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The role of exhaled nitric oxide in patients with chronic obstructive pulmonary disease undergoing laparotomy surgery – The noxious study

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) has been associated with major perioperative morbidities or mortalities, especially in surgical patients receiving general anesthesia. The severity of the COPD and the degree of bronchial hyperreactivity can determine the perioperative anesthetic risk; therefore they have to be assessed by a thorough preoperative evaluation in order to give the rationale on which to decide for optimum anesthetic management.

Objective: Aim of the study was to assess the predictive applicability of exhaled Nitric Oxide (NO) in smoking surgical population with COPD, on the basis of morbidity and mortality.

Methods: A prospective, observational study was undertaken in 70 smoking patients diagnosed with COPD scheduled for laparotomy surgery under general anesthesia COPD was evaluated with the GOLD Classification of Air Flow Limitation, the Modified MRC Dyspnoea Scale (mMRC), the BODE Index score and the 6 Minutes Walk Distance (6MWD) using spirometry parameters. All patients were observed for presenting perioperative and postoperative respiratory complications. A cut off value of 19 ppb was determined for fractional exhaled nitric oxide measured at expiratory flow of 50 mL/s (F_ENO_{50}) to differentiate patients poor prognosis from those with favorable outcome.

Results: Patients with severe COPD had high BODE index score as well as F_ENO_{50}. Elevated F_ENO_{50} is significantly related to multiple complications ($p = 0.004$) and postoperative cough ($p < 0.001$). Patients from the high F_ENO_{50} group that were not treated with steroids had a statistically significant higher incidence of extra hospital care need ($p < 0.001$). Increased F_ENO_{50} and ABCD classification are both related with the presentation of multiple complications (Odds ratio = 2.5, 95% CI 1.1 to 5.7, $p = 0.028$ for ABCD and Odds ratio = 6.39, 95% CI 1.33 to 30.5, $p = 0.020$ for F_ENO_{50}). Increased F_ENO_{50} and ABCD are related with extra hospital care ($p = 0.001$ and $p = 0.002$ respectively) and combined with corticosteroid administration could predict the necessity for extra hospital care (Odds ratio 4.09, 95% CI 1.1 to 15.3, $p = 0.036$ for corticosteroid treatment, odds ratio 2.4, 95% CI 1.1 to 5.1, $p = 0.029$ for ABCD and odds ratio 7.93, 95% CI 1.7 to 35.3, $p = 0.007$ for F_ENO_{50}).

Conclusion: The F_ENO_{50} may identify high risk smoking surgical patients with COPD receiving general anesthesia. Perioperative and postoperative complications in COPD smoking patients undergoing abdominal surgery can be predicted using not only ABCD GOLD 2011 classification but also the F_ENO_{50} as a preoperative marker.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by airway inflammation and

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progressive airflow limitation. As airway inflammation is featured in COPD, the measurement of inflammation biomarkers, in exhaled breath condensate could prove to be an inexpensive and efficient method to detect COPD in settings as preoperative examination. The perioperative risk for complications for patients with inflammatory diseases of the lung is high. According to Mathis and colleagues the incidence of perioperative morbidity or mortality, among adult outpatients undergoing common day case-eligible surgical procedures, was high for patients with COPD [1]. Patients suffering from COPD have more possibilities to present early postoperative pneumonia and prolongation of postoperative ventilator support. Subsequently it is important that all patients presenting signs of COPD should be recognized preoperatively and prepared with all precautions in order to minimize the risk for postoperative complications.

Nitric oxide (NO) is a gaseous free radical that plays an important role in many biological processes in lung physiology. It is produced by many different cell types, including epithelial cells, endothelial cells, neurons and inflammatory cells in the lung and is generated in cells by nitric oxide synthases [2,3]. NO acts as a neurotransmitter mediating bronchodilation in the lung and it is produced by inflammatory cells in the airways, where it is important for generating reactive species important in pathogen killing and tissue injury in inflammation [4,5]. There is a substantially growing evidence that endogenous NO plays a key role in the physiological regulation of airway inflammation and is implicated in the pathophysiology of various lower airway diseases [6]. The nitric oxide synthase found in lung macrophage is inducible by pro-inflammatory cytokines, meaning that large amounts of NO may be produced in the airways in COPD and may be measured in exhaled breath. Moreover, a relation between the changes in exhaled NO and changes in sputum neutrophils has been shown [7]. Exhaled NO, which can be easily measured noninvasively and accurately in exhaled air, in pediatric and adult patients with various respiratory pathologies, has been shown that correlates with disease activity and severity in an important manner [8]. The methods for measuring NO have been standardized and published by the American Thoracic Society, making exhaled NO analysis a widely adopted clinical and research tool in respiratory disease [9].

