Chronic obstructive pulmonary disease

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Purpose of review
Chronic obstructive pulmonary disease (COPD) is a common cause of primary hospital admission and also a common coexisting disease among surgical patients. This translational review focused on recent studies related to the perioperative care of COPD patients.

Recent findings
In addition to the crucial role of smoking cessation, the use of corticosteroids, antibiotics, regional anesthesia techniques and noninvasive ventilation has become a focus in the perioperative management of the COPD patient.

Summary
Perioperative management as well as modern intensive care concepts are based on avoidance of tracheal intubation if possible, use of regional anesthesia techniques and the early liberation from invasive mechanical ventilation. Noninvasive ventilation has become more and more utilized in recent years to stabilize patients with acute exacerbations of COPD and to treat postoperative pulmonary complications in order to avoid reintubation.

Keywords
anesthesia, chronic obstructive pulmonary disease, mechanical ventilation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is pathophysiologically characterized by an expiratory airflow limitation that is not fully reversible to antiobstructive treatment. The causes of this airflow limitation are the narrowing of small airways (obstructive bronchiolitis) and destruction of lung parenchyma (emphysema) due to chronic inflammatory processes. Clinically, the COPD patient may present with shortness of breath or chronic coughing. COPD is a common comorbidity found in the perioperative setting, and may be even the reason for surgical interventions itself (e.g. volume reduction surgery or lung transplant), thus an anesthesiologist may face this on a daily basis. As a recent article in this journal nicely addressed the intraoperative management [1▪▪], the current review is focused on recent translational findings that may help to improve the perioperative care of COPD patients.

EPIDEMIOLOGY

Although COPD is primarily diagnosed in middle-aged to elderly people, often with a history of nicotine abuse, de Marco *et al.* [2▪▪] reported interesting epidemiological data in young adults regarding long-term outcomes of COPD based on the European community respiratory health survey. In that cohort study, young adults without asthma and with a diagnosis of mild-to-moderate COPD showed higher hospitalization rates and declined lung function depending on their smoking habits and respiratory symptoms [2▪▪]. In contrast to exacerbated COPD, the impact of nonexacerbated COPD on morbidity and mortality in critical ill has not been fully elucidated yet. In a prospective observational trial studying critically ill, ventilated patients, Rodríguez *et al.* [3▪] found that COPD patients without acute exacerbation had a higher mortality rate. However, COPD patients in that study were older, had further comorbidities and presented with higher APACHE scores compared with controls. Interestingly, the incidence of

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Curr Opin Anesthesiol 2012, 25:24–29
DOI:10.1097/ACO.0b013e32834dd269

KEY POINTS

- Preoperative cardiopulmonal conditioning may decrease perioperative risk in COPD patients.
- Regional anesthesia techniques and noninvasive ventilation should be considered to avoid tracheal intubation.
- If tracheal intubation is necessary, perioperative management should be focused on the early liberation from invasive mechanical ventilation.
- Mechanical ventilation should aim at avoiding pulmonary hyperinflation and intrinsic positive end expiratory pressure (PEEP).

ventilator-associated pneumonia did not differ significantly between the groups [3▪]. On the contrary, COPD has been identified as an independent risk factor for mortality in critically ill patients presenting with ventilator-associated pneumonia [4]. Furthermore, COPD has been associated recently with increased rate of early reintubation after surgery [5] as well as morbidity and mortality after major surgery [6]. In contrast, the VENTILA trial identified chronic pulmonary disease, but not COPD itself, as an independent risk factor for difficult and prolonged weaning from mechanical ventilation [7▪▪].

PATHOPHYSIOLOGY

In general, the anatomical changes associated with COPD include alterations in the proximal and distal airways, lung parenchyma and pulmonary vasculature, which are accompanied by systemic effects [8▪▪,9]. Table 1 illustrates the most common pathophysiological consequences associated with COPD. The role of the pulmonary vasculature and spatial distribution of perfusion has been possibly underappreciated in this disease. Vidal Melo *et al.* [10▪] demonstrated that COPD patients had a significant redistribution of pulmonary blood flow associated with increased heterogeneity of pulmonary perfusion compared with healthy individuals. Patients with pulmonary hyperinflation at rest show decreased stroke volume and cardiac output response under exercise conditions [11].

