Postoperative exacerbation of chronic obstructive pulmonary disease. Does it exist?☆

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Abstract

Background: One of the characteristics of chronic obstructive pulmonary disease (COPD) is the tendency to develop acute exacerbation, defined by the presence of different clinical findings as worsening dyspnea, increase in sputum purulence and volume. This study was designed to verify if definition of acute COPD exacerbation is applicable to patients who underwent pulmonary surgery, and if it has any impact on postoperative morbidity and mortality.

Methods: This study was designed to prospectively enrol 1000 patients undergoing pulmonary resection for lung cancer from five different centres. Postoperative exacerbation of COPD was defined by the concomitant presence of three of the following five signs: deteriorating dyspnea, purulent sputum, bronchial secretion volume >10 ml/24 h, fever without apparent cause, and wheezing. The presence of concomitant pulmonary complications excluded the diagnosis of exacerbation, as they may present one or more of these signs. Results: In the absence of respiratory complications, postoperative stay in exacerbated patients was significantly longer as compared to patients without exacerbation (6.3 ± 1.3 vs 8.3 ± 1.1, p = 0.001). A postoperative exacerbation of COPD was recorded in 276 patients and 152 of them (55%) subsequently developed respiratory complications. Multivariate analysis established that risk factors for postoperative exacerbation are sex (female OR 0.54, CI 0.2—0.8), COPD class (OR 1.5, CI 1.1—8.1), and the postoperative prolonged use of antibiotics (OR 0.6, CI 0.2—0.9).

Conclusions: Postoperative exacerbation of COPD is an existing, frequent clinical entity after lung resection and, when present, it increases the risk of pulmonary complications. The existing guidelines for the treatment of acute exacerbation should be adapted for the management of patients after lung resection in order to test the hypothesis that they could reduce respiratory morbidity.

Keywords: Lung surgery; COPD; Exacerbation

1. Introduction

Surgery remains the mainstay of treatment for lung cancer, which is a frequent cause of death among patients with chronic obstructive pulmonary disease (COPD) [1,2]. When COPD patients undergo lung surgery for lung cancer, their risk of developing respiratory complications is increased [3], as compared to patients with a normal respiratory function.

One of the characteristics of COPD is the tendency to develop acute exacerbation [4], defined by the presence of different clinical findings such as worsening dyspnea and the increase in sputum purulence and volume [5].

Soon after lung resection, many COPD patients develop symptoms that match the definition of COPD exacerbation. Even if these symptoms do not represent per se a postoperative complication, they could cause the need for more intensive assistance, may require specific treatments and could prolong hospital stay in some instances. As the entity of postoperative exacerbation of COPD does not exist, this study was designed to verify if the definition of COPD exacerbation is applicable to patients who undergo pulmonary surgery, and if it has any impact on postoperative morbidity and mortality.

2. Materials and methods

The hypothesis of this study was that (1) a certain proportion of COPD patients develop symptoms of COPD exacerbation after thoracotomy, (2) in such a case there is an impact on postoperative outcome.
Given an overall expected 2% increase in postoperative mortality in patients developing exacerbation, this study was designed to prospectively enrol 1000 patients undergoing pulmonary resection for lung cancer from different thoracic surgery centres.

2.1. Definitions

2.1.1. COPD

COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as the ratio $\text{FEV}_1/\text{FVC} < 70\%$ and a post-bronchodilator $\text{FEV}_1 < 80\%$ [6]. Four categories were defined: mild COPD ($\text{FEV}_1/\text{FVC} < 70\%$ and $\text{FEV}_1 \geq 80\%$), moderate COPD stage Ila ($\text{FEV}_1/\text{FVC} < 70\%$ and not $< 50\% \leq \text{FEV}_1 < 80\%$) and IIb ($\text{FEV}_1/\text{FVC} < 50\%$ and $30\% \leq \text{FEV}_1 < 50\%$), severe COPD ($\text{FEV}_1/\text{FVC} < 70\%$ and $\text{FEV}_1 < 30\%$).

