Review Article

Is bronchodilator the correct treatment for COPD subjects before EBUS?

Veronica Leoni[1], Patrizia Pignatti[2], Dina Visca[3], Antonio Spanevello[1,3]

[1]Department of Medicine and Surgery, Respiratory Diseases, University of Insubria, Varese-Como, Italy; [2]Allergy and Immunology Unit, [3]Respiratory Medicine Unit, Istituti Clinici Scientifici Maugeri, IRCCS, Pavia, Italy

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Correspondence to: Patrizia Pignatti, PhD. Allergy and Immunology Unit, Istituti Clinici Scientifici Maugeri, IRCCS, via S. Maugeri, 10 27100 Pavia, Italy. Email: patrizia.pignatti@icsmaugeri.it.

Abstract: Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) is a reliable and commonly established technique, enabling real-time guidance of transbronchial needle aspiration of mediastinal and hilar structures and parabronchial lung masses. As EBUS-TBNA became more available and adopted by clinicians, questions emerged about the optimal performance of the procedure. Although EBUS is considered safe, there are few complications that could occur during the test, correlated with both the procedure itself and the patient's characteristics. Moreover, this technique is often addressed to patients with overlapping airways diseases, which might have higher risk of complications during the procedure. Chronic obstructive pulmonary disease (COPD) patients could experience EBUS-TBNA with a relative high frequency due to their risk of developing lung cancer. The irreversible bronchial constriction characteristic of the disease raises some questions on premedication before bronchoscopic procedures. It is mandatory to optimize every aspect of the procedure in order to minimize the risk of complications, especially for fragile patients. Whether the use of inhaled bronchodilators before the procedure could improve the outcome of the procedure in COPD patients is reviewed in this article. No clear indication emerged from the literature suggesting the need of more studies in order to clarify this point.

Keywords: β2-agonist; anticholinergic drugs; bronchoscopy; endobronchial; pre-medication

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Endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-TBNA) is a relatively novel, minimally invasive methodology to sample peribronchial masses with real-time guidance (1,2), widely used all over the world. The most common indications for EBUS are the staging of the mediastinum for suspected non-small cell lung cancer and the diagnosis of unexplained mediastinal lymphadenopathy. Usually EBUS is well tolerated, with very few major contraindications; guidelines suggest that patients who experienced myocardial infarction should wait 6 weeks before the procedure, which is however contraindicated when myocardial ischemia, arrhythmias, severe hypoxemia at rest, coagulation or platelet function disorders are present (1).

EBUS-TBNA is less available and more expensive than rigid bronchoscopy (RB) which remains the best choice for extraction of airway foreign bodies, when a flexible scope is not suited or in case of large biopsies. However, the diagnostic power of RB in terms of lung cancer staging or evaluation of peripheral pulmonary lesions is lower compared to EBUS-TBNA (3) in the general population and speculatively in COPD patients.

EBUS is generally considered safe (1,4), however, whether performed with anaesthesia or only light sedation, pre-procedural medications are routinely administered and may have side effects. Diagnostic sampling may lead to immediate, although rare, complications, such as intrabronchial bleeding, bronchospasm, hypoxemia, hemodynamic variations and pneumothorax (1,5,6).

We know from the literature that significant fall in Forced Expiratory Volume in 1 second (FEV_1), and forced vital capacity (FVC) occurs after endoscopic procedure, during both routine bronchoscopy and procedures, which include bronchoalveolar lavage (BAL) and biopsy (6). This impairment of the lung function reflects the gas exchange efficiency, with a reduction of the PaO_2 (7). These events were found in the entire population, both healthy and patients suffering from chronic respiratory disease. Severity of asthma, baseline FEV_1 or initial PaO_2 did not predict the degree of hypoxemia or the fall of FEV_1. It is intuitive that these effects are greater in people affected by respiratory airways disease and correlate with the duration of the procedure (7).

Similar data were also found in the pediatric population showing alveolar hypoventilation during flexible bronchoscopy particularly in cases requiring large amounts of sedation and in patients susceptible to complications from respiratory acidosis (8).

Patients with chronic obstructive pulmonary disease (COPD) can experience flexible bronchoscopy for different reasons. Cigarette smoking recognized as the major cause of COPD is also a major risk factor for malignancy, therefore patients with COPD have a higher incidence of carcinoma of the lung, and endoscopic evaluations can lead to earlier diagnosis. However, the authors did not report indication to cope with COPD patients who have low FEV_1 and no limit is reported.

Historically the attention on pre-medication for patients undergoing bronchoscopy was focused on asthmatic patients, because of higher grade of bronchial hyperresponsiveness (BHR). Different kind of bronchodilator agents were tested, such as a combination of β2-short acting and anticholinergic drugs, administered either topically and systemically (8-11). Therefore, the administration of nebulized bronchodilators has been requested before flexible bronchoscopy in asthmatic patients (12). While some indications are given for asthma, there are no clear results supporting the utility of giving bronchodilators before bronchoscopy in COPD patients. No mention about pre-medication with bronchodilators can be found both in the British Thoracic Society guidelines on diagnostic flexible bronchoscopy (12) and in CHEST guideline for EBUS-TBNA (1).

