to facilitate tolerance to the endotracheal tube. When the patient is awake and possesses appropriate airway reflexes, extubation can occur. Intravenous lidocaine may be of use in preventing bronchospasm with extubation.[19]

Inhalation anaesthesia in *status asthmaticus*

Status asthmaticus refers to acute asthma attacks in which the degree of bronchial obstruction is either severe from the onset or worsens and is not relieved by usual therapy in 30 to 60 min. The term refractory *status asthmaticus* describes those cases in which the patient's condition continues to deteriorate despite aggressive pharmacologic interventions and persists for more than 24 h.[10]

When conventional bronchodilators fail, the intensivist may resort to the use of drugs such as ketamine and inhalation anaesthesia. In this context, deep sedation is important not only to improve oxygenation but also to reduce cerebral metabolic requirements.[57]

Therapy with inhalational anaesthetic agents such as halothane, enflurane, isoflurane, and diethyl ether has been successfully used in the management of refractory *status asthmaticus*.[10, 58] Iwaku *et al.*[59] treated patients with *status asthmaticus* with isoflurane inhalation and observed that tidal volume, pH, and $PaCO_2$ improved after anaesthesia and that these patients stayed in the Intensive Care Unit (ICU) and underwent mechanical ventilation for a shorter period than those who were not treated with isoflurane.

Que and Lusaya [60] successfully used sevoflurane inhalation in a parturient in *status asthmaticus* for caesarean section. Schultz [61] reported the use of sevoflurane in a 26-year-old woman who presented to a rural critical access hospital emergency department in *status asthmaticus* and subsequently failed conventional therapy. Sevoflurane was administered for approximately 150 min, stabilizing the patient's condition enough to allow fixed-wing air transport to a tertiary facility. Likewise, Mazzeo *et al.*[57] reported an 8-year-old boy treated with ketamine and sevoflurane and observed no episode of haemodynamic instability despite severe prolonged hypercapnia. Oxygenation was maintained and successful recovery followed without *sequelae*.

Conclusions

Some anaesthetics have been used even for intractable *status asthmaticus*. Despite this, and the fact that the understanding of the pathophysiology of asthma has changed, there are only a few studies describing the sites and mechanisms of action of our frequently used anaesthetic agents in a chronically inflamed, hyper-responsive, and remodelled lung, as seen in asthmatic patients.

Knowledge of these mechanisms will stimulate a great revolution in anaesthetic management, allowing anaesthesiologists and intensivists to optimise the use of anaesthetic drugs and techniques in those patients, and it will direct researchers to develop new drugs effective not only on inhibiting hyper-responsiveness and producing bronchodilation, but also on reducing or even suppressing the underlying inflammation process and remodelling. Therefore, the incidence of anaesthetic complications and adverse events will be strongly minimized, which will be very beneficial to patients and physicians.