In COPD population the levels of fractional exhaled nitric oxide measured at expiratory flow of 50 mL/s (F_ENO_{50}) are found to be substantially elevated as compared with normal subjects [10–12]. Moreover, a negative correlation between forced expiratory volume in 1 s (FEV1) and F_ENO_{50} in patients with stable and exacerbated COPD has been recorded [5]. Regarding the critical cut point of exhaled NO, when Antus and Barta [13] used 27 ppb as a cut off value of F_ENO_{50} they concluded that both the number of exacerbations per patient-year and the hospitalization days due to exacerbations were significantly increased in patients from the low F_ENO_{50} group compared to those from the high F_ENO_{50} group [13]. According to the literature, F_ENO_{50} levels in COPD may be correlated with disease severity and intense exacerbation [14,15]. However, even though there are studies with COPD patients that indicate a wide range of F_ENO_{50} levels, that are positively associated with the number of exacerbations, there is no clear cut-off value proposed in the literature [16].

To the authors knowledge there is no existing evidence regarding the use of F_ENO_{50} as a predictor biomarker during the perioperative period for patients with COPD undergoing neither thoracic nor cardiac surgeries. The primary endpoint of this study was to evaluate the role of F_ENO_{50} in COPD patients undergoing major abdominal surgeries in predicting the risk of presenting perioperative and postoperative complications as well as the need for extra hospital care. Secondary aims were to compare the diagnostic performance of F_ENO_{50} in COPD patients with the existing tests as the BODE Index score and the GOLD 2011 classification.

2. Materials and methods

2.1. Study participants

During the time period from September 2014 until January 2016, all the patients from Achillopouleion General Hospital of Volos, scheduled for major abdominal surgeries were enrolled for the study. The inclusion criteria were age <75 years, a diagnosis of COPD according to the American Thoracic Society (ATS) criteria and an ASA physical status II, III or IV.

Patients with other organ failure, cancer, and inability to cooperate, as well as patients with a recent exacerbation (e.g. requiring hospitalization or oral corticosteroids) and those with another or coexisting respiratory disorder (e.g. COPD and bronchiectasis) were excluded from the study. No patient was on long term oxygen therapy. All the patients received regular treatment according to the ATS guidelines and had not participated in any other research study or clinical trial. At the start of the study they were all in a stable condition and had been free from exacerbations in the preceding four weeks.

The study protocol was approved by the ethics committee of Achillopouleion, General Hospital of Volos and the study was conducted according to the Declaration of Helsinki. Informed consent was obtained from the patients before enrolment into the study. The trial was submitted with the acronym “NOXIOUS” (exhaled **N**itric **OXI**de in patients with chronic **O**bstructive disease **U**ndergoing **S**urgery) for inclusion in the Australian New Zealand Clinical Trials Registry (ANZCTR) and has been registered and allocated the ACTRN: ACTRN12616000211460.

2.2. Study design

All consecutive adult patients diagnosed with COPD who were scheduled for major abdominal surgeries were included in the study. Their full medical history, as well as previous laboratory tests (no more than 1 week old) were recorded. One day before surgery all patients were examined by an experienced anesthesiologist and categorized according to the ASA classification. The anesthesiologist also performed a spirometric test according to the standard procedure, calculated the time they needed for a 6 min walking distance test (6 MWD) and evaluated the patients using the GOLD Classification of Air Flow Limitation, the Modified MRC Dyspnoea Scale (mMRC) and the BODE Index score [17,18].

2.3. Evaluation of COPD

Using the values from FEV1 (forced expiratory volume in 1sec) and FVC (forced vital capacity) as well as their fraction (FEV1/FVC), the 6MWD test (as recommended by the American Thoracic Society ATS), the mMRC and the body mass index (BMI), the BODE Index and the GOLD classification for each patient was computed. COPD patients should have proven cumulative consumption of at least 10 packs/year [19]. Patients were classified according to GOLD 2011 strategy in ABCD groups. The BODE Index is a composite marker of disease taking into consideration the systemic nature of COPD with a total score of 0–10 units. The revised in 2011 GOLD classification gives less emphasis on spirometric evaluation of disease severity and launches a combined assessment taking symptoms, spirometry and history of exacerbations into account [17,18].

2.4. Measurement of exhaled NO

Study participants sequentially undertook an exhaled NO