Case Scenario: Bronchospasm during Anesthetic Induction

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Case Report

A 25-yr-old woman with morbid obesity (body mass index: 54 kg/m²) and noninsulin-dependent diabetes was scheduled for cochlear implant surgery. She had two previous surgeries without incident during childhood. She denied any history of atopy or drug allergy. Chest auscultation was normal before anesthesia. She was premedicated with hydroxyzine (100 mg orally) the day before and 1 h before anesthesia, which was induced with sufentanil (20 µg intravenously) and propofol (350 mg intravenously). Tracheal intubation (Gormack and Lehane grade I) was facilitated with succinylcholine (130 mg intravenously). After tracheal intubation was performed, chest auscultation revealed a complete absence of bilateral breath sounds. Initial concentrations of end-tidal carbon dioxide (ETCO₂) were low. Because an esophageal intubation was suspected, the patient was immediately extubated and mask ventilation attempted. Mask ventilation was difficult to perform because of dramatically decreased lung compliance, whereas ETCO₂ demonstrated a marked prolonged expiratory upstroke of the capnogram. Therefore, bronchospasm was considered. Rapid arterial oxygen desaturation (oxygen saturation measured by pulse oximetry [SpO₂], 55%) followed by arterial hypotension (from 130/75 to 50/20 mmHg) associated with moderate tachycardia (100 beats/min) while at the same time ventilation became easier to perform along with the return of audible wheezing over both lung fields. As arterial blood pressure was restored, a localized erythema occurred. Hydrocortisone (200 mg) was intravenously administered. A blood sample was obtained to measure serum tryptase concentrations, 40 and 90 min after the clinical reaction. Surgery was post-

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poned, and the patient was transferred to the intensive care unit. No additional supportive vasopressor therapy was required. Respiratory symptoms resolved within 2 h after inhaled β2-agonist (salbutamol; i.e., albuterol) and intravenous corticoids (hydrocortisone, cumulative dose: 800 mg over 24 h). Subsequent clinical outcome was uneventful, and the patient was discharged home the following day and returned 6 weeks later for allergologic assessment (see section III).

Discussion

I. Diagnosis and Differential Diagnosis of Intraoperative Wheezing/Bronchospasm

Bronchospasm encountered during the perioperative period and especially after induction/intubation may involve an immediate hypersensitivity reaction including IgE-mediated anaphylaxis or a nonallergic mechanism triggered by factors such as mechanical (i.e., intubation-induced bronchospasm) or pharmacologic-induced (via histamine-releasing drugs such as atracurium or mivacurium) bronchoconstriction in patients with uncontrolled underlying airway hyperreactivity.1,2 Chest auscultation should be done to confirm wheezing, whereas decreased or absent breath sounds suggest critically low airflow.3 The differential diagnosis includes inadequate anesthesia, mucous plugging of the airway, esophageal intubation, kinked or obstructed tube/circuit, and pulmonary aspiration.3 Unilateral wheezing suggests endobronchial intubation or an obstructed tube by a foreign body (such as a tooth).3 If the clinical symptoms fail to resolve despite appropriate therapy, other etiologies such as pulmonary edema or pneumothorax should also be considered.

II. Diagnosis of a Perioperative Immediate Reaction

Immediate hypersensitivity is a clinical entity evoking allergy that varies in severity1 and is subdivided into nonallergic hypersensitivity (called anaphylactoid reaction by the American Academy of Allergy Asthma and Immunology) where an immune mechanism is excluded, and allergic hypersensitivity (also called IgE-mediated anaphylaxis).4 By definition, immediate hypersensitivity occurs within 60 min after the injection/introduction of the culprit agent.1 The initial diagnosis remains presumptive, whereas the etiologic diagnosis is linked to a triad including clinical features (the description of the clinical features according to the adapted Ring and Messmer clinical severity scale); blood tests (tryptase level measurements, serum-specific IgEs); and postoperative skin tests with the suspected drugs or agents.1

Grade I: Erythema, urticaria with or without angioedema; grade II: cutaneous-mucous signs ± hypotension ± tachycardia ± dyspnea ± gastrointestinal disturbances; grade III: cardiovascular collapse, tachycardia, or bradycardia ± cardiac dysrhythmia ± bronchospasm ± cutaneous-mucous signs ± gastrointestinal disturbances; grade IV: cardiac arrest.