2.1.2. COPD exacerbation

According to Anthonisen criteria, COPD exacerbation is defined by the presence of three main clinical findings (worsening of dyspnea, increase in sputum volume and increase in sputum purulence) and five other clinical criteria (upper respiratory infection in the preceding 5 days, fever without apparent cause, increased wheezing, increased cough, increase in respiratory rate or heart rate by 20% above the baseline) [5].

In order to apply these criteria to patients during the postoperative period, a multifactorial scoring system, the FLAM score [7,8] has been used to monitor, on a daily basis, seven clinical variables after lung resection (chest X-ray, oxygen need, dyspnea, quantity and quality of bronchial secretion, cough and chest auscultation). The score is briefly summarised in Table 1.

Postoperative exacerbation of COPD was defined by the concomitant presence of three of the following five signs: deteriorating dyspnea, purulent sputum, bronchial secretion volume $> 10\, \text{ml/24 h}$, fever without apparent cause, and wheezing. The presence of concomitant pulmonary complications excluded the diagnosis of exacerbation, as they may present one or more of these signs.

Other clinical signs mentioned in the Anthonisen definition were not useful in the postoperative setting. The increase in respiratory or heart rate by 20% above the baseline was not considered a parameter, as it is a frequent occurrence in the postoperative period, often due to pain or to preatrial fibrillation status. Upper respiratory infection in the preceding 5 days was not considered, as this would necessarily postpone elective surgery.

2.2. Population

The study population was composed of patients undergoing pulmonary resection for lung cancer in five different centres in France and Italy. After informed consent, all information on respiratory symptoms was collected. Patients with large volume ($> 10\, \text{ml/24 h}$) purulent secretions were excluded from the study and surgery was postponed until after antibiotic treatment. All patients had preoperative spirometry in accordance with ATS guidelines [9]. $\text{FVC}$ (expressed in litres), $\text{FEV}_1$ (l/s), total lung capacity (TLC, in litre) were expressed both as absolute values and as percentages of predicted values calculated for every patient on the basis of age, gender and height. TLC was assessed by the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
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<tbody>
<tr>
<td>Dyspnea: defined as a respiratory rate $\geq 20, \text{min}$ lasting more than 2 min or associated with a decrease in pulse oximetry $\geq 10%$ from the last value recorded</td>
<td>0 point: no dyspnea 5 points: dyspnea present only during chest physiotherapy or active mobilisation 10 points: dyspnea at rest</td>
</tr>
<tr>
<td>Oxygen</td>
<td>0–15 points: the highest rate of oxygen delivery (in number of litres of oxygen/min), to a maximum of 15 l/min, delivered over the previous 24-h period to maintain a haemoglobin saturation $\geq 94%$ as recorded by pulse oximetry 5 points: lobar atelectasis or lobar infiltrates 10 points: complete atelectasis, partial atelectasis after pneumonectomy, pneumonia involving the entire lung, and bilateral pneumonia</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>0 point: no abnormality 5 points: lobar atelectasis or lobar infiltrates 10 points: complete atelectasis, partial atelectasis after pneumonectomy, pneumonia involving the entire lung, and bilateral pneumonia</td>
</tr>
<tr>
<td>Quality of bronchial secretions</td>
<td>0 point: absent or mucous secretions 1 point: mucopurulent secretions 2 points: purulent secretions</td>
</tr>
<tr>
<td>Quantity of bronchial secretions</td>
<td>0 point: less than 5 ml/24 h 1 point: between 5 and 10 ml/24 h 2 points: greater than 10 ml/24 h</td>
</tr>
<tr>
<td>Cough</td>
<td>0 point: efficient 1 point: partially ineffective 2 points: ineffective</td>
</tr>
<tr>
<td>Auscultation</td>
<td>0 point: no anomaly 1 point: secretion soundings resolved by cough 2 points: secretion soundings not resolved by cough</td>
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The FLAM score for any given day was the sum of all seven parameters. The maximal possible score for patients without intubation was 43. Intubated patients were scored at 45 by definition.
helium dilution method. DLCO assessment (mmol/min/kPa), when performed, was determined by the single-breath technique utilising the Gaensler and Wright method [9].

