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Guideline-oriented perioperative management of patients with bronchial asthma and chronic obstructive pulmonary disease

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Abstract
Increased airway hyperresponsiveness is a major concern in the perioperative management of patients with bronchial asthma and chronic obstructive pulmonary disease. Guidelines using evidence-based medicine are continually being updated and published regarding the diagnosis, treatment, and prevention of these respiratory disorders. Perioperative management in these patients involves: (1) adequate control of airway hyperresponsiveness, including detection of purulent sputum and infection before surgery; (2) evidence-based control of anesthesia; and (3) the aggressive use of beta-2 adrenergic stimulants and the systemic administration of steroids for the treatment of acute attacks. Good preoperative control, including the use of leukotriene antagonists, can reduce the incidence of life-threatening perioperative complications. Awareness of recent guidelines is thus important in the management of patients with airway hyperresponsiveness. This review covers the most recent guidelines for the perioperative management of patients with bronchial asthma and chronic obstructive pulmonary disease.

Key words Bronchial asthma · Chronic obstructive pulmonary disease (COPD) · Perioperative management · Airway management · Airway hyperresponsiveness

Introduction

Rapid advances in our understanding of the pathophysiology and treatment of bronchial asthma and chronic obstructive pulmonary disease (COPD) have led to continual updates in evidence-based guidelines [1,2]. However, surgery in patients with preoperative respiratory disease is still often limited to nonradical and minimally invasive procedures [1,3,4]. Anesthesiologists must possess a thorough understanding of these disorders in order to select anesthetic agents and approaches that will optimize patient status [5]. Anesthetic agents have bronchodilator effects [6–8], but some can also induce bronchoconstriction [9,10]. Asthma and COPD account for the majority of obstructive airway diseases detected on preoperative evaluation [11], so anesthesiologists need to be familiar with these disorders to provide treatment and respiratory management. Asthma and COPD are related disorders and many aspects of their perioperative management are thus similar, but an understanding of specific differences between the disorders is also important.

This review discusses the diagnosis, staging, and pathophysiological mechanisms and treatment of asthma and COPD, including the most recent basic science and clinical literature, to facilitate the selection of appropriate anesthetic agents and provide optimal perioperative anesthetic management for these patients.

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Definition and pathology of bronchial asthma and COPD

Definition

Asthma and COPD are characterized by an obstructive pattern on pulmonary function testing. The prevalence of COPD has increased, to 4%–9% [2,12–16]. Likewise, the prevalence of asthma has also increased, to 4%–6% [2,17]. The two disorders display overlapping signs and symptoms that require careful differential diagnosis (Fig. 1) [1,2,18].

The World Health Organization (WHO) and the National Heart, Lung, and Blood Institute of the United States (NHLBI) launched the Global Initiative for Asthma (GINA) [1] as a collaborative effort to define

and establish evidence-based standards for the management of asthma, including guidelines for diagnosis, treatment, and prevention. GINA defines asthma as follows: "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung (*see Fig. 1, subset 2*) that is often reversible either spontaneously or with treatment (*see Fig. 1, subset 1*)."

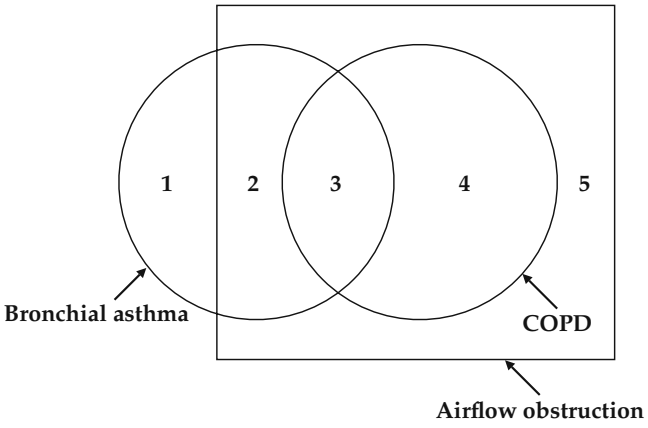

Fig. 1. Conceptual diagram of chronic obstructive pulmonary disease (*COPD*) and bronchial asthma. *Subset 2* implies bronchial asthma with airflow obstruction, while *subset 1* means bronchial asthma without airflow obstruction spontaneously or with treatment. *Subset 4* implies COPD patients with inevitable airflow obstruction. COPD patients having airway reactivity are categorized as *subset 3*. *Subset 5* means other diseases with airflow obstruction such as diffuse panbronchiolitis (DPB), bronchiectasis, and pneumoconiosis (modified from Snider [18], with permission)

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline [2] defines COPD as follows: "COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airway limitation that is not fully reversible (*see Fig. 1, subset 4*). The airway limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases." COPD patients having airway reactivity are categorized as subset 3 in Fig. 1.

Asthma and COPD are both chronic inflammatory disorders, and exacerbations are caused by a number of common factors, but many differences also exist in the mechanisms of onset, related inflammatory cells and mediators, sites of obstruction, pathology, clinical test findings, and treatment methods (Table 1) [2]. In men 40 years old or more with a history of smoking, the presence of chronic cough, sputum production, and dyspnea on exertion suggests COPD. Asthma is characterized by cough and wheezing, particularly in the late evening to early morning.

Exogenous risk factors for COPD include smoking [18] and air pollution, while alpha-1 antitrypsin deficiency represents an important endogenous risk factor [19,20]. Exogenous risk factors for asthma include house dust and house dust mites, while endogenous risk factors include an allergic predisposition and hereditary factors [1].

Table 1. Differences in pulmonary inflammation between bronchial asthma and chronic obstructive pulmonary disease (COPD)

	COPD	Asthma	Severe asthma
Cells	Neutrophils ++ Macrophages +++ CD8+ T cells (Th1)	Eosinophils ++ Macrophages + CD4+ T cells (Th2)	Neutrophils + Macrophages CD4+ T cells (Th2) CD8+ T cells (Th1)
Key mediators	IL-8 TNF-α, IL-1β, IL-6 NO +	Eotaxin IL-4, IL-5, IL-13 NO +++	IL-8 IL-5, IL-13 NO ++
Site of disease	Peripheral airways Lung parenchyma Pulmonary vessels	Proximal airways	Proximal airways Peripheral airways
Consequences	Squamous metaplasia Mucous metaplasia Small airway fibrosis Parenchymal destruction Pulmonary vascular remodeling	Fragile epithelium Mucous metaplasia ↑ Basement membrane Bronchoconstriction	
Response to therapy	Small b/d response Poor response to steroids	Large b/d response Good response to steroids	Smaller b/d response Reduced response to steroids

From Rabe et al. [2], with permission
NO, nitric oxide; b/d, bronchodilator; CD, cluster of differentiation; Th, helper T; IL, interleukin; TNF, tumor necrotizing factor

The definition, diagnosis, and treatment of COPD and asthma have changed considerably over the past 20 years, but both the GINA and GOLD guidelines mention little with specific reference to perioperative management [21]. The GOLD 2006 guidelines emphasize that COPD may be a preventable and treatable disease [2]. Anesthesiologists, in addition to evaluating risk factors, can therefore also provide treatment and increase the safety of perioperative management for patients with these disorders.