III. Etiology of This Perioperative Immediate Hypersensitivity in the Current Case

The sudden occurrence of bronchospasm after anesthetic induction, with cardiovascular disturbances and cutaneous signs, clinically suggested a drug-induced anaphylactic reaction. Succinylcholine-induced anaphylaxis was the most likely etiology, because neuromuscular blocking agents are the most frequent agents involved in perioperative anaphylaxis in adults.1,5 Skin testing remained negative in response to propofol, sufentanil, succinylcholine, and latex solutions (Allerbio, Varennes en Argonne, France and Stallergènes, Antony, France). Tryptase levels (ImmunoCAP, Phadia SAS, Uppsala, Sweden) were unchanged (5.4, 4.3 µg·L⁻¹ and N less than 13.5 µg·L⁻¹) in blood samples obtained 40 and 90 min, respectively, after the onset of the reaction. Serum-specific IgEs (ImmunoCAP) against succinylcholine and latex were not detectable. Specific serum IgE against quaternary ammonium was slightly increased (2.08 kU/L, N less than 0.1). A basophil activation test was also performed and analyzed using a FACSCanto II flow cytometer (Becton-Dickinson, Rungis, France). Succinylcholine induced neither CD63 nor CD203c up-regulation.

Clinical Considerations. The chronology of evolving clinical features is crucial to understand the pathophysiologic mechanism of an immediate hypersensitivity reaction.

Cardiovascular disturbance is the hallmark of severe IgE-mediated anaphylaxis. In patients with neuromuscular blocking agent-induced perioperative anaphylaxis, cardiovascular signs are usually the inaugural clinical event and occur within minutes after the drug challenge. These cardiovascular signs may be associated with or followed by bronchospasm in 19–40% of patients, more likely in those with underlying asthma or chronic obstructive pulmonary disease.1 Drug-induced anaphylactic bronchospasm may occur either before or after instrumentation of the airway2 (fig. 1).

Latex-induced anaphylaxis typically occurs in patients with a history of atopy.9 Because atopy is the strongest identifiable predisposing factor for the development of asthma,7 severe clinical features occurring during latex-induced anaphylaxis usually involve cardiovascular signs followed by or associated with bronchospasm and cutaneous signs.5 As latex proteins are slowly absorbed, latex-induced anaphylaxis usually occurs up to 30–60 min after the beginning of surgery (i.e., mucous membrane exposure).8

Acute increases in airway responsiveness may also occur in the absence of an antigen challenge and result from irritation of the well-innervated upper airway by a foreign body (e.g., endotracheal tube or suction catheter).2 Thus, nonallergic bronchospasm immediately follows nonspecific stimuli and usually is not associated with cardiovascular symptoms9 (fig. 1). Nevertheless, positive end-expiratory pressure with severe bronchospasm may lead to a decrease in venous return and hence of cardiac output. In addition, the association of hypoxia and respiratory failure from inadequate ventilation may lead to cardiovascular collapse.9
IV. Distinguishing the Pathophysiologic Mechanism of Perioperative Bronchospasm Clinically

Four clinical variables were identified as independent predictors of allergic compared with nonallergic perioperative bronchospasm: the presence of any cutaneous symptoms; shock; episodes of desaturation; and the prolonged duration of clinical features (longer than 60 min). Compared with that of patients who did not present with these “predictive” signs as part of the clinical syndrome, the occurrence of hypotension or episodes of oxygen desaturation were 27 and 21 times, respectively, more likely to be associated with IgE-mediated anaphylaxis. In addition, symptom duration longer than 60 min or the presence of skin changes was two and seven times, respectively, more likely to be associated with IgE-mediated anaphylaxis. In the current case, inaugural severe bronchospasm triggered by endotracheal tube insertion and followed by cardiovascular collapse, likely related to subsequent hypoxemia after the patient’s extubation, yields clinical insight into the pathophysiologic mechanism of the reaction and suggests nonallergic bronchospasm. Cutaneous signs, such as erythema, are not specific for IgE-mediated anaphylaxis per se and may also be observed during nonallergic bronchospasm. The morbid obesity of the patient is of clinical interest and could also have been a precipitating factor of rapid arterial desaturation despite appropriate preoxygenation.