The main differences in patient care between centres are listed in Table 2. French patients were referred to surgeons by their pneumologists and consequently COPD patients were on optimal treatment at the time of surgical advice. Management of COPD patients in Italy differed between centres. In one case (Turin), patients' respiratory preparation was managed by a pneumology department over a period of 3–4 weeks when needed. In the other two centres (EIO and NCI, Milan), the surgeon decided which patients needed a specific preoperative respiratory treatment.

2.3. Postoperative management

After short-term antibiotic prophylaxis, no routine antibiotic treatment was continued after thoracotomy in all centres but two, in which a 5-day antibiotic treatment with amoxicillin/clavulanate was routinely used. After surgery, the first chest drain was usually removed on POD 3, and the second on POD 4–5 if possible (fluid <200 cc/24 h, no air leak). Patients had two 15-min sessions of chest physiotherapy, daily for the first 7 postoperative days. All patients had daily FLAM score assessment for the first 7 postoperative days. The first evaluation of the FLAM score was performed during the ward round by the surgeon and was subject to modification during the day when further evaluations were obtained. When different scores were obtained for the same variable during the day, the maximum-recorded score was considered.

2.4. Postoperative complications

Postoperative death was defined as any death occurring during postoperative hospital stay or during the first month after surgery.

Respiratory complications were classified as follows: (1) acute respiratory failure, defined as postoperative ventilator dependence >12 h or reintubation for controlled ventilation; (2) ARDS, defined as respiratory failure with acute onset, \( \text{PaO}_2/\text{fraction of inspired O}_2 < 200 \text{ mmHg} \) and infiltrates seen on chest X-ray, pulmonary wedge pressure <20 [10]; (3) ALI, defined with the same criteria as ARDS but with \( \text{PaO}_2/\text{fraction of inspired oxygen} < 300 \text{ mmHg} \); (4) pneumonia, defined by the presence of at least three of the following criteria: persistent lung infiltrate on chest X-ray, fever >38°C, white cell blood count >10,000/mm\(^3\) or <3000/mm\(^3\), purulent secretions, documented presence of microorganisms on sputum or bronchoaspirate; (5) sputum retention, defined as lobar or whole-lung atelectasis requiring bronchoscopy; (6) pulmonary embolism documented by lung ventilation/perfusion scintigraphy or angioscan; (7) pulmonary edema, defined as a transient respiratory failure reversed by diuretics administration; and (8) chronic respiratory failure, defined as the need for continuous oxygen therapy for more than 1 month after discharge.

Other considered complications were cardiac (cardiac rhythm problems, angina, myocardial infarction, cardiogenic shock), surgical (hemothorax, bronchial fistula, empyema, chylothorax, cardiac dislocation) and others.

2.5. Study organisation

On July 4 2004, a meeting was held in Nice to explain the definitions, protocol of FLAM data collection and the use of the database. Six thoracic surgery departments participated: University Hospital of Nice, University Hospital of Bordeaux, Regional Hospital of Albuquerque, European Institute of Oncology, Milan, National Cancer Centre, Milan, and the University Hospital of Turin. Active recruitment started on September 1, 2004. After 2 months, Albuquerque decided to abandon the study. All information was sent to the coordinating centre (Nice) early after patient discharge. Data from patients with incomplete postoperative outcome records were excluded from the central study database. The study terminated on March 18, 2006; at that time, 1006 records had been sent to the coordinating center.

2.6. Statistical analysis

The clinical course of patients fitting the definition of postoperative exacerbation of COPD was analysed. In order to evaluate the impact of exacerbation on respiratory morbidity, postoperative data was analysed by dividing it into four groups categorised by a progressively worsening outcome: patients without exacerbation and without respiratory complications (RC), patients with exacerbation but without RC, patients without exacerbation but with RC, patients with exacerbation and RC. Comparison between groups was performed using Fisher’s exact test.