Airway pathology in bronchial asthma and COPD

As shown in Table 1 [2], asthma is triggered by inhaled antigens, and the pulmonary inflammation is mediated by complex cellular interactions, including CD4-positive T cells (Th2), eosinophils, and mast cells, causing widespread central and peripheral airway inflammation [1,22,23]. These antigens induce the production and release of specific immunoglobulin (Ig)E antibodies from B lymphocytes and the production of cytokines from T lymphocytes to cause inflammation [24]. The airway inflammation occurs as a result of inflammatory cell infiltration and interactions between various cell mediators and cytokines [25]. This inflammation causes smooth muscle contraction, submucosal edema, and hypersecretion of mucus, which can lead to airway remodeling and irreversible structural and functional changes [26].

In COPD, which is mainly caused by smoking, inflammation is caused by alveolar macrophages, CD8-positive T cells (Th1), and eosinophils, primarily involving the peripheral airways and alveolar regions [2,27,28]. This leads to peripheral airway fibrosis and narrowing, and alveolar destruction. Factors involved in the mechanism of onset include exposure to noxious gases, proteinase/antiproteinase imbalance, and oxidant/antioxidant imbalance [2,29,30]. Apoptosis occurs in the lung tissue of COPD patients and plays a role in the development of emphysematous lesions [31].

Preoperative evaluation and management

Preoperative evaluation

Life-threatening episodes of asthma can occur during surgery [5,32–34]. Patients with coexisting COPD may develop postoperative respiratory complications, with a relative risk (depending on evaluation criteria) of 2.7–4.7 [4,35,36]. To increase safety in asthma and COPD patients, the anesthesiologist must take an adequate medical history and, when preoperative intervention is indicated, obtain early consultation and appropriate treatment. Preoperative evaluation of the patient includes: (1) activities of daily living (ADL) and physical status; (2) presence of infectious symptoms; (3) amount and purulence of sputum; (4) presence of allergies; (5) factors known to trigger attacks or exacerbations; (6) use and effectiveness of medications; (7) presence of late evening or early morning symptoms; (8) responses to cold air, house dust, and cigarette smoke; (9) previous history of surgery and anesthesia; (10) coexisting disorders (e.g., ischemic heart disease, renal failure, diabetes mellitus, neuromuscular disease); and (11) obesity or sleep apnea syndrome [1,2,32]. The GOLD 2006 guidelines emphasize that COPD not only involves the lungs but also represents a systemic inflammatory disorder [2]. COPD is highly prevalent in elderly patients, who must also be carefully evaluated for coexisting disorders such as weight loss and malnutrition, musculoskeletal problems, myocardial ischemia, osteoporosis, diabetes and depression.

Preoperative examination before the induction of anesthesia should include respiratory rate and rhythm, auscultation of both lung fields (presence or absence of adventitious lung sounds) and observation of respiratory rate and rhythm. This information is essential in the selection of perioperative anesthesia and for the early detection and treatment of any acute attacks or exacerbations. Shortness of breath (SOB) can be evaluated using the Fletcher-Hugh-Jones classification [37]. It is important to remember that elderly patients and those with chronic respiratory insufficiency may not complain of "dyspnea", so clinical evaluation should include laboratory testing. Hnatiuk et al. [38] questioned the need for routine preoperative pulmonary function tests, but these are indicated for asthma and COPD patients. The purpose of preoperative testing is not to detect early mild disease, but to predict the possibility of respiratory complications and to evaluate risk. Ultimately, this reduces the morbidity and mortality associated with respiratory complications and improves outcomes. Essential laboratory testing in asthma and COPD patients includes chest radiography, pulse oximetry oxygen saturation (Sp_{O_2}), pulmonary function tests (spirometry), and clinical biochemical tests [1]. Additional testing, if necessary, can include arterial blood gas analysis, measurement of theophylline levels, bronchodilator response, computed tomography or magnetic resonance imaging, airway hyperresponsiveness, diffusion capacity of carbon monoxide (DL_{CO}), and lung volumes (gas diffusion and body plethysmography), including total lung capacity (TLC) and residual volume (RV) [39]. In COPD patients undergoing lung resection, pulmonary gas distribution and exercise tolerance testing may also be indicated.

Forced vital capacity (FVC) and forced expiratory volume in 1.0 s ($FEV_{1.0}$) are determined from pulmonary function tests and used to calculate percent vital

capacity (%VC) and percent forced expiratory volume in 1.0 s ($FEV_{1.0}$%). These two indices are used to assess whether the pattern of ventilatory impairment is obstructive, restrictive, or a combination of both. Flow-volume curves can reflect anatomical and pathological changes, and COPD and asthma are each associated with characteristic convex patterns [40]. This can be useful in evaluating peripheral airway disease, which is difficult to detect by spirometry. Maximum expiratory flow rates ($\dot{V}_{max}$) at 50% and 25% of vital capacity are called the expiratory flow rates at 50% vital capacity ($\dot{V}_{50}$) and 25% vital capacity ($\dot{V}_{25}$). A decrease in these values or an increased $\dot{V}_{50}/\dot{V}_{25}$ ratio suggests peripheral (small) airway disease, an early finding in COPD [41,42]. Measurement of lung volume using body plethysmography shows an increase in RV during asthma exacerbations and an increase in RV and TLC in COPD. This test is difficult to perform on a routine basis, but inspiratory capacity (IC) measured by standard spirometry indicates air trapping in COPD and correlates well with exercise tolerance and severity of dyspnea [43–45]. Pulmonary diffusion capacity is often decreased in COPD, but is relatively well preserved in asthma [1,2].

Both the GINA and GOLD guidelines use disease-staging classifications that reflect differences in recommended treatments. To exclude the influence of age, sex, and body habitus, $FEV_{1.0}$ is divided by predicted $FEV_{1.0}$ to calculate the $FEV_{1.0}$% used to determine disease stage. Asthma and COPD can each be classified into four stages, based on frequency of symptoms, including nighttime symptoms and limitations in ADL [1,2]. Depending on symptom severity, treatment may include beta-2 adrenergic agonists and increases or decreases in steroid doses (step-up or step-down regimen). Due to variations in airflow limitation in asthma, portable peak flow meters are available for use at home or in outpatient emergency departments for repeated measurements of peak expiratory flow (PEF), to objectively evaluate and control symptoms [46]. PEF, when measured by patients using the same instrument and proper technique, correlates well with $FEV_{1.0}$% [47], so this is also used for disease-staging classification.