Allergologic Assessment: Blood Tests and Skin Testing. A tryptase increase is specific for mast cell activation such as that occurring during IgE-mediated anaphylaxis. Increased tryptase levels appear to distinguish clearly between allergic and nonallergic perioperative bronchospasm. Thus, Fisher suggested that an allergologic assessment is unnecessary in patients with isolated bronchospasm occurring after airway instrumentation without an increase in tryptase. In the current case, allergic mast cell activation was ruled out because tryptase levels measured within the recommended time frame remained unchanged. Skin tests were negative in response to the medications received (i.e., propofol, sufentanil, and succinylcholine) as well as latex. These results were corroborated by basophil activation tests showing an absence of CD63 and CD203c up-regulation with succinylcholine, ruling out basophil sensitization by specific IgE toward succinylcholine and undetectable specific serum IgEs against succinylcholine. Serum IgEs against quaternary ammonium was slightly increased (2.08 kU/L, N less than 0.1), but these assays appear to be less sensitive than skin tests and do not prove that the drug/agent is responsible for the reaction.

Succinylcholine-induced anaphylaxis was therefore ruled out according to clinical, biologic, and allergologic evidence. This is of particular importance because succinylcholine is thereby allowed to be used for future anesthetics in this patient. In turn, uncontrolled asthma was suggested to be the main trigger of this nonallergic bronchospasm after endotracheal tube insertion. Wheezing induced by bronchial infection during childhood or triggered by cold weather and exercise in adulthood was elicited from the patient’s history during the postoperative evaluation.

V. Asthma Is a Frequently Underdiagnosed Condition

Asthma is one of the most common chronic airway diseases worldwide, with a higher prevalence and incidence in the Western world. The estimated annual death rate worldwide is 250,000. However, this condition frequently remains underdiagnosed. In 2008, the following definition for
Asthma was suggested: “Asthma is a chronic disorder of the airway in which many cells and cellular elements play a role. The chronic inflammation is associated with airway responsiveness 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, that is often reversible either spontaneously or with treatment.” This proposal was ratified in the United States. Accordingly, a European and American Task Force issued by the corresponding Respiratory Societies suggested that the definition of asthma includes two domains (symptoms and variable airway obstruction) being assessed in clinical practice, with two additional domains (airway inflammation and hyperresponsiveness) characterizing the underlying disease. An individual may have features of any or all of these domains.13 Airway hyperresponsiveness is induced by a variety of changes in the airway and sustained by underlying airway inflammation, the hallmark of asthma.

Recently, a crucial modification in the approach to asthma management was proposed with a classification by the level of asthma control (controlled, partly controlled, or uncontrolled) rather than asthma severity per se while linking the classification of asthma control to asthma treatment.12

**Two Main Phenotypes of Asthma Can Be Distinguished.**
Two main phenotypes of asthma, allergic and nonallergic, are most commonly discussed; overlap may occur within these groups.14

**Allergic Asthma.** The largest overall phenotype in children and adults is allergic asthma. Although allergic asthma is a chronic and often lifelong disease, its onset occurs primarily in early childhood. However, more than 50% of asthma is allergic in adults.4 It results from immunologic reactions, mostly initiated by IgE antibodies, and is also called IgE-mediated allergic asthma. Genetic factors may promote the development of allergic asthma (inheritable component). Environmental factors such as tobacco smoke, air pollutants, and exposure to allergens including indoor (mites, animals, plant pollen, e.g., flicus), outdoor (pollens, molds) or occupational allergens may trigger asthma. Obesity, diet, and a hygiene hypothesis may also trigger asthma.11 Thus, any potential risk factor must eventually interact with an underlying genetically determined pathway to result in the manifestation of disease (epigenetic component). However, atopy, the genetic predisposition for the development of an IgE-mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma.7 Two major factors such as airborne allergens and viral respiratory infections seem to be the most important in the development, persistence, and possibly the severity of allergic asthma.7