It is well established that smoking is one of the key noxious stimuli that lead to the development of COPD. Grumelli *et al.* [12] found that an increased expression of CD46 can protect ex-smokers from the development of COPD by protecting them from autoimmune reactions and development of chronic inflammation. Another study emphasized also the importance of LTA_4H, a proinflammatory enzyme that generates leukotriene B_4, in the pathogenesis of COPD [13]. Proline-glycine-proline (PGP), an important biomarker of COPD and substrate of LTA_4H, has been identified to be responsible for the persistence of neutrophils in the lungs yielding in chronic inflammation [13]. In acute inflammation, PGP was degraded by LTA_4H and therefore decreased inflammation. On the contrary, cigarette smoking inhibited LTA_4H, which led to the accumulation of PGP and the development of chronic inflammation. Consequently, blocking LTA_4H to reduce leukotriene B4 mediated inflammation may increase PGP levels and facilitate chronic neutrophil accumulation.

The COPDGene study, a large clinical trial consortium, has investigated the underlying genetic factors of COPD in more than 10 000 patients. Although smoking still remains a greater risk factor for the development of COPD, they reported a genetic variant (FAM13A) that was associated with the development of COPD [14].

In a further analysis, the COPDGene investigators reported greater lung emphysema and airway wall thickness, measured by computed tomography (CT) scans, were associated with COPD exacerbations independent from lung function, assessed by the severity of airflow limitation [15]. Holanda *et al.* [16] found that continuous positive airway pressure (CPAP) at least 10 cmH_2O resulted in increased emphysemateous hyperinflation, whereas CPAP of 5 cmH_2O was associated with regional lung deflation in some patients, as measured with high-resolution CT .

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND COEXISTING DISEASES

COPD is often associated with a broad range of coexisting diseases that may complicate the perioperative management of these patients. Due to the high percentage of smokers in the COPD population, it is not astonishing that this disease is also associated with the development of lung cancer. Furthermore, pre-existing COPD may decrease outcome after lung cancer diagnosis and treatment [17]. COPD has also been described as a contributing factor for the development of pulmonary arterial hypertension. Cuttica *et al.* [18] reported in 4930 COPD patients a prevalence of pulmonary arterial hypertension of around 30% . In their study, pulmonary arterial hypertension was an independent predictor for a reduced 6 min walk distance. Stone *et al.* [19] identified pulmonary arterial hypertension in COPD patients as an independent risk factor for 1-year mortality. Another frequent comorbidity in COPD patients is the overlap syndrome, which

Table 1. Pathophysiology of chronic obstructive pulmonary disease

Site	Consequence
Proximal airways (trachea, bronchi >2 mm ID)	
Cellular level	Chronic bronchitis
↑ Macrophages	Increased mucus production
↑ $CD8^+$ (cytotoxic) T lymphocytes	Decreased mucociliary clearance
↑ Goblet cells	Bronchial wall thickening
Structural changes	
Enlarged submucosal glands	
Squamous metaplasia of epithelial cells	
Peripheral airways (bronchioles <2 mm ID)	
Cellular level	
↑ Macrophages	Airway narrowing
↑ T lymphocytes ($CD8^+ > CD4^+$)	Obstructive bronchiolitis
↑ B lymphocytes and lymphoid follicles	Inflammatory exsudate
↑ Fibroblasts	Airway hyper-responsiveness
Few neutrophils or eosinophils	Bronchospasm
Structural changes	
Airway wall thickening	
Peribronchial fibrosis	
Luminal inflammatory infiltration	
Lung parenchyma (respiratory bronchioles and alveoli)	
Cellular level	
↑ Macrophages	Expiratory airway collapse
↑ $CD8^+$ (cytotoxic) T lymphocytes	Emphysema
Apoptosis of epithelial and endothelial cells	Fibrosis
Structural changes	
Alveolar wall destruction	
Centrilobular emphysema (commonly seen in smokers)	
Panacinar emphysema (commonly seen in α-1-antitrypsin deficiency)	
Pulmonary vasculature	
Cellular level	
↑ Macrophages	Pulmonary hypertension
↑ $CD8^+$ (cytotoxic) T-Lymphocytes	
Endothelial cell dysfunction	
Structural changes	
Intimal wall thickening	
Increased smooth muscle tone	
Systemic effects	
Chronic inflammation	Increased risk of pulmonary and systemic postoperative complications
Malnutrition	
Osteoporosis	