Spirometry is dependent on effort and if a patient lacks an understanding of the proper technique, considerable variation can be seen in measured values [48]. Arterial blood gas analysis is performed to more accurately evaluate gas exchange. Diagnostic criteria for respiratory insufficiency include Pa_{O_2} of 60 mmHg or less. Below this value, mixed venous oxygen pressure (Pv_{O_2}), which reflects systemic oxygen supply and demand, is below the normal limits of 35 mmHg [49]. COPD staging is an important prognostic factor [50–52], and prognosis is poor if respiratory insufficiency is present [53,54] (Fig. 2).

Chronic respiratory insufficiency is classified as type I if only hypoxemia is present and as type 2 if hypercapnia is also apparent. Arterial blood gas analysis is an invasive technique and repeated measurements are difficult unless an indwelling catheter is used. Pulse oximetry has gained widespread use for the measurement of Sp_{O_2} due to convenience and repeatability and so is routinely used in outpatient clinics. The respiratory status of COPD patients during sleep can also be evaluated.

Monitoring of transcutaneous carbon dioxide pressure (Ptc_{CO_2}) has recently been introduced into clinical practice [55,56]. Acute changes in Ptc_{CO_2} cannot be measured, but the placement of a probe on the ear lobe or chest wall can allow continued monitoring for 8–12 h [57,58]. Monitoring is easily performed, and a high correlation between Pa_{CO_2} and Ptc_{CO_2} has been reported [59,60]. In patients with respiratory tract disorders, end-tidal carbon dioxide pressure ($P_{ET_{CO_2}}$) may not reflect Pa_{CO_2} because of nonuniform gas exchange, so Ptc_{CO_2} can be used for intraoperative Pa_{CO_2} monitoring or for the preoperative evaluation of respiratory insufficiency [55].

Smoking is a risk factor both for lung cancer and COPD [61]. Treatment of lung cancer involves the lung tissue itself, so postoperative respiratory complications are common. Coexisting COPD increases the risk of postoperative complications and mortality [62]. Olsen et al. [63] described the usefulness of exercise testing using ergonometry to predict postoperative respiratory complications and mortality. Exercise tolerance involves an interaction between pulmonary and cardiac function and reflects gas exchange, ventilation, tissue oxygenation, and cardiac output, so evaluation is important. Ortega et al. [64] noted that the assessment of resting lung function by spirometry could not accurately predict exercise tolerance in patients with severe respiratory disease. However, the need to perform detailed testing in all patients remains contentious [65]. Evidence does suggest the importance of exercise tolerance testing in the perioperative management of patients with a history of respiratory symptoms affecting ADL. Even if pulmonary function test results are normal preoperatively, patients with poor exercise tolerance display a higher risk of postoperative complications [66]. A history of subjective symptoms and objective assessment is needed to evaluate preoperative risk.

Preoperative management

The preoperative management of asthma and COPD is described below, but as mentioned previously, these disorders display similar features and at times coexist. Recommendations in common for both disorders include avoidance of triggering factors (e.g., smoking),

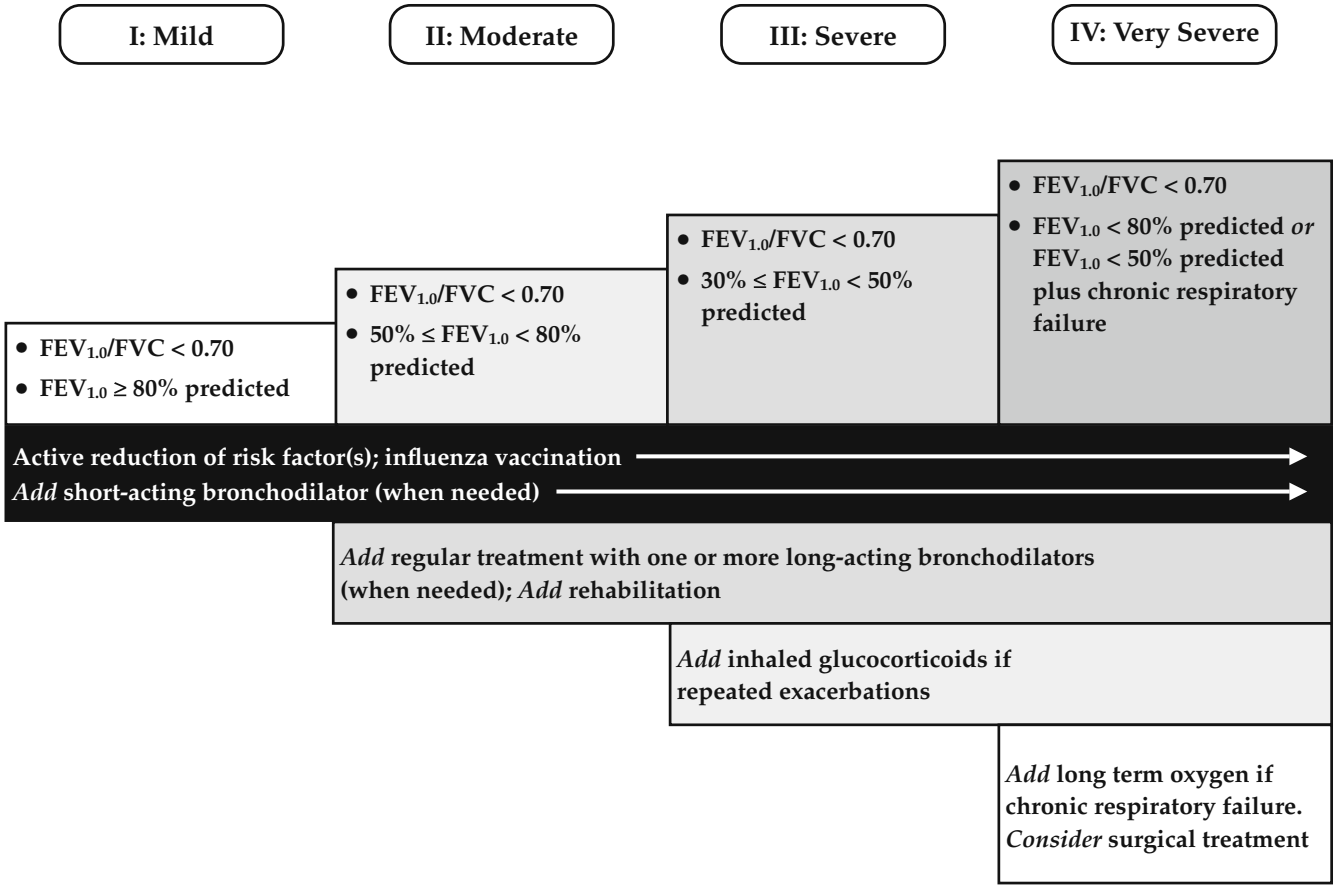

Fig. 2. Therapy at each stage of chronic obstructive pulmonary disease (COPD). Postbronchodilator forced expiratory volume in 1.0 s ($FEV_{1.0}$) is recommended for the diagnosis and assessment of severity of COPD. *FVC*, Forced vital capacity (from Rabe et al. [2], with permission)

pulmonary physiotherapy, control of respiratory infections, and fluid and electrolyte correction. However, preoperative pharmacotherapy in COPD consists of anticholinergic agents, whereas in asthma steroids and beta-2 adrenergic stimulants are used. COPD patients with malnutrition should receive supplemental nutrition, and obese asthma patients should lose weight.

