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Automated oxygen administration vs. conventional oxygen therapy after major abdominal or thoracic surgery: study protocol for an international multicenter randomized controlled study.

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ABSTRACT

Introduction

Hypoxemia and hyperoxia may occur after surgery with potential related complications. The FreeO_2 Post-Op trial is a prospective, multicenter, randomized, controlled trial that evaluates the clinical impact of automated O_2 administration vs. conventional O_2 therapy after major abdominal or thoracic surgeries. The study is powered to demonstrate benefits of automated oxygen titration and weaning in term of oxygenation, which is an important surrogate for complications after such interventions.

Methods and Analysis

After extubation, patients are randomly assigned to the *Standard* (manual O_2 administration) or *FreeO_2* group (automated closed-loop O_2 administration). Stratification is performed for the study center and a medical history of COPD. Primary outcome is the percentage of time spent in the target zone of oxygen saturation, during a 3-days time frame. In both groups, patients will benefit from continuous oximetry recordings. The target zone of oxygen saturation is SpO_2 = 88-92% for COPD and 92-96% for non-COPD patients. Secondary outcomes are the nursing workload assessed by the number of manual O_2 flow adjustments, the time spent with severe desaturation (SpO_2 <85%) and hyperoxia area (SpO_2> 98%), the time spent in a hyperoxia area (SpO_2> 98%), the oxygen consumption, the duration of oxygen administration during hospitalization, the frequency of use of mechanical ventilation (invasive or noninvasive), the duration of the post-recovery room stay, the hospitalization length of stay and the survival rate.

Ethics and Dissemination

The Institutional Review Board of the University Hospital of Brest (France) approved the trial for all French centers (IDRCB RB14-060), and the institutional review board from the Québec Heart and Lung Institute (Canada) approved the trial for their own center. The results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Trial registration: clinicaltrials.gov identifier NCT02546830

Keywords: oxygen therapy, postoperative complications, thoracic surgery, abdominal surgery, hypoxemia, hyperoxia

Strengths and limitations: the study is powered to demonstrate benefits of automated oxygen titration and weaning in term of oxygenation in major thoracic and abdominal surgery; our results will not be transposable to other surgery types.

INTRODUCTION

Background and Rationale

Current standards for prescribing oxygen recommend providing adequate flows to correct hypoxemia and avoid hyperoxia.[1,2] While deleterious effects of hypoxemia are well known, the potential harmful effects of hyperoxia are underappreciated. Yet, hyperoxia may increase mortality in severe COPD patients [3-5] and may cause cardiac and neurological adverse toxicities in certain situations.[6-8] Precise control of O_2 flows is difficult to achieve in clinical practice and time-consuming.[9]

The FreeO_2 system is an innovative device, developed in collaboration between our researchers from Brest-France, Québec-Canada University Hospitals and Oxynov Inc. a R&D Spin-off from Laval University-Québec. FreeO_2 is a closed-loop device that automates oxygen administration to spontaneously breathing patients, in response to pulse oximetry (SpO_2) continuous measurements.[10] Automated O_2 administration allows to maintain constant SpO_2 within a pre-determined range using variable O_2 flows, as opposed to manual O_2 administration where the flow is kept constant, with variable SpO_2 values. In preterm infants receiving mechanical ventilation, automated O_2 control results in more time spent within the intended SpO_2 target.[11-13] In a healthy adult model with induced hypoxemia, such a system was more efficient to maintain SpO_2 within the oxygenation target, while ensuring a significant reduction of hypoxemia and hyperoxia periods, as compared to constant O_2 flows.[14] Its efficacy has also been validated in hospitalized COPD patients,[15] or during the early emergency care of patients with acute respiratory distress.[10]

Following major abdominal or thoracic surgery, the risk of hypoxemia may be high while considering patients' clinical status (OSA, restrictive pathologies related to obesity, frequent co-morbidities …etc…), the type of surgery and anesthesia.[16-21] Hypoxemia may occur either during the immediate postoperative period (they are mainly related to surgery or anesthesia) or may be delayed up to 3-days without clear trigger or underlying pathologies. The potential interest of the FreeO_2 system, using artifical intelligence closed-loop

adjustments and predictive analytics, will thus be 1- to perform frequent and rapid O_2 adjustments in response to oxygenation condition variations (up to each second), or to any physiological condition changes (movement, speech, eating …); 2- to enable remote monitoring and data recording in isolated clinical settings (*i.e.* non-ICU surgical ward), in order to detect clinical deterioration at a very early stage through integration and fusion of informations; 3- to avoid maintenance of un-necessary high O_2 flow that may be potentially deleterious (hypercapnia worsening, coronary and/or cerebral arteries vasoconstriction…).

Objectives

The FreeO_2 Post-Op trial aims to evaluate the clinical impact of automated O_2 administration vs conventional O_2 therapy in terms of oxygenation and hypoxemia prevention after major abdominal or thoracic surgeries.

Trial design

The FreeO_2 PostOp study is an investigator-initiated, prospective, multicenter, randomized, control, open trial on medical devices comparing two strategies of oxygen therapy following major surgeries with either standard treatment or automated closed-loop oxygenation. Patients are randomly assigned to the *Standard* (manual O_2 administration) or *FreeO_2* group (automated closed-loop O_2 administration).

METHODS: PATIENTS, INTERVENTIONS AND OUTCOMES

Study setting

The FreeO_2 PostOp study is taking place in 5 different university hospitals in France and Canada (Brest, Clermont-Ferrand, Montpellier, Poitiers, Québec). The Institutional Review Board of the University Hospital of Brest (France) approved the trial for all French centers (IDRCB RB14-060). The institutional review board from the Québec Heart and Lung Institute (Canada) approved the trial for their own center. The FreeO_2 Post-Op study is conducted in accordance with the declaration of Helsinki and was registered on September 11, 2015 at http://www.clinicaltrials.gov with trial identification number NCT02546830. First patient inclusion was performed on January 14th of 2016.

