Practice of Oxygenation and Respiratory Support during Fiberoptic Bronchoscopy: The Oxy-FOB STUDY

# Summary of the study

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# INTRODUCTION

Fiberoptic bronchoscopy (FOB) is a diagnostic and sometimes therapeutic procedure commonly performed both in elective and emergency conditions for airway, lung parenchymal or mediastinal disorders. Plug removal, bleeding management and endobronchial foreign body removal represent the main therapeutic indications for FOB. FOB is also utilized for diagnostic purposes alone or in combination with bronchoalveolar lavage (BAL), brushing, bronchial and transbronchial lung biopsy, intrathoracic lymph node sampling by means of EBUS. According to the patient’s status and the clinical indications, FOB may be performed in various settings from a dedicated room for outpatients to the intensive Care Unit (ICU).

The majority of patients undergoing FOB suffers from conditions that may impair gas exchange such as pneumonia, interstitial lung diseases and neoplasms. During the procedure the arterial partial pressure of oxygen (PaO2) drops to a varying extent, with an increased risk of occurrence of respiratory distress [1-2]. Furthermore, respiratory mechanics are altered during FOB. In non-intubated patients, the fiberscope occupies about 10% of the cross-sectional area of the trachea, and 15% of the cricoid ring, which increases patient airway resistance and accordingly increases the work of breathing [3]. In patients with bronchial hyperreactivity periprocedural bronchospasm may complicate FOB. When suction is applied, the end-expiratory lung volume is reduced, which may reduce lung compliance and cause V/Q mismatch and venous admixture [3-5].

These respiratory changes revert after FOB, but their reversal may take from 15 minutes to several hours in severe parenchymal lung diseases [3].

In addition, while on the one hand during FOB it has been reported that cardiac output may increase by 50% because of sympathetic stimulation, and it returns to baseline in 15 min after its completion [3, 6], on the other hand the changes in intra-thoracic pressure, consequent to the increased inspiratory effort, may affect venous return and afterload and reduce the cardiac output [7], precipitating heart failure in patients with underlying cardiovascular disorders. Indeed, electrocardiographic alterations during FOB have been described found in up to 21% of awake patients over 60 years [8].

Finally, some procedures (i.e. FOB with BAL) may be performed with an extensive topical anesthesia and/or light sedation [9-10], while others, such as EndoBronchial UltraSound (EBUS), may require heavier sedation with different pharmacological strategies including either sedatives or analgesics, or both. It must be recognized that these drugs can modify the critical closing pressure of the upper airways, inducing their collapse [11-12], and they can affect the breathing pattern and/or the respiratory drive, with a dose-response relationship [13-14].

According to patients’ conditions and type of procedure, several forms of support, including standard oxygen therapy (SOT), high flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), non-invasive ventilation (NIV) and even invasive mechanical ventilation (iMV) have been proposed to prevent respiratory failure or worsening of gas exchange and to reduce some drawbacks during FOB [15].

In spite of a relevant number of available studies, most investigations consider physiological rather than clinical outcome variables with heterogeneous populations with respect to severity, type of procedure and supportive means. Because of these limitations, no guidelines on respiratory are today available and the daily clinical practice varies among centers [15].

# AIMS

The primary aim is to describe the current practice of supports in patients undergoing FOB, stratified by baseline respiratory condition, co-morbidities, FOB procedure and hospital settings.

In addition, we aim to assess:

* the occurrence of adverse events (i.e. severe desaturation, need for procedure interruption, hypotensive or hypertensive events, new onset of cardiac arrhythmias or myocardial ischemia or electrocardiographic ST-alterations);
* the lowest oxygen saturation;
* maximum intraprocedural drop in oxygen saturation from baseline;
* need to increase inspired oxygen fraction (FiO2);
* the adopted sedation strategies;
* need for escalating respiratory support;
* need for ICU admission (only for patients not admitted in ICU);
* hospital length of stay;
* mortality.

Secondary outcomes will be assessed within 1, 12, 24 and 48 hours from the end of the FOB procedure and/or until the hospital discharge.

# METHODS

This is a multicentre, international, prospective, observational study on adult patients requiring any type of FOB. The study protocol is designed and it will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

The study will be prospectively registered on one of the Primary Registries meeting requirements by the World Health Organization (WHO) Registry Network and International Committee of Medical Journal Editors (ICMJE).

For all involved centers, Ethics approval or a waiver is mandatory to start with enrolments. Request of patients/legal representative informed consent will be requested according to the national law.