Preoperative management of asthma

Asthma is more amenable to treatment than COPD and treatment can be started preoperatively. Bronchoconstriction can be controlled in asthmatic patients by the avoidance of specific antigens (mainly house dust mites) and the use of a beta stimulant and/or steroid inhaler in accordance with the guidelines [1]. The GINA guidelines state: "If $FEV_{1.0}$ values are less than 80 percent of the patient's personal best, a brief course of glucocorticosteroids is required to reduce airflow limitation" [67,68]. "Furthermore, patients who have received systemic glucocorticosteroids within the past 6 months should have systemic coverage during the surgical period (i.e., 100 mg hydrocortisone every 8 h intravenously) and rapidly reduced within 24 h following surgery. Prolonged glucocorticosteroid therapy inhibits wound healing" [69].

According to Enright [70], preoperative management in asthmatics should include the following measures:

1. Correction of fluid and electrolyte imbalance, given that high-dose beta-2 adrenergic stimulants can cause hypokalemia, hyperglycemia, and hypomagnesemia. In addition to this imbalance, a decreased response to beta-2 agonists and a predisposition toward cardiac arrhythmias may be present.
2. Continued prophylactic cromolyn treatment to prevent degranulation of mast cells and release of mediators.
3. Treatment of other conditions such as cor pulmonale.

Epidemiological surveys of asthma and obesity suggest that obesity increases the risk of asthma, particularly in women [71–74]. In patients scheduled for surgery, early consultation with an anesthesiologist is recommended. COPD patients with malnutrition should

be instructed on nutritional supplementation, and asthma patients with obesity should be advised to continue to exercise and lose weight before surgery.

Preoperative management of COPD

COPD is progressive, with little variation in symptoms, and it is generally irreversible, so preoperative management involves more general comprehensive treatment. The GOLD guidelines state: "To prevent postoperative pulmonary complications, stable COPD patients clinically symptomatic and/or with limited exercise capacity should be treated, before surgery, intensely with all the measures already well established for stable COPD patients who are not about to have surgery" [1]. The GOLD guidelines emphasize that cessation of smoking is the most effective way to prevent further disease progression (Table 2). Preoperative management is thus aimed at advising patients to quit smoking. Smoking not only affects the respiratory tract but also affects cardiovascular function and blood clotting factors [75]. Preoperative cessation of smoking decreases airway secretions and improves airway hyperresponsiveness and mucociliary transport within 2–4 weeks. Smoking cessation, even just prior to surgery, decreases carboxyhemoglobin levels and improves tissue oxygen utilization [76]. Smoking increases hemoglobin concentrations and platelet aggregation, thus increasing the risk of thrombosis [77].

The GOLD guidelines, created using evidence-based medicine, evaluated the effects of exercise, nutrition, patient education, and comprehensive pulmonary rehabilitation using physiotherapy on: (1) improving exercise tolerance; (2) decreasing dyspnea; (3) improving health-related quality of life (QOL); (4) reducing the numbers and days of hospitalization; and (5) reducing anxiety and depression as the highest level of evidence (A) and (6) improving survival rate as evidence level B [1]. In surgical patients as well, such pulmonary rehabilitation can also improve function in severe respiratory insufficiency [78], so preoperative pulmonary rehabilitation is important, including respiratory muscle training and abdominal breathing. Deconditioning and dyspnea in COPD patients leads to reduced food intake, muscle disuse, cachexia, and muscle wasting in the upper and lower extremities. Malnutrition is closely linked to overall condition and prognosis, so nutritional supplementation is clinically significant [1]. In patients with anorexia before surgery, nutritional supplements are important to improve body weight gain and function. The choice of nutritional supplements should include consideration of: (1) fats to improve gas exchange and respiratory quotient [79]; (2) omega fatty acids for antiinflammatory effects [80]; and (3) branched chain amino-acid (BCAA) supplementation of the amino-acid composition [81]. Bronchodilators include inhaled anticholinergic agents, inhaled beta-adrenergic stimulants, and oral or intravenous theophylline. GOLD does not specifically comment on a selection of or preference for specific agents [1]. Cholinergic tone mediated through the vagal nerve is the only reversible component in COPD, so anticholinergics represent the agents of first choice [82], but the use of multiple agents may improve efficacy and reduce adverse effects [83,84]. GOLD recommends "add-on" therapy to prevent decreased respiratory function over time in COPD patients [1], so bronchodilators used before surgery should be continued, with additional bronchodilator therapy, in conjunction with pulmonary consultation, for more severe symptoms. Matsuyama et al. [85] reported a reduction in postoperative complications in patients with long-term administration of tiotropium and the addition of other bronchodilators. Accumulation of secretions increases the risk of infection and airway hyperresponsiveness, so the preoperative reduction of mucous secretions is important. However, the guidelines raise some doubts about the usefulness of oral mucolytic drugs such as ambroxol hydrochloride and acetylcysteine [1,2,86]. Fluid replacement and the use of heated nebulizer solutions can reduce the viscosity of secretions.

Table 2. Brief strategies to help the patient willing to quit smoking

1. ASK: Systematically identify all tobacco users at every visit.
Implement an office-wide system that ensures that, for *EVERY* patient at *EVERY* clinic visit, tobacco-use status is queried and documented.
2. ADVISE: Strongly urge all tobacco users to quit.
In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. ASSESS: Determine willingness to make a quit attempt.
Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).
4. ASSIST: Aid the patient in quitting.
Help the patient with a quit plan; provide practical counseling; provide intratreatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.
5. ARRANGE: Schedule follow-up contact.
Schedule follow-up contact, either in person or via telephone.

From Rabe et al. [2], with permission

Informed consent and shared decision-making

The patient should receive careful explanation before surgery indicating that treatment options for COPD are more limited than in asthma. Patients prefer a definitive prognosis, and several studies have investigated safety thresholds for surgery. Schuurmans et al. [87] reported that patients undergoing lung resection who have an

$FEV_{1.0}$ of 50% or less of the predicted value and/or a DL_{CO} of 50% or less of the predicted value display a higher risk of intra- and postoperative complications. These thresholds cannot be determined based solely on the severity of the respiratory tract disease. Both the GINA and GOLD guidelines indicate a higher risk for upper abdominal and thoracic surgery near the diaphragm [1,2]. Other risk factors include smoking, general health status, age, and obesity in GOLD, and duration of surgery in GINA. Other relevant factors identified by our group to predict postoperative pulmonary complications include arterial blood gas analysis results and intraoperative blood loss. Our predicted score correlates well with postoperative pulmonary complication and mortality rates [88]. The possible need for postoperative respiratory care must be explained to COPD and asthma patients.