Postoperative exacerbation was considered as an outcome variable in a logistic regression model, using the following covariates (risk factors): referring centre, age, sex, smoking status, preoperative ASA score, induction chemotherapy and/or radiotherapy, FEV1%, postoperative analgesia, type of thoracotomy, antibiotic administration (short-term prophylaxis vs 5-day amoxicillin), duration and type of operation. The odds ratio and the corresponding 95% CIs were reported for covariates which were considered clinically relevant or statistically significant at the 0.05 significance level (Wald chi-square test). These were then successively included in the final multivariate model.
3. Results

Patients’ characteristics are listed in Table 3. Overall mortality was 3.7% (32 deaths), 1.5% after lobectomy (12/752), 8.6% after pneumonectomy (15/187) and 6.1% after sublobar resection (5/81), due to poor pulmonary function conditioning the choice of suboptimal lung resection (eight of them underwent sublobar resection for the treatment of lung cancer and concomitant severe emphysema). Mean postoperative stay was 7.9 ± 5.1 days. The respiratory complication rate was 23.4% (n = 236). No difference was detected in terms of the mortality and morbidity rate between centres, apart from a significant reduction in the postoperative pneumonia rate in the centres adopting standard antibiotic therapy (11.8%) as compared to the other three centres adopting short-term prophylaxis (18.2%, p = 0.01).

3.1. Incidence and outcome of COPD exacerbation

Postoperative exacerbation of COPD was recorded in 276 patients, 266 occurring within the first 72 postoperative hours. The most frequent clinical signs were worsening dyspnea, purulent secretions and wheezing. Radiological and laboratory findings did not show any specific pattern for exacerbation. Overall mortality and respiratory complication rates were increased in exacerbated patients (5.4% and 55%) as compared to patients who had no exacerbation (2.3% and 11.5%, respectively, p = 0.01 for both comparisons).

One hundred and twenty-four exacerbated patients had an otherwise uneventful hospital stay. Nevertheless, their hospitalisation was longer as compared to patients without exacerbation (6.3 ± 1.3 vs 8.3 ± 1.1, p = 0.001).

One hundred and fifty-two exacerbated patients developed one or more respiratory complication within 48 h after diagnosis of exacerbation. Comparing them to the 84 patients who developed respiratory complications without previous exacerbation, the study found that they had a similar hospital stay (12.6 ± 7.1 vs 13.6 ± 7.7 respectively, p = 0.20), and a similar mortality rate (9.8% vs 10.7%) but required a longer ICU stay (8.4 ± 2 vs 3.2 ± 2.2, p = 0.02).

The type of respiratory complications differed between exacerbated and non-exacerbated patients. In the first group, multiple respiratory complications were found in 52 cases (34.2%, as compared to 4.7% in non-exacerbated patients), the most frequent pattern being single or multiple atelectasis preceding pneumonia. Moreover, in exacerbated patients, acute respiratory failure without apparent cause occurred in 15 cases (9.8%), while it was exceptional in non-exacerbated patients (one case, 1.1%).

The median FLAM score values recorded during the first postoperative week are shown in Table 3. Patients with no complications had the highest value on POD1 with the FLAM score progressively decreasing. In patients with complications, the score progressively increased during the first 72 h, maintaining higher values in those who had postoperative exacerbation before the onset of complications (Fig. 1).

3.2. Risk factors

Univariate analysis identified sex, COPD class and duration of surgery as risk factors for the occurrence of postoperative COPD exacerbation. Additionally, there was a trend towards significance for the protective role of prolonged amoxicillin administration. All these factors were tested in the multivariate model. Sex (female OR 0.54, CI 0.2—0.8), COPD class (OR 1.5, CI 1.1—8.1), and the use of amoxicillin (OR 0.6, CI 0.2—0.9) were confirmed as independent risk factors for postoperative exacerbation.