All consecutive patients that are eligible according to the inclusion criteria should be included in the study.

# POPULATION

We will include all patients with all the following criteria:

1. Either male or female
2. Age ≥ 18 years
3. Need for any procedure with flexible FOB
4. Either outpatients in dedicated ambulatories, and admitted to any hospital ward or Intensive Care Unit (ICU)
5. Informed consent (if required)

No specific exclusion criteria are indicated for enrolment in this project.

# DATA COLLECTION

Case report forms will be provided for the recording of the data and a web-based electronic CRF will be used.

All epidemiological and clinical information required by the eCRF should be clearly documented and retrievable from the patient’s (either on paper or electronic) medical chart. All data will be anonymous and only the local principal investigator will know the decoding list in order to link the enrolment number to the correspondent patient.

We will collect:

* Patient’s baseline data: age, gender, height, weight, type of admission (outpatient, ward, ICU), peripheral oxygen saturation, arterial blood pressure, baseline arterial blood gases (ABGs) and pulmonary function test (if available), presence of comorbidities (Charlson Comorbidity Index), indication to the FOB, need for long-term oxygen therapy or NIV.
* Type of FOB procedure: toilet bronchoscopy (for secretions, blood, mucus plugs removal), broncho-aspirate (BAS), bronchoalveolar lavage (BAL), brushing for cytology, biopsy, endobronchial ultrasound (EBUS). The type and size of bronchoscope (with or without an internal/external camera) and the time of the procedure will be also recorded.
* Type of supportive strategy: no support, SOT, HFNC, CPAP trough mask, CPAP through helmet, NIV trough mask, NIV through helmet, iMV. For every type of support, settings will be recorded.
* Sedation: topical anesthesia, midazolam, propofol, remifentanil, fentanyl, dexmedetomidine, neuromuscular blocking agents. Drug dose, mode of administration (bolus versus continuous infusion) and combination of different drugs will be recorded. In addition, the level of sedation will be recorded according to the Richmond Agitation Sedation Scale (RASS).
* Intraprocedural parameters: lowest peripheral oxygen saturation (SpO2) detected, lowest and highest heart rate, lowest and highest systolic blood pressure, volume of sterile normal saline unrecovered (in case of BAS or BAL), duration of the procedure.
* Occurrence of adverse events: desaturation (i.e. SpO2< 90% for at least 10 seconds), severe desaturation (i.e. SpO2< 80%), need for procedure interruption, hypotensive (systolic blood pressure <90 mmHg) or hypertensive (systolic blood pressure >140 mmHg) events, new onset of cardiac arrhythmias (specify the rhythm) or myocardial ischemia or electrocardiographic ST-alterations, neurological events (i.e. severe sensorium depression, psychomotor agitation).
* Post-procedural parameters (15 minutes after the procedure): SpO2, heart rate, systolic blood pressure, dyspnea (as evaluated by a numeric rating scale from 0, no dyspnea, to 10, worst dyspnea), patient’s comfort during the procedure (as evaluated by a numeric rating scale from 0, maximal discomfort, to 10, best comfort) and ABGs (if available).
* Clinical outcomes: need for support escalation, from SOT (lowest support) to HFNC, CPAP, NIV or iMV (highest grade of support); need for admission to ward (for outpatient) or ICU (for outpatients and ward-admitted patient).

# DEFINITIONS

* Standard Oxygen Therapy (SOT): consisting of low oxygen flow administration through nasal prongs, oxygen mask with or without reservoir, and Venturi mask.
* High Flow oxygen through Nasal Cannula (HFNC): administration of high flows (up to 60 L/min) of air/oxygen admixtures, heated (at temperatures ranging from 31 to 37°C) and fully humidified (up to 44 mg H2O/L), providing an inspired oxygen fraction ranging from 21 to 100%
* Continuous Positive Airway Pressure (CPAP): the application of positive end-expiratory pressure (PEEP) throughout the whole respiratory cycle by means of interfaces such as mask or helmet
* Non-Invasive Ventilation (NIV): application of a PEEP by means of a mask or helmet, with an inspiratory pressure support triggered by the patient and delivered by a ventilator and through interfaces such as mask or helmet
* Invasive Mechanical Ventilation (iMV): application of a ventilatory assistance in controlled or partial assisted modalities through an endotracheal or tracheostomy tube.