References

1. Beasley R, Crane J, Lai CK, Pearce N. Prevalence and etiology of asthma. J Allergy Clin Immunol 2000;105: S466-72.
2. Sunyer J, Anto JM, Tobias A, Burney P. Generational increase of self-reported first attack of asthma in fifteen industrialized countries. European Community Respiratory Health Study (ECRHS). Eur Respir J 1999;14:885-91.
3. CDC. From the Centers for Disease Control and Prevention. Self-reported asthma prevalence and control among adults-United States, 2001. JAMA 2003;289: 2639-40.
4. Arif AA, Borders TF, Patterson PJ, Rohrer JE, Xu KT. Prevalence and correlates of paediatric asthma and wheezing in a largely rural USA population. J Paediatr Child Health 2004;40:189-94.
5. McFadden Jr ER. Asthma. In: Kasper DL, Braunwald EL, Fauci AS, Hauser SL, Longo DL, Jameson JL *et al.* editors. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw-Hill Companies, Inc.; 2005.p.1510-1.
6. Homer RJ, Elias JA. Airway remodeling in asthma: therapeutic implications of mechanisms. Physiology 2005;20:28-35.
7. Chen FH, Samson KT, Miura K, Ueno K, Odajima Y, Shougo T *et al.* Airway remodeling: a comparison between fatal and nonfatal asthma. J Asthma 2004;41:631-8.
8. Nakagawa T, Hoshino M. Airway remodeling in asthma: an introduction. Clin Rev Allergy Immunol 2004;27:1-2.
9. Vignola AM, Mirabella F, Costanzo G, Di Giorgi R, Gjomarkaj M, Bellia V *et al.* Airway remodeling in asthma. Chest 2003;123:S417-22.
10. Jagoda A, Shepherd SM, Spevitz A, Joseph MM. Refractory asthma, Part 1: Epidemiology, pathophysiology, pharmacologic interventions. Ann Emerg Med 1997;29:262-74.
11. Enright A. Bronchospastic disease and emergency surgery. Middle East J Anesthesiol 2004;17:927-38.
12. Xisto DG, Farias LL, Ferreira HC, Picanco MR, Amitrano D, Lapa ES Jr *et al.* Lung parenchyma remodeling in a murine model of chronic allergic inflammation. Am J Respir Crit Care Med 2005;171:829-37.
13. Tulic MK, Hamid Q. Contribution of the distal lung to the pathologic and physiologic changes in asthma: potential therapeutic target Roger S. Mitchell lecture. Chest 2003;123:S348-55.
14. Tulic MK, Christodoulopoulos P, Hamid Q. Small airway inflammation in asthma. Respir Res 2001;2:333-9.
15. Warner DO, Warner MA, Barnes RD, Offord KP, Schroeder DR, Gray DT *et al.* Perioperative respiratory complications in patients with asthma. Anesthesiology 1996;85:460-7.
16. Bishop MJ, Cheney FW. Anesthesia for patients with asthma. Low risk but not no risk. Anesthesiology 1996;85:455-6.
17. Groeben H. Strategies in the patient with compromised respiratory function. Best Pract Res Clin Anaesthesiol 2004;18:579-94.
18. Celiker V, Basgul E. Anaesthesia in aspirin-induced asthma. Allergol Immunopathol 2003;31:338-41.
19. Stasic AF. Perioperative implications of common respiratory problems. Semin Pediatr Surg 2004;13:174-80.
20. Bremerich DH. Anesthesia in bronchial asthma. Anasthesiol Intensivmed Notfallmed Schmerzther 2000;35:545-58.
21. Silvanus MT, Groeben H, Peters J. Corticosteroids and inhaled salbutamol in patients with reversible airway obstruction markedly decrease the incidence of bronchospasm after tracheal intubation. Anesthesiology 2004;100:1052-7.
22. Maslow AD, Regan MM, Israel E, Darvish A, Mehrez M, Boughton R *et al.* Inhaled albuterol, but not intravenous lidocaine, protects against intubation-induced bronchoconstriction in asthma. Anesthesiology 2000;93:1198-204.
23. Barnes PJ. Mechanisms of action of glucocorticoids in asthma. Am J Respir Crit Care Med 1996;154:S21-6; discussion S6-7.
24. Kabalin CS, Yarnold PR, Grammer LC. Low complication rate of corticosteroid-treated asthmatics undergoing surgical procedures. Arch Intern Med 1995;155: 1379-84.
25. Burwell DR, Jones JG. The airways and anaesthesia I. Anatomy, physiology and fluid mechanics. Anaesthesia 1996;51:849-57.
26. Barnes PJ. What is the role of nerves in chronic asthma and symptoms? Am J Respir Crit Care Med 1996;153:S5-8.
27. Jagoda A, Shepherd SM, Spevitz A, Joseph MM. Refractory asthma, Part 2: Airway interventions and management. Ann Emerg Med 1997;29:275-81.
28. Groeben H, Schlicht M, Stieglitz S, Pavlakovic G, Peters J. Both local anesthetics and salbutamol pretreatment affect reflex bronchoconstriction in volunteers with asthma undergoing awake fiberoptic intubation. Anesthesiology 2002;97:1445-50.
29. Kuczkowski KM. Labor analgesia for the parturient with respiratory disease: what does an obstetrician need to know? Arch Gynecol Obstet 2005;272:160-6.
30. Kim ES, Bishop MJ. Endotracheal intubation, but not laryngeal mask airway insertion, produces reversible bronchoconstriction. Anesthesiology 1999;90:391-4.
31. Kil N, Zhu JF, VanWagnen C, Abdulhamid I. The effects of midazolam on pediatric patients with asthma. Pediatr Dent 2003;25:137-42.
32. Goff MJ, Arain SR, Ficke DJ, Uhrich TD, Ebert TJ. Absence of bronchodilation during desflurane anesthesia: a comparison to sevoflurane and thiopental. Anesthesiology 2000;93:404-8.
33. Rooke GA, Choi JH, Bishop MJ. The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. Anesthesiology 1997;86:1294-9.
34. Habre W, Scalfaro P, Sims C, Tiller K, Sly PD. Respiratory mechanics during sevoflurane anesthesia in children with and without asthma. Anesth Analg 1999;89:1177-81.
35. Scalfaro P, Sly PD, Sims C, Habre W. Salbutamol prevents the increase of respiratory resistance caused by tracheal intubation during sevoflurane anesthesia in asthmatic children. Anesth Analg 2001;93:898-902.
36. Correa FC, Ciminelli PB, Falcao H, Alcantara BJ, Contador RS, Medeiros AS *et al.* Respiratory mechanics and lung histology in normal rats anesthetized with sevoflurane. J Appl Physiol 2001;91:803-10.
37. Takala RS, Soukka HR, Salo MS, Kirvela OA, Kaapa PO, Rajamaki AA *et al.* Pulmonary inflammatory mediators after sevoflurane and thiopentone anaesthesia in pigs. Acta Anaesthesiol Scand 2004;48:40-5.
38. Brown RH, Wagner EM. Mechanisms of bronchoprotection by anesthetic induction agents: propofol *versus* ketamine. Anesthesiology 1999;90:822-8.
39. Howton JC, Rose J, Duffy S, Zoltanski T, Levitt MA.

Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. Ann Emerg Med 1996;27:170-5.
40. Youssef-Ahmed MZ, Silver P, Nimkoff L, Sagy M. Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm. Intensive Care Med 1996;22:972-6.
41. Alves-Neto O, Tavares P, Rocco PR, Zin WA. Respiratory mechanics and morphometric changes during anesthesia with ketamine in normal rats. Braz J Med Biol Res 2001;34:1217-23.
42. Wu RS, Wu KC, Sum DC, Bishop MJ. Comparative effects of thiopentone and propofol on respiratory resistance after tracheal intubation. Br J Anaesth 1996;77: 735-8.
43. Ouedraogo N, Roux E, Forestier F, Rossetti M, Savineau JP, Marthan R. Effects of intravenous anesthetics on normal and passively sensitized human isolated airway smooth muscle. Anesthesiology 1998;88:317-26.
44. Pizov R, Brown RH, Weiss YS, Baranov D, Hennes H, Baker S *et al.* Wheezing during induction of general anesthesia in patients with and without asthma. A randomized, blinded trial. Anesthesiology 1995;82:1111-6.
45. Eames WO, Rooke GA, Wu RS, Bishop MJ. Comparison of the effects of etomidate, propofol, and thiopental on respiratory resistance after tracheal intubation. Anesthesiology 1996;84:1307-11.
46. Habre W, Matsumoto I, Sly PD. Propofol or halothane anaesthesia for children with asthma: effects on respiratory mechanics. Br J Anaesth 1996;77:739-43.
47. Peratoner A, Nascimento CS, Santana MC, Cadete RA, Negri EM, Gullo A *et al.* Effects of propofol on respiratory mechanic and lung histology in normal rats. Br J Anaesth 2004;92:737-40.
48. Nishiyama T, Hanaoka K. Propofol-induced bronchoconstriction: two case reports. Anesth Analg 2001;93: 645-6.
49. Jooste E, Klafter F, Hirshman CA, Emala CW. A mechanism for rapacuronium-induced bronchospasm: M2 muscarinic receptor antagonism. Anesthesiology 2003;98:906-11.
50. Groeben H, Schwalen A, Irsfeld S, Stieglitz S, Lipfert P, Hopf HB. Intravenous lidocaine and bupivacaine dose-dependently attenuate bronchial hyperreactivity in awake volunteers. Anesthesiology 1996;84:533-9.
51. Groeben H, Silvanus MT, Beste M, Peters J. Combined intravenous lidocaine and inhaled salbutamol protect against bronchial hyperreactivity more effectively than lidocaine or salbutamol alone. Anesthesiology 1998;89: 862-8.
52. Bulut Y, Hirshman CA, Brown RH. Prevention of lidocaine aerosol-induced bronchoconstriction with intravenous lidocaine. Anesthesiology 1996;85:853-9.
53. Groeben H, Grosswendt T, Silvanus MT, Pavlakovic G, Peters J. Airway anesthesia alone does not explain attenuation of histamine-induced bronchospasm by local anesthetics: a comparison of lidocaine, ropivacaine, and dyclonine. Anesthesiology 2001;94:423-8.
54. Groeben H, Grosswendt T, Silvanus M, Beste M, Peters J. Lidocaine inhalation for local anaesthesia and attenuation of bronchial hyper-reactivity with least airway irritation. Effect of three different dose regimens. Eur J Anaesthesiol 2000;17:672-9.
55. Hunt LW, Frigas E, Butterfield JH, Kita H, Blomgren J, Dunnette SL *et al.* Treatment of asthma with nebulized lidocaine: a randomized, placebo-controlled study. J Allergy Clin Immunol 2004;113:853-9.
56. Shono S, Higa K, Harasawa I, Sugano H, Dan K. Disappearance of wheezing during epidural lidocaine anesthesia in a patient with bronchial asthma. Reg Anesth Pain Med 1999;24:463-6.
57. Mazzeo AT, Spada A, Pratico C, Lucanto T, Santamaria LB. Hypercapnia: what is the limit in paediatric patients? A case of near-fatal asthma successfully treated by multipharmacological approach. Paediatr Anaesth 2004;14: 596-603.
58. Miyagi T, Gushima Y, Matsumoto T, Okamoto K, Miike T. Prolonged isoflurane anesthesia in a case of catastrophic asthma. Acta Paediatr Jpn 1997;39:375-8.
59. Iwaku F, Otsuka H, Kuraishi H, Suzuki H. [The investigation of isoflurane therapy for *status asthmaticus* patients]. Arerugi 2005;54:18-23.
60. Que JC, Lusaya VO. Sevoflurane induction for emergency cesarean section in a parturient in *status asthmaticus*. Anesthesiology 1999;90:1475-6.
61. Schultz TE. Sevoflurane administration in *status asthmaticus*: a case report. AANA J 2005;73:35-6.

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