**Allergic Rhinitis and Allergic Asthma Belong to the Same Airway Disease.** The effect of allergic rhinitis on asthma should also be highlighted15 because the link of this disturbance with asthma remains poorly understood. Rhinitis is characterized by nasal symptoms including sneezing, nasal blockage, and/or itching of the nose; is either intermittent or permanent; and is classified as mild, moderate, or severe.15 More than 80% of asthmatic individuals have rhinitis, and 10–40% of patients with rhinitis have asthma. A combined strategy should ideally be used to treat the upper and lower airways (allergen avoidance is crucial but inhaled/intranasal corticosteroid is the most consistently effective long-term control therapy attenuating airway inflammation).7,15 Because the presence of asthma must be considered in all patients with rhinitis, those with severe and/or persistent uncontrolled allergic rhinitis should be evaluated for asthma before surgery.

**Nonallergic Asthma: Aspirin-induced Asthma.** The other main variant of asthma in adults includes a widely underdiagnosed phenotype not seen in childhood, such as aspirin-induced asthma. Aspirin-induced asthma is characterized by eosinophilic rhinosinusitis, nasal polyposis, aspirin or nonsteroidal antiinflammatory drug sensitivity, and asthma. Asthma and sensitivity to aspirin usually appear approximately 1–5 yr after the onset of rhinitis,16 whereas rhinorrhea, nasal congestion, and anosmia are usually the first clinical features of aspirin-induced asthma. This phenotype results from the inhibition of cyclooxygenase enzymes by aspirin-like drugs in the airway of sensitive patients and is not sustained by an allergic mechanism.16

**VI. Perioperative Bronchospasm**
Asthma is considered to be more prevalent in westernized countries.11 Surprisingly, no academic society of anesthesiology issued from the European or the North American continent has published recommendations concerning the perioperative management of the asthmatic patient. The literature on this topic remains scarce.

**Epidemiology of Perioperative Bronchospasm.** The occurrence of perioperative bronchospasm has been reported in up to 9% of asthmatic patients given general anesthesia, mainly after endotracheal tube insertion.17 Smoking also represents a major risk. Compared with that of nonsmokers, the relative risk of perioperative bronchospasm in smokers appears higher in females and in young smokers (16–39 yrs old) and is higher in patients with chronic bronchitis than in asymptomatic patients.18

**Why and When Does Perioperative Bronchospasm Occur?** Of the 4,000 incidents reported in Australia, 103 reports of perioperative bronchospasm (3%) showed that an allergic mechanism was less frequently involved (21%) than a nonallergic mechanism (79%).19 Among these nonallergic cases, 44% occurred during the induction of anesthesia, 36% during the maintenance phase, and 20% during the emergence/recovery stage. During induction of anesthesia, bronchospasm was mainly related to airway irritation (64%), whereas remaining causes were due to tube misplacement (17%), aspiration (11%), and other pulmonary edema or unknown causes (8%). During the maintenance stage of anesthesia,
allergy (34%), endotracheal tube malposition (23%), airway irritation (11%), and aspiration with a laryngeal mask airway (9%) together accounted for almost 80% of the occurrences of bronchospasm. During induction or maintenance of anesthesia, bronchospasm caused by airway irritation occurred more frequently in patients who had one or more predisposing factors such as asthma, heavy smoking, or bronchitis. Others showed that an allergic mechanism accounted for 60% of the cases in patients experiencing bronchospasm during induction of anesthesia.2 A previous history of asthma was present in 50% and 60% of patients with nonallergic and allergic bronchospasm, respectively. Thus, uncontrolled asthma/chronic obstructive pulmonary disease is frequently involved with either pathophysiologic mechanisms (allergic vs. nonallergic), regardless of the stage of anesthesia (induction or maintenance).

Morbidity and Mortality Rates. Respiratory events accounted for 28% of claims concerning anesthesia-related brain damage and death in the United States.20 In this series, bronchospasm was included in the other categories and together corresponded to 11% of total respiratory events. In the United Kingdom, respiratory and airway incidents accounted for 3% and 8%, respectively, of all claims including severe and fatal outcomes.21 Bronchospasm was not detailed. Nevertheless, airway incidents belong to the claims with the highest overall cost and respiratory complications with the highest mean cost per closed claim. Seven percent of anesthesia-related deaths were attributed to bronchospasm in France.22

In conclusion, bronchospasm remains a serious life-threatening perioperative event. Its dramatic consequences involving brain damage or death may be partly explained by substandard care and/or inadequate practice and system failures.20,22 Optimal management of perioperative bronchospasm should therefore be encouraged through teaching applications such as an anesthesia simulator to compensate for the low frequency with which the average practitioner would encounter severe bronchospasm during routine clinical care.