Concept of management

Important points in perioperative management include: (1) suppression of neural reflexes; (2) inhibition of increased intracellular Ca^{2+} concentrations in airway smooth muscle cells; (3) control of airway inflammation; (4) elimination of airway secretions; and (5) maintenance of the ventilation/perfusion ratio.

Suppression of neural reflexes

Airway contraction and relaxation is under the control of the autonomic nervous system. Vagal nerve impulses in the airway originate in the nucleus ambiguus of the brainstem; nerve ganglia are present in airway walls and postganglionic nerve fibers innervate airway smooth muscle, blood vessels, and secretory glands (Fig. 3) [89]. Acetylcholine, released by vagal stimulation, binds to muscarinic receptors to induce smooth muscle contraction in the airways. Intubation to secure the airway or improper anesthesia technique can activate the peripheral terminals of C-fiber afferents via axonal reflexes, causing the release of transmitters such as substance P and neurokinin A. This results in airway smooth muscle contraction [90–92] and increased vascular permeability and local vasodilation [93]. In addition, acetylcholine is released by the central nervous system via vagal efferents [5]. Our first goal as anesthesiologists is to suppress these neural reflexes in response to intubation and

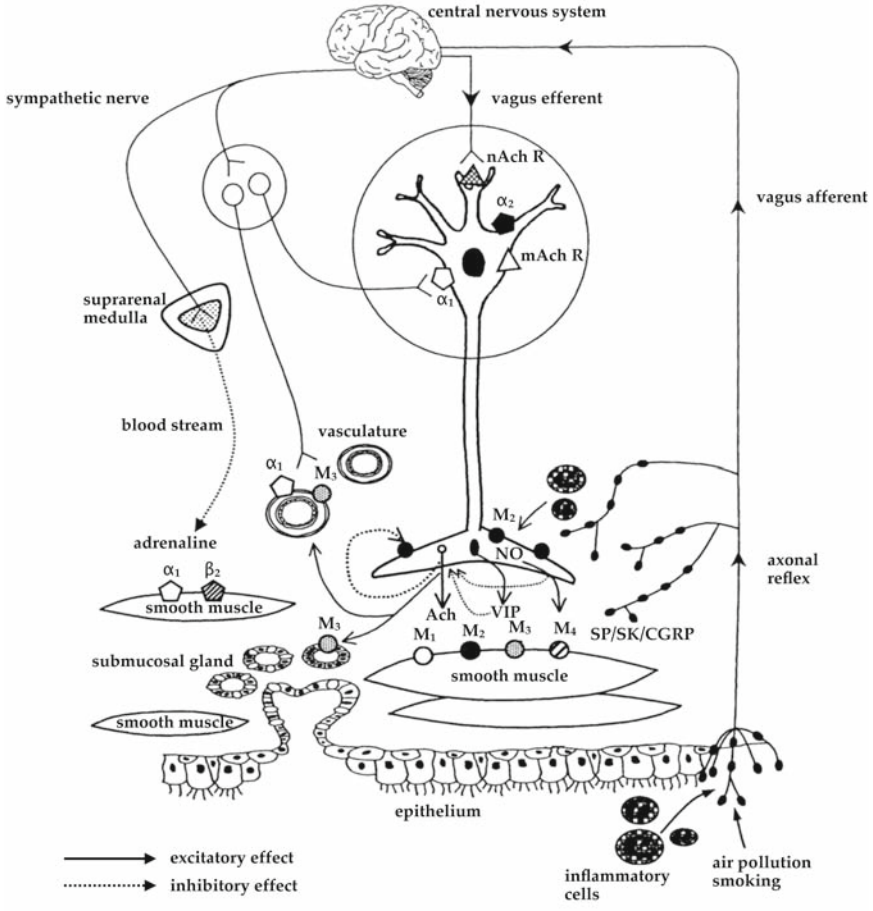

Fig. 3. Schema of autonomic nervous system controlling airway smooth muscle. *nAch R*, Nicotinic acetylcholine receptor; *mAch R*, muscarinic acetylcholine receptor; *NO*, nitric oxide; *VIP*, vasoactive intestinal polypeptide; *SP*, substance P; *SK*, substance K; *CGRP*, calcitonin gene-related peptide (modified from Langley [89], with permission)

surgical stimulation. The three main options are general anesthesia alone, regional anesthesia alone, or a combination of both. In surgery on the lower extremities when airway maintenance is not necessary, neural block (regional anesthesia) is preferable. In actual practice, however, there is often no choice between general anesthesia to maintain the airway and regional anesthesia. Lower risk has been reported with spinal or epidural anesthesia compared to general anesthesia, but a lack of consensus exists on this issue [1]. Inadequate anesthesia can induce vagal reflexes, so, rather than regional anesthesia, preventive methods against airway contraction, the use of inhalational anesthetics and the intravenous anesthetic propofol, and the selection of suitable opioid and neuromuscular blocking agents (NMBAs) can decrease anesthetic risk. Epidural block is effective for postoperative analgesia, but decreased respiratory function due to paralysis of the diaphragmatic or respiratory muscles remains a concern. Groeben et al. [21] performed high thoracic segment epidural anesthesia in COPD and asthma patients undergoing breast surgery and reported only small decreases in $FEV_{1.0}$. Kalko et al. [94] also reported that epidural anesthesia for abdominal aortic aneurysm repair through minilaparotomy was feasible and should be seriously considered in patients with severe COPD when endovascular treatment cannot be performed. In patients with severe COPD with $FEV_{1.0}$ of 50% or less, Savas et al. [95] reported that abdominal surgery could be safely performed using regional anesthesia alone. Spinal and epidural anesthesia represent attractive options for planning anesthesia in patients in whom intubation should be avoided. Flores et al. [96] reported good results using combined spinal and epidural anesthesia in COPD patients undergoing infrarenal repair of abdominal aortic aneurysm.