Modified with permission from [8■■] and [9].

describes the coincidence of COPD and obstructive sleep apnea. Marin *et al.* [20■] showed that patients with the diagnosis of overlap syndrome had an increased overall mortality as well as higher risk for hospitalization due to COPD exacerbations. Those authors found that CPAP treatment was associated with improved survival and decreased hospitalization rate. Although obesity contributes to various pathologies, the so-called obesity paradoxon has recently been introduced into the critical care literature. Different studies suggested that mortality in critically ill obese patients is similar or even decreased compared with nonobese patients [21–23]. The obesity paradoxon has been also demonstrated in a subgroup of COPD patients, admitted to an ICU for acute exacerbation [24]. Although this phenomenon is not fully elucidated yet, there are some interesting findings regarding obesity and improved respiratory mechanics that may contribute to these findings. Ora *et al.* [25■] suggested altered lung elastic properties, raised intra-abdominal pressure, reduced lung hyperinflation and preserved inspiratory capacity in obese patients. Another group showed that increasing BMI was associated with decreased lung hyperinflation and expiratory flow limitation as well as improved inspiratory capacity [26].

CORTICOSTEROIDS AND ANTIBIOTICS IN THE ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with acute exacerbation of COPD may benefit from systemic corticosteroids, but the appropriate dosage (low vs. high) and best route of administration (oral vs. intravenous) has been intensively debated. Recently, a pharmacoepidemiological cohort study conducted at 414 US hospitals reported similar effects of low-dose oral compared with high-dose intravenous steroids in acute exacerbated COPD [27].

Antibiotics may also be useful in such patients. Rothberg *et al.* [28] demonstrated that the early administration of antibiotics in patients hospitalized for acute exacerbation of COPD improved outcomes. Certainly, in acute exacerbation of COPD, postponing of elective surgery is justified.

PERIOPERATIVE PREPARATION AND CHOICE OF ANESTHESIA TECHNIQUE

One of the most important interventions capable of improving survival, especially in the preoperative period, is the sustained smoking cessation [29]. However, short-term preoperative pulmonary conditioning before major surgery has been also shown to improve outcomes. Dreger *et al.* [30■■] reported a significant reduction in the percentage of GOLD stage III and IV patients from 55.6 to 27.8% by applying a preoperative regimen including budesonide, salbutamol and ambroxol. Furthermore, avoidance of tracheal intubation will likely reduce the incidence of pulmonary complications in COPD patients, particularly the need for invasive mechanical ventilation in the postoperative period. Van Lier *et al.* [31■■] reported a 50% reduction in the risk of postoperative pneumonia when surgery was conducted with epidural anesthesia only in COPD patients. Accordingly, Abd Elrazek *et al.* [32] reported the well tolerated use of awake thoracic epidural anesthesia in two patients with severe COPD undergoing abdominal surgery. In addition, Kapala *et al.* [33] reported on the successful use of combined spinal–epidural anesthesia with noninvasive ventilation (NIV) in a patient with severe COPD undergoing elective sigmoid resection.