Basic Science: Mechanisms of Reflex-induced Bronchoconstriction. The mechanisms of asthmatic exacerbations resulting in bronchoconstriction are complex and involve airway nerves, smooth muscle, epithelium, and inflammatory cells. However, reflex-induced bronchoconstriction induced by irritation of the upper airway by a foreign body such as an endotracheal tube is modulated by synapse of afferent sensory pathways in the nucleus of the solitary tract, which projects to the airway-related vagal preganglionic neurons. The excitatory neurotransmitter glutamate modulates the excitatory outflow from the airway-related vagal preganglionic neurons back to the airway is common to obesity and asthma phenotypes have been identified. Reduced functional residual capacity and decreased tidal volume as a result of obesity result in greater contractile responses of airway smooth muscle, causing potentially in-
Increased airway reactivity.\(^{34-35}\) Although gastroesophageal reflux resulting from obesity may potentially trigger a latent asthmatic condition,\(^{11}\) this condition was ruled out with an esophageal transit test.

Hormonal influences may also be involved as the effect of obesity on asthma is stronger in females than males.\(^{35}\) In addition, the hormone leptin produced by adipocytes and that acts in the hypothalamus to signal satiety\(^ {35}\) has effects on immune cell function and inflammation. Serum leptin levels in adulthood were shown to be higher in women than men with a higher prevalence of asthma.\(^ {34}\) The association between asthma and obesity may be of recent origin, suggesting that recent changes in lifestyle and diet are now associated with both asthma and obesity.\(^ {11}\) However, weight gain antedates asthma or asthma symptoms, ruling out the hypothesis that this association might be the result of reduced physical activity by asthmatic patients leading to obesity.\(^ {34}\)

**VIII. Sleep-disordered Breathing and Asthma**

Sleep-disordered breathing is more prevalent in asthmatic individuals than in those without asthma, whereas sleep-disordered breathing and asthma share common risk factors such as obesity.\(^ {35}\) The reasons for the association between both conditions remain unknown.\(^ {35}\) Asthma remains underdiagnosed in obese patients because respiratory symptoms are frequently attributed to being overweight, as was the case in our patient. In such patients, underlying airway hyperreactivity should be cautiously assessed during the preoperative evaluation (see section IX).

In the current case and after the clinical postanesthetic evaluation, borderline sleep-disordered breathing was also detected through polysomnography.

**IX. Prevention of Perioperative Bronchospasm**

The controls of airway inflammation and corresponding asthma symptoms are essential to optimize perioperative and postoperative care. The National Asthma Education and Prevention Program Expert Panel Report 3 recommends that the level of asthma control, medication use (especially oral systemic corticosteroid within the past 6 months), and pulmonary function be reviewed before surgery.\(^ {7}\) The Global Initiative for Asthma guidelines suggest that perioperative and postoperative complications rely on the severity of asthma at the time of surgery, the type of surgery (thoracic and upper abdominal surgeries being at increased risk), and modalities of anesthesia (general anesthesia with tracheal intubation is at higher risk).\(^ {12}\) Others suggest that uncontrolled or poorly controlled asthma may be assessed through the degree of asthma control (increased use of inhaled short-acting \(\beta_2\)-agonists, previous/current use of inhaled corticosteroids, recent use of oral/injected corticosteroids, recent exacerbations of asthma symptoms, emergency department or hospital visit within the last months) and potential risks or complication factors (recent infection of the respiratory tract, previous bronchospasm after intubation, pulmonary complications during/after previous surgical procedure, long-term use of a systemic corticosteroid for severe asthma, associated gastroesophageal reflux or smoking).\(^ {36}\) The common key point of these recommendations focuses on the level of asthma control before surgery.
surgery.7,12,36 as uncontrolled asthma is considered to be the main risk factor for bronchoconstriction during surgery.36