Bronchoscopic procedures are considered rather safe in COPD patients compared to asthmatics with high BHR. There are only few studies that investigate the preoperative use of bronchodilators on COPD population and not conclusive.

A recent study by Georgiou and colleagues showed that, among a cohort of 92 patients with advanced COPD undergoing EBUS for the evaluation of peripheral pulmonary lesion, 10.6% of them experienced acute respiratory failure (13).

Hattotuwa *et al.* performed endobronchial biopsy and BAL in patients with mild, moderate and severe COPD with 44.5% as mean FEV_1, without exacerbation of disease and with suspension of inhaled corticosteroids (ICS) for at least 8 week before the bioptic procedure. Symptoms were treated with salbutamol and/or ipratropium bromide; 2.5 mg of salbutamol were administered to all subjects with the exception of patients with mild disease. Prolonged coughing and transient decreases of oxygen saturations (lowest 88%) occurred in the enrolled patients during BAL, treated successfully with supplemental oxygen. Low incidence of adverse events needing hospital treatment (2%) and low incidence of hemoptysis which resolved spontaneously (3%), were reported in the study, concluding that fiberoptic bronchoscopy, endobronchial biopsies, and BAL can be carried out in selected patients with COPD with a low incidence of adverse events (14).

Stolz and colleagues presented the results of a randomized, double-blind, placebo-controlled trial to evaluate the protective effect of salbutamol in COPD patients who experienced bronchoscopy, and they found that the decrease in FEV_1 was similar in salbutamol and placebo arms (15). In this study, the combination of an opiate with a benzodiazepine used for sedation did not cause excessive oxygen desaturation, suggesting that this drug combination could be a reliable choice to sedate these subjects. Furthermore, salbutamol added prior the procedure, represented, in a subgroup of patients, an addition to the maximum combination therapy of two bronchodilators, one long-acting β2 agonist plus one anticholinergic drug, and/or ICS.

No evaluations can be drawn on the protective effect of ICS in reducing bronchial hyperreactivity in these patients before bronchoscopy. Another study, by Inoue and colleagues, investigated the effect of two anticholinergic agents, intramuscular atropine and inhaled ipratropium bromide, on bronchoconstriction in 29 patients who

were undergoing diagnostic bronchoscopy. In both the placebo and the atropine group, the lidocaine used as local anaesthesia produced a significant fall of FEV_1 and peak expiratory flow rate (PEFR), whereas in the subjects treated with ipratropium bromide, no significant FEV_1 and PEFR fall was reported after local anaesthesia. Moreover, the bronchoscopic procedure determined significant decreases in FEV_1 and PEFR, but with lesser variations than those reported in the placebo and atropine treated patients, suggesting that an inhaled anticholinergic drug, unlike atropine, might protect patients towards excessive bronchoconstriction during bronchoscopy (16).

In this uncertain scenario, the proper management of COPD patient seems to be the only clear cornerstone.

As showed above, the impairment of lung function and respiratory gas exchange is expected during endoscopic procedures, both routine bronchoscopy and EBUS. There is no clear evidence regarding the utility of short-acting bronchodilators in COPD patients' prior bronchoscopy. It becomes even more important to optimize the maintenance therapy of these subjects, in order to prevent, as much as possible, the drop of lung function parameters and, consequently, the risk of hypoxemia. This concept might be fundamental in COPD with high BHR, who might have more side effects during procedures (17). BHR can cause increase in cough and dyspnea and more severe BHR in COPD is associated with a higher degree of airway obstruction as reflected by lower FEV_1 and FEV_1/FVC values (18).

In the past years, some studies provided evidence that the decline in post-bronchodilator FEV_1 can be reduced by long-term ICS treatment (19-21). Another study showed a deterioration of FEV_1, after steroid withdrawal in COPD population (22). In this subset of patients, long-term ICS treatment should be recommended in order to reduce BHR before EBUS procedure.

The proper long-acting bronchodilator must be chosen considering symptoms and exacerbation risk of the patient (23). We know from literature that COPD bronchodilator responsiveness is a continuous variable and classifying patients as "responders" and "non-responders" can be misleading because it changes over the time (24). Recently some studies were conducted trying to evaluate if individual's reversibility could predict the future response to a combination of bronchodilators (25,26). Both short-acting and long-acting medications were tested. These studies showed that the overall extent of clinical benefit obtained with an association of two bronchodilators is related to the response to the single compound. Post-hoc pooled analyses of the same data by Donohue and colleagues showed that the benefits of dual long-acting bronchodilators (umeclidinium/vilanterol) versus single drug were more than additive in subjects who did not respond to both umeclidinium and vilanterol, and additive in responders to only one bronchodilator.

In contrast, umeclidinium/vilanterol had a lower than additive effect in dual responders (26). These results could be the basis for future studies on bronchodilation before EBUS in COPD patients.

The goal should be reaching the highest lung performance that a patient could achieve in order to minimize any possible risk of bronchospasm or lung function impairment during the invasive procedure.

In conclusion, the use of bronchodilators in COPD subjects before EBUS is recommended in order to reduce or minimize the bronchoconstriction due to this procedure, but the type of bronchodilator to be used needs to be more investigated.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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