VENTILATORY SUPPORT OF THE PATIENT WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In COPD patients receiving mechanical ventilation, avoidance of dynamic hyperinflation and development of intrinsic PEEP is crucial [1■■,34]. This can be accomplished by the anesthetist by monitoring pressure and flow tracings at the ventilator. Breath-by-breath increase in airway pressures and cycling of the ventilator at expiratory flow higher than zero strongly suggest dynamic hyperinflation. Once intrinsic PEEP has been detected, it is important to find and individualize balance between decreased respiratory rate and increased tidal volumes. Alternatively, or additionally, a compromise between decreased inspiratory-to-expiratory time ratios and increased airway pressures must be found. Although prolonged expiratory times and external PEEP will likely decrease or even avoid hyperinflation, safety limits for peak airway pressures should be considered, especially in the presence of emphysemateous bullae to avoid the risk of barotrauma. These goals are more easily achieved with pressure than volume-controlled ventilation.

Due to ultrastructural changes in their lung architecture, COPD patients are at increased risk of ventilator-associated lung injury. Therefore, one can define three main objectives for the ventilatory management of those patients: to avoid invasive mechanical ventilation, to ventilate with lowest possible tidal volumes and pressures and to wean from the ventilator as fast as possible. The use of NIV is of particular interest in COPD patients. NIV has been shown to be effective to avoid both tracheal intubation during acute exacerbations and the need for reintubation in the postoperative period. Berkius *et al.* [35■] recently showed that the benefits of NIV lasted as long as 5 years after the initial treatment, provided patients did not undergo secondary intubation. NIV also proved to be beneficial if applied as long-term treatment after acute exacerbation in patients who remained hypercapnic [36]. Similar results were also reported by Machado *et al.* [37], who showed that CPAP treatment improves survival in COPD patients receiving long-term oxygen treatment.

Compared with invasive mechanical ventilation using a highly resistive tracheal tube, NIV is associated with resistive unloading of the respiratory system. Due to its lower density, helium can further reduce the resistance of gas flow, so that the combination of helium with NIV could be potentially useful to avoid intubation in acute exacerbation of COPD. However, such claim could not be confirmed in a recent multicenter trial [38]. Despite the concern that high-frequency oscillatory ventilation may favor air trapping and hyperinflation in COPD patients, Frerichs *et al.* [39] showed that this differentiated strategy can improve oxygenation and pulmonary compliance in patients who previously failed NIV during acute exacerbation of COPD and hypercapnic respiratory failure. Another modern approach to mechanical ventilation of COPD patients is the use of closed-loop systems, for example adaptive support ventilation. Iotti *et al.* [40] found that adaptive support results in higher tidal volumes, but lower airway pressures and respiratory frequencies, compared with conventional mechanical ventilation in COPD patients ventilated. Also, CO_2 removal was improved, whereas oxygenation did not differ significantly among groups. In addition, those authors suggested that adaptive support ventilation lowers minute ventilation and reduces the inspiratory work of breathing, at comparable blood gases [40].

Perhaps the most difficult task when ventilating COPD patients is the weaning from the ventilator. In a recent Cochrane Review, Burns *et al.* [41■■] could show that NIV consistently reduces mortality and the incidence of ventilator-associated pneumonia when used for weaning from mechanical ventilation. Recent evidence also suggests that weaning of COPD patients presenting with systolic arterial pressure of at least 140 mmHg can be facilitated by administration of intravenous nitroglycerine [42]. Such effect was ascribed to the capability of nitroglycerine to restore weaning-induced cardiovascular compromise.

CONCLUSION

COPD is a common cause of primary hospital admission and also a common coexisting disease in the perioperative setting. Due to the deterioration of pulmonary structure and function, mechanical ventilation is often challenging in those patients. Perioperative management as well as modern intensive care concepts are based on avoidance of tracheal intubation if possible, use of regional anesthesia techniques and the early liberation from invasive mechanical ventilation. The use of NIV has increased in recent years to stabilize patients with acute exacerbations of COPD and to treat postoperative pulmonary complications in order to avoid reintubation. When mechanical ventilation of the COPD patient cannot be avoided, ventilator settings should aim at avoiding pulmonary hyperinflation and development of intrinsic PEEP. Apart from investigating basic mechanisms of COPD, future studies are warranted to prove evidence for different mechanical ventilation strategies or combined pharmacological and ventilatory interventions.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 112–113).

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