Preoperative Clinical and Physical Examination. Careful clinical and physical examinations are therefore crucial for preoperative pulmonary risk assessment to identify findings suggestive of unrecognized underlying airway hyperreactivity. Decreased breath sounds as seen in markedly decreased expiratory airflow, sibilants, rhonchi, and prolonged expiratory phase, as well as recent and/or frequent exacerbations of respiratory symptoms including wheezing, cough, exercise intolerance, unexplained dyspnea, and gastroesophageal reflux disease should raise concern during the preoperative evaluation.3 Among these different findings, decreased breath sounds, dullness to percussion, wheezing, rhonchi, and a prolonged expiratory phase predict an increase in the risk of perioperative pulmonary complications.37 Thus, poorly controlled asthma usually favors perioperative pulmonary complications,3,36,38 whereas airway instrumentation may induce life-threatening bronchospasm, perioperative complications, and prolonged intensive care treatment.20 Conversely, controlled asthma does not promote additional risk.36,38

Corticosteroids Are the Key Point of Antiasthma Long-term Control Therapy. Long-term therapy is used daily to achieve and maintain asthma control. Asthma is an inflammatory condition. Thus, inhaled glucocorticosteroids are currently the most effective antiinflammatory drug for the treatment of persistent asthma.7,12 Glucocorticosteroids reduce asthma symptoms, improve lung function, decrease airway hyperreactivity, modulate airway inflammation, and reduce asthma exacerbations and asthma mortality.11,12 Inhaled long-acting β2-agonists (formoterol, salmeterol) should never be used as single therapy because these β2-agonists improve lung function without antiinflammatory effects.12 Thus, significant clinical concerns regarding an increase in asthma-related deaths in patients on long-acting β2-agonists39 have led to revisions of product labels by the United States Food and Drug Administration stating that long-acting β2-agonists should never be used concomitantly inhaled corticosteroid therapy.40 Thus, β2-agonists are most efficient when combined with glucocorticosteroids, when inhaled glucocorticosteroids alone fail to relieve asthma symptoms.7,12,36 Corticosteroids increase the bronchodilatory effect of β2-agonists and increase the number of β2-adrenergic receptors and their response to β2-agonists.41 In turn, rapid-acting inhaled β2-agonists are used for quick relief of acute asthma exacerbations.7,12 Additional studies are necessary to determine whether iotropium and possibly other long-acting anticholinergic agents are effective and safe alternatives to long-acting β2-agonists for the long-term treatment of asthma.42

Preoperative Pulmonary Evaluation. In the presence of active bronchospasm, elective surgery should be postponed. The cause and corresponding clinical symptoms should be actively treated until baseline status is achieved.3 Patients should be free of wheezing, cough, or dyspnea.36 Individuals having symptoms suggestive of asthma, outside the context of an emergency situation, should undergo preoperative assessment performed by pulmonologists to assess the degree of airway reactivity and optimize preoperative treatment. Measurement of lung function to prove airflow limitation and the demonstration of reversibility of lung function abnormalities enhance diagnostic confidence.12 Forced expiratory volume in 1 s (FEV1) or peak expiratory flow (PEF) are valid measures of airway caliber and better indicators of the severity of asthma exacerbation than clinical symptoms.7,12 FEV1 (normal is approximately 80–100% of predicted) expressed as a percentage of the vital capacity is the standard index for assessing and quantifying airflow limitation. Reversibility with the use of a bronchodilator is defined as an increase in FEV1 of at least 12% or 200 ml. FEV1/forced vital capacity (normal is greater than 75%) appears to be a more sensitive measure of severity and control.1 In turn, a peak flow meter, which measures the highest expiratory flow rate in liters of air expired per second or per min (normal is greater than 80% of predicted), is designed for monitoring due to the wide variability in reference values.7,12 Before surgery, PEF or FEV1 greater than 80% of the predicted or personal best is recommended.38 If PEF or FEV1 is less than 80%, a brief course of oral corticosteroids should be considered to reduce airflow limitation.12 Patients with asthma who are also smokers have poorer control of asthma.36 Abstinence from smoking before surgery reduces perioperative pulmonary complications rates. At least 2 months of preoperative cessation is required to drastically reduce perioperative pulmonary complications risk.38 A stepwise approach of either initiation or optimization of asthma treatment according to the level of asthma was proposed into either five12 or six steps7 reflecting increasing intensity of treatment required to achieve asthma control (table 1). Combined with educational and environmental measures, therapy for asthma is subdivided into two categories (quick-relief and long-term control treatment). Briefly, rapidly acting β2-agonist should be prescribed as needed at each step. The first step concerns patients with occasional daytime symptoms where rapid acting β2-agonist may be sometimes requested. The second through fifth steps concern a pattern of features involving partly controlled to severely uncontrolled asthma where regular treatment is requested. Low-dose inhaled corticosteroid is recommended for the second step. The combination of a low-dose inhaled corticosteroid with an inhaled long-acting β2-agonist or a medium- or high-dose inhaled corticosteroid with an inhaled long-acting β2-agonist is recommended for the third and fourth steps, respectively. Oral corticosteroids may be useful when added to other medications during the fifth step, which concerns patients with frequent exacerbations and daily lim-