Our analysis has demonstrated that the three most significant risk factors for the occurrence of respiratory complications are exacerbation, sex and FEV1, exacerbation being the strongest predictor (OR 5.5, CI 3.5—8.5; female sex OR 1.77 CI 1.1—3.1; FEV1 > 80% 0.43 0.26—0.7).

![Median FLAM score values](image.png)

**Fig. 1.** In uneventful patients (group A), the FLAM score peak was recorded on POD1 and then progressively decreased. Patients who developed respiratory complications after exacerbation (group B) had higher values as compared to those who had complications without preexisting exacerbation (group C). Median FLAM value differences between group B and C were statistically significant (p < 0.05) on POD 5, 6 and 7.
4. Discussion

The idea for this study arose in 2002, when the American College of Chest Physicians (ACCP) published a leaflet on guidelines in the management of acute exacerbation of COPD, developed in association with the American College of Physicians and the American Society of Internal Medicine (ACP-ASIM) [11].

On examination of the definitions of acute exacerbation, it was evident that many patients undergoing lung surgery fit into these definitions during the postoperative period. In order to confirm this however, two elements were lacking: an effective tool to diagnose exacerbation and a large population on which to test this hypothesis. The first step was to develop a score (the FLAM score) able to monitor the parameters representing the main criteria of COPD exacerbation (dyspnea, quality and amount of bronchial) on a daily basis. The second problem was solved by the use of a multicentric enrolment programme, which permitted the recruitment of more than 1000 patients over a 2-year period.

Results from this study have shown that 50% of lung cancer patients undergoing surgery are COPD patients, and that more than 50% of them develop postoperative acute exacerbation of COPD. The overall impact on outcome was evident, as mortality exceeded 5% in exacerbated patients, as compared to 2% in patients without exacerbation. This increased mortality is not only due to exacerbation but also to the detrimental effect of exacerbation on respiratory complications, which are the principle determining factors of postoperative mortality. From a theoretical point of view, postoperative exacerbation may represent the physiopathological link between a low preoperative FEV1 and post-operative risk. Multivariate analysis provides statistical documentation of this speculation, confirming exacerbation as the strongest predictor of respiratory complications.

COPD exacerbation also had an impact on patients who did not develop respiratory complications, as it increased hospital stay by 48 h. Given this data, it can be debated that exacerbation be considered as a distinct complication, requiring additional hospitalisation and specific treatments.

A theoretical advantage of diagnosing exacerbation early in the postoperative period could be achieved by utilising the pre-existing treatment guidelines [12], after adaptation to the postoperative setting. This could significantly reduce respiratory morbidity and mortality. The key points of treatment are steroids, antibiotics and non-invasive ventilation. In the case of severe or moderate exacerbation, GOLD guidelines suggest the use of 2-week prednisolone administration (40 mg). The safety of such a regimen after lung resection has not been clearly established. However, postoperative use of steroids represents common practice after lung transplantation. The use of antibiotics, which is advocated by the GOLD guidelines in the case of severe exacerbation, is controversial, given that the positive effect of short-term prophylaxis has been extensively demonstrated on surgical-site infections only. Nevertheless, the use of 5-day amoxicillin–clavulanate treatment has resulted as a protective factor and was associated with fewer episodes of pneumonia. A possible explanation is that selective decontamination of the airways is obtained in these patients, reducing the risk of bacteria triggering exacerbation [13].

Even more interesting, is the use of non-invasive positive pressure ventilation (NPPV), suggested in the case of moderate and severe COPD exacerbation. Its use may be beneficial to the outcome of patients who have developed respiratory failure due to exacerbation, as it has already been reported that NPPV decreases the incidence of endotracheal intubation as well as other severe complications resulting from elective major abdominal surgery [14].