Inhibition of increased intracellular Ca^{2+} concentrations in airway smooth muscle cells

The contraction of airway smooth muscle is regulated by acetylcholine released from vagal nerves, catecholamines released by the adrenal glands, and histamine derived from mast cells [8]. Acetylcholine released by vagal stimulation binds with muscarinic receptors (mAChR) in airway smooth muscle. This increases excitatory junctional potentials and intracellular Ca^{2+} concentrations and causes contraction (Fig. 4) [89]. Increased intracellular Ca^{2+} concentrations in airway smooth muscle cells occur via the following mechanism: (1) L-type voltage-dependent calcium channels in cell membranes open by the depolarization of airway smooth muscle cells, resulting in extracellular to intracellular Ca^{2+} movement and (2) the binding of acetylcholine to M_3-mAChR, via G proteins, activates phospholipase C and produces inositol triphosphate (IP_3). IP_3 then causes the release of Ca^{2+} from the sarcoplasmic reticulum. The increased intracellular Ca^{2+} interacts with contractile proteins (actin and myosin), leading to smooth muscle contraction [7]. Our second goal as anesthesiologists is to prevent these increases in intracellular Ca^{2+} concentrations. Parasympathetic muscarinic receptors in the lung and trachea include M_1, M_2, M_3, and M_4 subtypes [97]. M_1 receptors located in the parasympathetic ganglia promote neural excitation. M_2 receptors in parasympathetic postganglionic nerve terminals provide negative

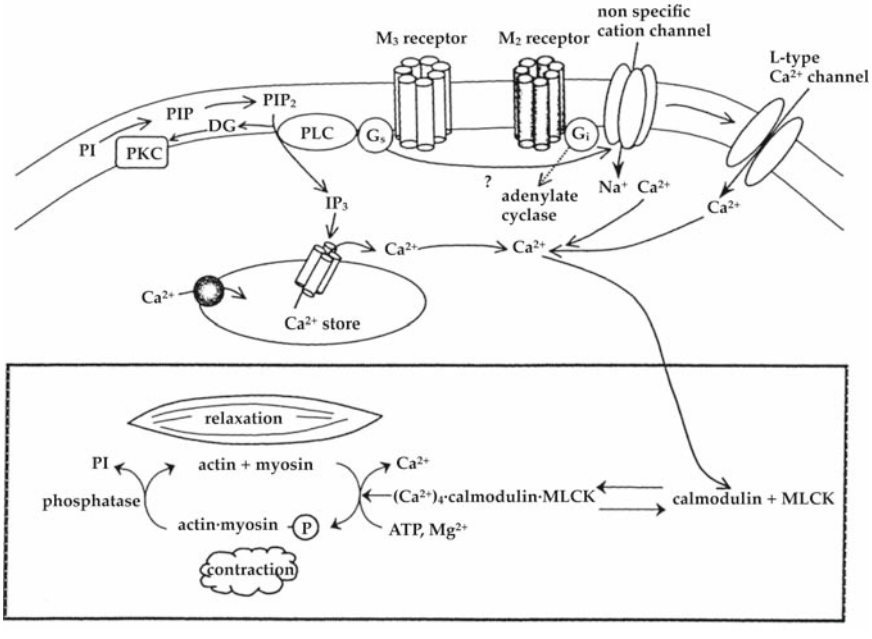

Fig. 4. Schema showing mechanisms of airway smooth muscle contraction by M_3 and M_2 acetylcholine receptors. *PI*, Phosphatidyl inositol; *PIP*, phosphatidyl inositol phosphate; *PIP_2*, phosphatidyl inositol diphosphate; *DG*, diacyl glycerol; *PKC*, protein kinase C; *PLC*, phospholipase C; *G_s*, stimulatory G protein; *G_i*, inhibitory G protein; *IP_3*, inositol triphosphate; *MLCK*, myosin light chain kinase; *ATP*, adenosine triphosphate (modified from Langley [89], with permission)

feedback to decrease the release of acetylcholine. M_3 receptors in airway smooth muscle play a role in smooth muscle contraction. Control can be achieved by stimulating M_2 receptors or by blocking M_3 receptors.

Airway smooth muscle cell membranes possess numerous beta-2 receptors and when agonists bind with these receptors, intracellular cyclic adenosine monophosphate (AMP) increases and intracellular Ca^{2+} concentrations decrease, resulting in smooth muscle relaxation. To reduce perioperative cardiac complication and mortality rates, the American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend beta-1 blockers [98]. Although commonly used to treat intraoperative tachycardia, beta-blockers also have a beta-2 receptor-blocking effect, causing smooth muscle contraction. Using short-acting and selective beta-1 adrenergic blocking agents (e.g., landiolol and esmolol), we have demonstrated in vitro and in vivo safety in patients with asthma [99].

Four histamine receptors are known (H_1-H_4) and each is a 7-transmembrane G-protein-coupled receptor. H_1 receptors couple to phospholipase C via $G_q/11$ protein and stimulation of this receptor increases intracellular Ca^{2+}. Anesthetic agents include some with histamine-releasing effects. Avoiding the administration of these agents is important.

Research has been performed on highly specific calcium antagonists for airway smooth muscle to prevent increases in intracellular Ca^{2+} concentrations, but none of these agents are currently clinically available [100].

Control of airway inflammation

The perioperative period is associated with the systemic inflammatory response syndrome with hypercytokinemia [101]. Asthma and COPD are both chronic inflammatory disorders of the lungs, so control of lung inflammation is essential. The systemic administration of steroids before surgery reduces the risk of asthma attacks and inhibits the production of cytokines in the lung parenchyma [102]. Asthma attacks and acute exacerbations of COPD are closely linked to cytokine production [1,2], so steroid doses should be based on surgical stress factors, including duration of surgery and amount of bleeding.

Elimination of airway secretions

In patients with heavy sputum production, secretions should be removed by endotracheal intubation. Intraoperative suction of the airways can cause vagal reflexes, so anesthesia should be deep. Fluid management is important not only preoperatively but also intra- and postoperatively.

Maintenance of ventilation/perfusion ratio

Worsening of the ventilation/perfusion ratio decreases arterial oxygenation, so central venous pressure or pulmonary arterial pressure should be monitored when administering fluids.

Intraoperative management of bronchial asthma and COPD

Premedication

Stress is closely related to the development of asthma [103,104]. In patients with mild asthma with preoperative anxiety, the use of sedatives is a reasonable choice. Oral benzodiazepines can be safely used in pediatric patients with asthma [105]. In vitro studies have shown that benzodiazepines inhibit airway contraction [106,107]. However, because of their dose-dependent effects on the inhibition of tidal volume and minute volume [108], the preoperative administration of benzodiazepines should be avoided in patients with severe asthma or COPD [109]. The administration of sedatives during asthma attacks has been linked to some deaths [1]. The administration of atropine is supported by its inhibitory effects on vagal reflexes, but some experts advise against using this drug, because the viscosity of airway secretions can also be increased. Although clear-cut evidence is lacking, atropine may be effective against airway contraction when vagal reflexes are an important factor [110,111].

In the future, preoperative inhalation of anticholinergic agents that are highly selective for M_3 receptors may play a more prominent role in premedication [112].