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Expert Panel Report 3

**Global Initiative for Asthma**

- Low-dose inhaled corticosteroid
- Medium-dose inhaled corticosteroid combined with an inhaled long-acting β₂-agonist
- Medium- or high-dose inhaled glucocorticosteroid with an inhaled long-acting β₂-agonist
- Addition of oral glucocorticosteroids to other controllers

Table 1. Stepwise Approach for Asthma Treatment

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<th>Level of Asthma Control</th>
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<th>Treatment</th>
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<td>At each step, short-acting β₂-agonist is recommended as needed</td>
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X. Treating Perioperative Bronchospasm

The aims of treatment are to relieve airflow obstruction and subsequent hypoxemia as quickly as possible.

**General Measures.** When isolated perioperative bronchospasm occurs, oxygen concentration should be increased to 100%, and manual bag ventilation immediately started to evaluate pulmonary compliance and to identify all causes of high-circuit pressure.

Inhaled Short-acting β₂-Selective Agents Belong to Immediate Therapy. Short-acting β₂-selective agents (mainly using terbutaline and salbutamol) are key drugs for the fast relief of bronchoconstriction. Their onset of action occurs within 5 min, peak effect is within 60 min, and duration of action is 4–6 h. They should be immediately administered via a nebulizer (8–10 puffs to achieve appropriate therapeutic levels, may be repeated at 15- to 30-min intervals) or, if available, with a metered-dose inhaler (5–10 mg/h) connected to the inspiratory limb of the ventilator circuit. There is no difference in efficacy between terbutaline and salbutamol.

Continuous rather than intermittent administration of salbutamol results in greater improvement in PEF and FEV₁. Moreover, nebulized epinephrine has no beneficial effect compared with terbutaline or salbutamol.

**Systemic Glucocorticosteroids Should Not Be Omitted.** Parenteral steroids also remain a key drug in the treatment of bronchospasm because they speed resolution of exacerbations by decreasing airway inflammation. Systemic glucocorti-
Corticosteroids such as methylprednisone (1 mg·kg⁻¹) are preferred over cortisone because their antiinflammatory effect is more potent. However, the antiinflammatory benefit is not immediate.

### Alternative Agents

The use of an antimuscarinic inhaled medication (e.g., ipratropium bromide) has been shown to attenuate reflex-induced bronchoconstriction with efficacy similar to inhaled β₂-agonists. Thus, combined nebulized ipratropium bromide (0.5 mg 4–6 times hourly) with a nebulized β₂-agonist produces greater bronchodilatation than a β₂-agonist alone and may be used to treat life-threatening bronchospasm or in those with a poor initial response to β₂-agonist treatment. Magnesium plays a beneficial role in the treatment of asthma through bronchial smooth muscle relaxation, leading to the use of intravenous (single dose of magnesium sulfate: 2 g over 20 min) or inhaled preparations (doses from 110 mg to 1,100 mg) in patients with severe bronchospasm that fails to be relieved with β₂-agonists. Accordingly, salbutamol administered in isotonic magnesium sulfate provides greater benefit when compared with that diluted with saline. Intravenous aminophylline has no indication in acute bronchospasm because its use does not result in additional bronchodilatation, whereas adverse effects such as arrhythmia and vomiting have been reported when intravenous aminophylline was used.