The main limitation of the study is the definition of postoperative exacerbation, which is an arbitrary definition obtained from a clinical score. This problem is common to the vast majority of studies dealing with COPD exacerbation, as ‘many definitions exist, many authors use substantially different criteria, and many studies describe their inclusion criteria poorly’ [12]. Moreover, some minor criteria are not applicable after surgery, such as the increase in the heart or respiratory rate by 20% above baseline, which is the rule after lung resection. Continued research will be required to obtain a more specific and acceptable definition, while maintaining simplicity, to guarantee its practical application in daily use.

Nevertheless, results from this study have shown that postoperative exacerbation of COPD is a frequent and existing clinical entity following lung resection and that, when present, is likely to cause pulmonary complications. Existing guidelines for the treatment of acute exacerbation should be adapted for the management of patients after lung resection, in order to test the hypothesis that early treatment of exacerbation could reduce respiratory morbidity and, possibly, mortality.

Acknowledgements

The authors thank the following: (1) Lorenzo Spaggiari (EIO, Milan), Ugo Pastorino (NCI, Milan), Jacques Jougon (CHU Bordeaux), Jean Francois Velly (CHU, Bordeaux) and Alberto Oliaro (Turin University Hospital) for their contribution as co-authors of the study. They are not mentioned in the author list due to EJCTS restrictions to the number of authors. (2) M. Ile Marylene Anziani, for her contribution to the creation of the FLAM score. (3) Mrs Kendall Katze, for the careful revision of the final version of the manuscript. (4) Dott Brunilda Tatani for the cooperation in data collection at the European Institute of Oncology. (5) Chest physiotherapists from all centres for their strict cooperation with researchers.

References

Appendix A. Conference discussion

Dr G. Di Rienzo (Lecce, Italy): Congratulations for the nice presentation. I see that regarding patients operated with FEV1 less than 30% with a high level of mortality. I guess 25% something like that.

My question is: why were these patients operated on, I mean patients with FEV1 less than 30%.

Dr Leo: I can answer about three cases in the management of which I was directly involved. There were emphysematous patients with a synchronous lung cancer and a wedge resection plus volume reduction was decided. I don’t have details of the other patients, but I guess that the clinical situation was the same.

Dr T. Szczesny (Warsaw, Poland): Congratulations. I would like to ask you whether you would recommend systemic administration of steroids after a surgery in patients who had exacerbation of COPD?

Dr Leo: Guidelines for COPD exacerbation treatment are based on the use of steroids and antibiotics. Apart from early experience in lung transplantation, we don’t have the evidence of a direct adverse effect of short course steroids administration on bronchial healing. There is a paper from the group of Rome showing that in sleeve resection a limited use of steroids did not effect cicatrization. So, the problem is that probably we should decide which dose of steroids, when and for how long we should use but it is another study.

About the use of antibiotics as I said before, there are two different attitudes. The two centres that used prolonged antibiotics administration had 6% reduction in postoperative pneumonia, even if the number of events were equal and the postoperative infections evaluation was not an endpoint of the study, this trend is noteworthy.

Dr H. Eid (Dubai, UAE): From the different centres that you have involved in your trial, was there any difference in postoperative care as per inhalation of bronchodilators? We find a great deal of variations in our own units. Variations from unit to unit in the routine they are giving to patients so this frequent complication arises. Was that controlled for your study?

Dr Leo: There was a complete different attitude between centres, as in France patients are usually referred to the surgeon by pneumologists. So in term of respiratory care, they are more prepared to surgery.

In Italy, in Turin there is a pneumology department which deals with patients preoperative and the two cancer centres in Milan they don’t have such a department. In this situation, it is sure that the preparation of patients is less than optimal.

Dr K.M. De Groot (Cape Town, South Africa): This was a nice prospective organised study. Which patient would you deny a resection? Is it the COPD patient, depending on this study? Which parameters do you deny a resection for the patient?

Dr Leo: Every centre decided at the multidisciplinary meeting for the surgical indication, the study was just observational. From the functional point of view. Generally, the value of preoperative predicted FEV1 contraindicating surgery was 30% in Milan, 40% in Turin and in France.