Airway management

When using general anesthesia, the anesthesiologist must select whether to use a face mask, airway instrumentation such as a laryngeal mask airway, or tracheal intubation. However, tracheal intubation can cause marked stimulation of the airways and oropharynx [113,114]. To prevent increased airway resistance or postoperative respiratory complications with tracheal intubation, bronchodilators, steroids, and lidocaine can be used. Inhaled beta-2 adrenergic stimulants before tracheal intubation have been reported to prevent increased airway resistance [115,116]. Conversely, another study reported that in healthy children, administration of beta-2 stimulants or anticholinergic agonists during anesthesia induction did not decrease respiratory adverse events [117]. The preoperative combination of corticosteroids and inhaled salbutamol can significantly reduce the incidence of wheezing after

tracheal intubation in patients with reversible airway obstruction [118]. In addition, the combination of intravenous lidocaine and salbutamol in patients with airway hyperreactivity is much more effective than either agent alone [119]. Albuterol protects against intubation-induced bronchoconstriction in asthma, whereas intravenous lidocaine has no effect [120]. Groeben et al. [121] found that both inhaled and intravenous lidocaine attenuated bronchoconstriction, but this effect was achieved at lower plasma concentrations with inhalation. They also reported increased airway resistance in healthy subjects immediately after inhaled lidocaine, and so they recommended intravenous administration before securing the airway.

Ventilator settings

Neither the GINA [1] nor the GOLD [2] guidelines specifically mention ventilation methods, but to avoid increases in airway pressure and barotrauma associated with volume-control ventilation, we use pressure-control ventilation. Alkalinization of the extracellular pH in vitro inhibits airway smooth muscle contraction [122,123]. In patients with severe respiratory acidosis, excessive ventilation decreases Pa_{CO_2} and causes alkalosis (post-hypercapnic alkalosis). Not only can this lead to a worsening of bronchoconstriction but cardiovascular complications such as arrhythmia may also occur [124]. Darioli and Perret [125] advocate the use of mechanical controlled hypoventilation.

Of course, no-one recommends hypoxemia, but in vitro research has demonstrated that relaxation of airway smooth muscle occurs in the event of hypoxemia [126]. Positive end-expiratory pressure (PEEP) improves oxygenation, but it should not be used during an asthma attack, to prevent auto-PEEP (Fig. 5). However, auto-PEEP usually exists in COPD patients because of the fragile elastic components of their lungs. Pressure-controlled ventilation with optimal PEEP is often useful so as not to increase the closing volume due to auto-PEEP. Perioperative oxygen concentrations should be based on systemic oxygen demand.

Airway warming and humidification

Exercise increases ventilation volume and exercise-induced bronchoconstriction can develop due to airway cooling and loss of moisture [2]. However, direct inhalation of water can also induce asthma [127]. Airway warming and humidification using an artificial nose is important [128].

Choice of anesthetics

Inhalational anesthetics

Inhalational anesthetics have inherent bronchodilator effects [6–8]. These effects are mediated by the regulation of voltage-dependent calcium channel activity, by an increase in intracellular cyclic (c) AMP via beta receptors, and by a decrease in intracellular Ca^{2+} concentrations, leading to the relaxation of smooth muscle. Sevoflurane and isoflurane are widely used anesthetics and are appropriate for use in patients with obstructive lung disease. These agents are sometimes used for status asthmaticus, which is refractory to medical therapy [129,130]. Some inhalational anesthetics such as desflurane are unsuitable for anesthesia induction in patients with severe airway hyperreactivity [131,132]. This is due to the respiratory tract irritation caused by these inhalational anesthetics. Sevoflurane is suitable for anesthesia induction by volatile anesthetic [133]. The bronchodilator effects of isoflurane and sevoflurane are more prominent in the peripheral airways than in the central airways [134], and these effects can be useful in COPD with peripheral airway involvement. Volta et al. [135] reported that isoflurane and sevoflurane decreased respiratory system resistance in COPD patients.

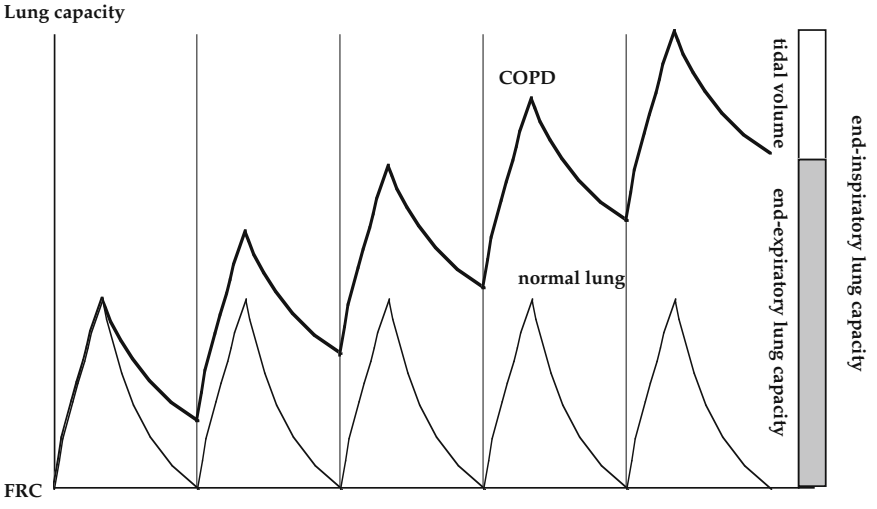

Fig. 5. Dynamic hyperinflation in patients with chronic obstructive pulmonary disease (COPD). Dynamic hyperinflation can be aggravated by artificial ventilation during general anesthesia. *FRC*, Functional residual capacity

Intravenous anesthetics

The intravenous anesthetic propofol has a protective effect against increased airway resistance during tracheal intubation [9]. The mechanism involves direct or vagally mediated relaxation of airway smooth muscle [136–140]. Barbiturates, as compared to propofol, produce weaker inhibition of airway contraction [141,142], and when used alone, may actually induce airway smooth muscle contraction [9]. Ketamine has bronchodilatory effects [140] and is suitable for tracheal intubation in asthmatic patients [143]. Because ketamine increases airway secretions, however, propofol is preferable as an intravenous anesthetic.

Opioids

Opioids should be administered to suppress the cough reflex and to achieve deep anesthesia [144]. However, prolongation of these effects can cause postoperative respiratory depression. Remifentanil is ideal because no drug accumulation occurs [145]. All opioids have some histamine-releasing effects [10], but fentanyl and analogous agents can be safely used in patients with obstructive ventilatory impairment [146,147]. The use of opioids during intubation can prevent increased airway resistance. However, muscle rigidity due to opioid administration can decrease lung compliance and functional residual capacity (FRC), thus impairing ventilation [148,149]. Opioid-induced muscle rigidity can be decreased by the combined use of intravenous anesthetics and neuromuscular blocking agents (NMBAs) [150].