# STATISTICS

In view of the observational nature of the study, a formal sample size calculation is not done, but a target sample of at least 10.000 patients is planned. The enrollment will be conducted over a first 4-week participation period over 2 months, and a second one (4 weeks) 6 months after the first, for each unit.

Statistical analysis will be performed by an independent expert statistician, in collaboration with the investigators.

The Kolmogorov-Smirnov test and histograms visualization will be used to value the variables distribution. The data with a non-normal distribution will be assessed with Mann-Whitney test and the median and selected centiles (25th to 75th) value will be given. The data with a normal distribution will be assessed with the Student t -test. Categorical variables will be presented as proportions and analysed with the use of the chisquare test or Fisher exact test, as appropriate. A P value <0.05 will be considered significant. The discriminatory powers will be evaluated by the respective areas under the receiver-operating characteristics (ROC) curves (AUCs). The Kaplan Meier method will be used for the survival analysis.

# ETHICS

As this is an observational study, some countries and sites may waive the need for informed consent.

Where applicable, Informed consent will be obtained from the subject or nominated representative.

# STUDY ORGANIGRAMME

## NATIONAL COORDINATORS

National Coordinators (NCs) will be appointed by the Steering Committee and will have a key role in the conduction of the study in the individual countries as leaders of the project. The role/responsibilities of the NC include the following:

* Advertise the study in each country and identify participating hospitals and local investigators.
* Apply for regulatory approval in a national level where applicable and ensure that ethical committee (EC) approvals or waivers for all the participating hospitals in the country are in place prior to the initiation of the study. The NC will receive scanned copies of the EC approvals from all centers, will check them and report to the Principal Investigator (PI). The checked by the NC scanned copies of the EC approval will be sent altogether to the PI prior to the initiation of the study.
* Assist with the translation of the study protocol/CRF where required.
* Ensure the distribution of study material to the centers (protocol, CRF, instruction manuals etc.) and that the local investigators are familiar to the study material prior to the start date.
* Ensure good communication with the participating sites in the respective country and to animate local investigators to achieve optimal recruitment and follow up during the period of the study. During the period of database quality control (data ‘cleaning’) the NC should animate the individual to reply in possible queries.

## LOCAL INVESTIGATORS

There will be one local investigator per hospital.

The Local investigator(s) will have the following role/responsibilities:

* Lead the study in their hospital.
* Inform the respective NC of their participation (or interest to participate) in the study if they were informed for the study through channels other than the NC.
* Apply for EC committee approval in their hospital and ensure that approval is in place prior to the initiation of the study. The local investigators should send scanned copy of the EC approval to their NC.
* Ensure accurate data collection and accurate and timely eCRF completion. In case of centers that have not access to eCRF completion, copies of the paper CRF should be sent to the PI by post or fax (as advised by the PI).
* Reply promptly to possible queries during the period of database quality control (data ‘cleaning’).
* Guarantee the integrity, consistency and quality of data collection and ensure that the EC approval and the paper CRFs will be kept in a safe and locked place for the period of time set in the study protocol.
* Guarantee good communication with the NC.

# DATA MANAGEMENT

## DATA PROPERTY

Data provided by the local investigators are primarily the property of the hospital that collected the data. Local investigators shall have access to their data after they have been entered in the central database.

## DATA CONTROL

Local investigators may be contacted by the PI for queries in case of outliers, excessive missing values and other reasons deemed relevant by the PI.

## USE OF DATA BY THE PRINCIPAL INVESTIGATOR AND STEERING COMMITTEE

The PI and Steering Committee have the right to use the data in the central database for scientific purposes. Investigators will be informed about ongoing analyses and related study activities such as presentations at meetings.

All investigators have the right to submit study questions after the analyses described in the protocol have been completed. The Steering Committee will decide whether the proposed analysis can be performed, and only if there is no conflict with other ongoing or completed analysis.

Data in the database will not be distributed to third parties without explicit and written agreement of the local investigator.

## ARCHIVING

Local investigators will keep the CRFs according to local regulations.

## PUBLICATION RULES

Steering Committee members will be part of the writing committee and listed as authors of the final manuscript.

The primary analysis of the study will be submitted preferentially to a journal that allows all local investigators to be added as authors, albeit that a minimum of 150 patients should have been included in the study.

If the manuscript arising from the primary analysis will not be accepted in one of the top three medical journals (NEJM, JAMA or Lancet), the manuscript will be submitted to European Respiratory Journal. Authorship for the national coordinators and local investigators will be based on patient enrollment, participation in data analysis as well as contribution to the final manuscript.

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