### Therapeutic Rationale for Epinephrine

Epinephrine should be used in cases of associated cardiovascular collapse suggestive of IgE-mediated anaphylaxis. During isolated bronchospasm, its inhaled/systemic use is not recommended because no study has proven its efficiency when compared with β₂-agonists such as salbutamol or terbutaline and deleterious adverse effects, including takotsubo cardiomyopathy, have been reported during asthma care. Others propose systemic epinephrine but emphasize that no advantage has been proven of systemic therapy over nebulization. Currently, no recommendations regarding epinephrine can be proposed, except that its use would be reasonable as a rescue therapy in patients with severe asthma complicated by hypotension that is not secondary to dynamic hyperinflation. Elective surgery should be postponed unless bronchospasm persists at baseline despite maximal medical optimization of the patient and further care provided in a monitored setting.

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**Fig. 3.** Stepwise approach to treatment of perioperative bronchospasm according to the clinical scenario. * May be used in life-threatening bronchospasm or those with a poor initial response to β₂-agonist; † may be used in cases of severe bronchospasm that fails to relieve with β₂-agonist; ‡ for further details, see Reference 1.
remain poorly understood.

nerves and directly modulate airway smooth muscle tone
the role of tachykinins and other C fiber neurotransmitters in
the interaction between anesthetics, airway irritation, and
Basic science advances are needed in the understanding of
pared with airway devices such as the laryngeal mask airway.
higher risk of morbidity in the perioperative period com-
specifically the assumption that intubation of the trachea carries
bronchoconstriction have not been rigorously studied, spe-
tors. Moreover, basic assumptions regarding the manage-
matic patients and those with chronic obstructive pulmonary
Anesthesiology 2011; 114:1200–10 Dewachter
XI. Knowledge Gap

Although factors contributing to airway inflammation in
asthma are multiple and not completely understood, factors
trigerging perioperative bronchospasm are identified. Both
basic science and clinical research efforts could improve the
prevention and treatment of bronchospasm associated with
anesthesia. Clinical research leading to the prevention of
bronchospasm will require a better identification of patients
at risk and then a better classification of the phenotypes,
therapies, and level of control of asthma in patients during
the preoperative period. Nevertheless, it should be ques-
tioned whether perioperative bronchospasm is a clinical en-
tity of its own occurring in predisposed patients (e.g., asth-
matic patients and those with chronic obstructive pulmonary

dease or acute bronchitis) and triggered either by mecha-
nical, pharmacologic, or inflammatory (i.e., anaphylaxis) fac-
tors. Moreover, basic assumptions regarding the manage-
gement of general anesthesia in patients at risk for
bronchoconstriction have not been rigorously studied, spe-
cifically the assumption that intubation of the trachea carries
a higher risk of morbidity in the perioperative period com-
pared with airway devices such as the laryngeal mask airway.
Basic science advances are needed in the understanding of
the interaction between anesthetics, airway irritation, and
the role of tachykinins and other C fiber neurotransmitters in
the control of airway tone. Moreover, the mechanisms by
which intravenous and inhaled anesthetics affect airway
nerves and directly modulate airway smooth muscle tone
likely involve modulation of plasma membrane ion channels,
membrane potential, and intracellular calcium sensitivity but
remain poorly understood.

In our patient, extubation was performed because of
suspected esophageal intubation. Verification of correct
endotracheal tube position would have been the appropri-
ate procedure. The patient’s extubation was associated
with oxygen arterial desaturation and subsequent hemo-
dynamic disturbances.

Table 2. Example of Targeting Questions to Identify
Patients at Risk with Undiagnosed Airway Hyperreactivity

Do you smoke?
Do you have gastroesophageal reflux disease?
Have you ever felt chest tightness or difficulty catching
your breath? If so, at rest or with physical effort?
Have you ever been told that you have wheezing or
asthma?
Have you ever used an inhaled medication for your
breathing?
Have you ever visited an emergency department for
breathing problems?
Have you ever had frequent bronchitis?
Have you ever had rhinitis?
Do you frequently cough?
Do you have allergies to latex or tropical fruits (kiwi,
banana, papaya, avocado)?

An international consensus promoted by the different

Anesthesiology 2011; 114:1200–10 Dewachter et al.

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