NMBAs

NMBAs are selected based on three criteria: (1) affinity for M_2 and M_3 receptors; (2) histamine-releasing effects; and (3) duration of action. NMBAs with greater affinity for M_2 receptors than M_3 receptors (pipecuronium and rapacuronium) can induce and worsen bronchoconstriction [151]. However, NMBAs with more affinity, or at least equivalent affinity, for M_3 receptors (vecuronium, rocuronium, pancuronium) can be safely used. Atracurium and mivacurium display dose-dependent histamine-releasing effects and can cause bronchoconstriction [152]. Rocuronium usually has no prolonged postoperative effects and is preferred in Japan.

Reversal of neuromuscular blockade

Nondepolarizing NMBAs may cause postoperative residual curarization [153,154] and should be carefully selected to minimize postoperative residual curarization if administered perioperatively to patients with asthma or COPD. Anticholinesterase drugs (neostigmine or physostigmine) that inhibit NMBAs also increase airway secretions and induce bronchospasm, so some experts recommend avoiding these agents in patients with obstructive respiratory disease [155]. Conversely, with the addition of atropine, these drugs have been safely used in COPD patients [156]. Slow injection of a neostigmine ($40\,\mu g \cdot kg^{-1}$)-atropine ($10\,\mu g \cdot kg^{-1}$) mixture could safely be used for patients with airway hyperreactivity if needed [156]. The administration of rocuronium, whose metabolites have no muscle-relaxation effects, can help to avoid the use of anticholinesterase drugs. Some anesthesiologists believe that if remifentanil is used, the perioperative administration of NMBAs may be unnecessary (administration of atracurium or cisatracurium during intubation does not hamper cardiac surgery) [157]. In these cases, use of an antagonist can also be avoided.

Sugammadex (Org 25969, Schering-Plough, Kenilworth, NJ, USA), a novel reversal agent for steroidal nondepolarizing NMBAs, potently binds at a 1:1 ratio to reverse muscle relaxation [158]. The drug has no anticholinesterase activity and can be safely used in patients with severe airway hyperresponsiveness.

Local anesthetics

Lidocaine can be safely used for epidural anesthesia [93]. Bupivacaine or ropivacaine can also be used safely [21].

Treatment of intraoperative bronchospasm

Differential diagnosis

The differential diagnosis of intraoperative bronchospasm as listed in both the GINA and the GOLD guidelines includes mechanical obstruction of the tracheal tube, endobronchial intubation, pulmonary aspiration, pulmonary embolism, pulmonary edema, tension pneumothorax, negative-pressure inspiration, anaphylaxis, adrenal crisis, and heart failure [1,2]. Chest auscultation, $S_{P_{O_2}}$, arterial blood gas analysis, airway pressure, and capnometer CO_2 waveforms are useful in the differential diagnosis. Adequate oxygenation should be ensured. Secure the airway if this has not been performed previously and deepen the anesthesia if necessary.

Beta-2 adrenergic stimulants

Beta-2 stimulants are administered by inhalation or intravenously [159]. Compared to anticholinergics, beta-2 stimulants are less effective against COPD [160]. The efficacy of salmeterol [161–165] and formoterol [165,166] has been demonstrated clinically. When inhaled beta-2 stimulants are administered to patients undergoing mechanical ventilation during surgery, the use of a spacer (e.g., AeroVent, Monaghan Medical, Plattsburgh, NY, USA) is effective. GINA does not

recommend the use of epinephrine [1]. Some COPD patients with significant airway reversibility (asthmatic component) may display wheezing on forced expiration. In such patients, even if COPD is present, beta-2 stimulants may be effective. If adequate bronchodilation is achieved with a beta-2 stimulant, the addition of an inhaled anesthetic may have no further effect [167].

Corticosteroids

GOLD 2006 defines COPD exacerbation based on clinical symptoms and signs as follows: "An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD (*Table 1*) [2]."

Based on this definition, the perioperative administration of steroids is appropriate [168]. Steroids can be given by inhalation or intravenously [169]. The benefit of inhalation is a reduction in adverse reactions, but the drug may not reach the peripheral airways if mucous secretions are thick. In such cases, systemic (intravenous) administration is preferable.

Anticholinergics

Anticholinergics are also administered by inhalation or intravenously [170]. Reversible airway constriction in COPD patients depends mainly on acetylcholine derived from the vagal nerve. Anticholinergics thus represent the most effective drugs for monotherapy in COPD patients. The mechanism involves the inhibition of M_3 receptors in airway smooth muscle. In severe asthma, anticholinergics can be coadministered with, or in lieu of, beta-2 stimulants, if discontinuation of the latter is necessary due to severe adverse effects.

Extubation

Both the GINA and GOLD guidelines recommend criteria for extubation [1,2]. Controversy remains as to whether extubation should be performed when patients are fully awake or when they are still under anesthesia. However, a risk of aspiration exists if patients are extubated before complete recovery.

Postoperative management

Postoperative analgesia (epidural anesthesia) is useful to block afferent pathways mediating pain from abdominal viscera, in order to maintain respiratory muscle function. The use of epidural anesthesia with local anesthetics increases tidal volume and vital capacity and preserves diaphragmatic function during thoracotomy or laparotomy. A recent metaanalysis [171] reported that, compared with systemic opioid administration, the injection of opioids into the epidural space decreased postoperative atelectasis, but the overall incidence of pulmonary complications was not decreased. Compared with systemic opioids, the epidural injection of local anesthetics was associated with a reduction in postoperative pulmonary infections and complications. In another study, postoperative analgesia did not significantly change the incidence of pulmonary complications [172]. At present, no consensus has been reached regarding systemic opioid administration or drugs for use in the epidural space. There is no doubt, however, that appropriate postoperative analgesia increases patient QOL.

Respiratory rehabilitation should be performed by a team of physicians, nurses, physiotherapists, nutritionists, and pharmacists, together with the patient's family, if necessary. The head tilt-up position is preferable to prevent atelectasis. Postoperative control of the amount of sputum, and recovery and maintenance of ventilatory gas exchange become possible with early respiratory rehabilitation, leading to prevention of complications, recovery of the ADL, and early discharge from hospital.

Conclusions

We have discussed the perioperative management of patients with airway hyperresponsiveness based on recent guidelines for bronchial asthma and COPD. Recommendations include: (1) adequate control of airway hyperresponsiveness, including detection of purulent sputum and infection before surgery; (2) evidence-based control of anesthesia; and (3) aggressive treatment of acute attacks, including the use of anticholinergics in COPD, the use of beta-2 adrenergic stimulants in asthma, and the systemic administration of corticosteroids. Good preoperative control, including the use of leukotriene antagonists, can reduce the incidence of life-threatening perioperative complications. Anesthesiologists should be aware of recent guidelines for the proper management of patients with airway hyperresponsiveness.

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