Eligibility criteria

Inclusion criteria

To be included, adult patients (≥ 18 years) may be screened for scheduled abdominal or thoracic surgery during the anesthesia consultation and be considered as requiring general anesthesia with an expected duration of two hours or more in the participating centers.
Patients with intermediate to high risk for postoperative pulmonary complications following abdominal surgery with general anesthesia are eligible for participation. To identify such patients, the ARISCAT risk score will be used.[22] An ARISCAT risk score ≥ 26 is associated with an intermediate to high risk for postoperative pulmonary complications.
Informed consent is to be signed before the surgery. (Figure 1).

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: life-threatening condition requiring an unplanned emergent surgery, lack of informed consent prior to randomization, non-adult patients (age <18 years), patients with a body mass index ≥35

kg/m^2, patients with obstructive sleep apnea, and pregnant patients to provide a relatively homogenous study population and avoid potential confounding factors in the interpretation.

Randomization criteria

Patients will be randomized if they fulfill all the following criteria: availability of the FreeO_2 prototype; absence of criteria of severity justifying the immediate utilization of ventilatory support (loss of consciousness with a Glasgow Coma Score ≤ 12, serious ventricular rhythm disorders, hemodynamic instability (SBP <80mmHg or recourse to vasopressors), cardiac or respiratory arrest, pH < 7.35 and $PaCO_2$ > 55 mm Hg (if measured), necessity of an O_2 flow less than 15 L/min to maintain a SpO_2 higher than 92%; no emergent surgery required for an adverse event; pulse oximetry signal is available.

Study intervention

Patients eligible for randomization will be randomly assigned to the *Standard* or *FreeO_2* group (Figure 2). The maximal study duration is 3 days. The study was stopped before 3 days if patient was discharge earlier from hospital or in case of discomfort while keeping nasal prongs and sensors.

Automated O_2 administration is performed using the FreeO_2 system (Oxynov Inc., Québec, QC, Canada) that is set to maintain SpO_2 between 92-96% for non-COPD patients or between 88-92% for COPD patients. FreeO_2 is equipped with a SpO_2 monitor and an electronically-controlled valve that automatically adjusts O_2 flows from 0 to 20 L/min on a per second basis, with a 0.1 L/min precision, according to a closed-loop algorithm in order to reach the predetermined SpO_2 target.[14] Conventional O_2 is administered using manual flowmeters, according to standard procedures. All participating units were encouraged to use the same standardized SpO_2 target as in the automated O_2 administration group, as recommended in international guidelines.[1,2] In both arms, oxygen can be administered either using nasal prongs for low flow (O_2 < 6 L/min), or standard face mask in all cases (O_2 = 0-20 L/min).
Continuous oximetry recordings are performed in each group during the 3 days of the study, using the FreeO_2 monitoring system connected to Nonin© 6000 CA flexible adult single-use digital sensors. Position of the sensors is to be controlled at least every 12-hours. In the FreeO_2 group, the FreeO_2 will be used both for oxygen administration and for recording. In

the Standard group, the $FreeO_2$ will be used in the recording only and the oxygen administration will be set manually.

Standard procedures

Considering the variety of pathological cases for patients attending the recovery room, medical treatment, including the other respiratory support, is determined by the attending physicians based on clinical needs assessment. All other aspects of patient care after inclusion in the study, including fluid administration, prophylactic antibiotics and postoperative pain management, are made at clinicians' discretion based on the expertise of the staff at each center and routine clinical practice.

Primary outcome measure

The primary outcome measure will be the percentage of time spent in the target zone of oxygen saturation, during a 3-days time frame. In both groups (*Standard* and *$FreeO_2$*), patients will be connected to the $FreeO_2$ system to enable continuous oximetry recordings of one SpO_2 value per second, either in the recording mode for patients assigned to the *Standard* group, or in the automated closed-loop mode for patients assigned to the *$FreeO_2$* group.

The target zone of oxygen saturation is SpO_2 = 88-92% for COPD and 92-96% for non-COPD patients.

Secondary outcome measures

Several secondary outcome measures will be evaluated during a 3-days time frame : nursing workload assessed by the number of manual O_2 flow adjustments and airway management procedures (twice daily assessment); time spent with severe desaturation (SpO_2<85%); time spent with hyperoxia (SpO_2> 98%); oxygen consumption measured at the end of administration;. All data related to oxygenation will be recorded in both groups using the $FreeO_2$ device.

Other outcome measures will be assessed during a maximal 28-days time frame: duration of oxygen administration during hospitalization, number of complications related to the

administration of oxygen; frequency of use of ventilation (invasive or noninvasive); duration of hospitalization; survival rate.

Participant timeline

Figure 1 shows the Consort diagram of the $FreeO_2$ PostOp study.

Sample size

Based on previous studies and data from the literature, we estimated a 85% time within oxygenation range with the automated closed-loop oxygen administration system ($FreeO_2$) during the 3 days following surgery and a standard deviation equal or more than 30%. A total number of 180 patients will be needed to demonstrate a 15% decrease in absolute difference between the *Standard* and *$FreeO_2$* groups (90 patients in each group). The α risk is 5% and the β risk is 10% with a bilateral formulation. The expected duration of patient enrolment will be 3 years.

METHODS: ASSIGNMENT OF INTERVENTION

Allocation and sequence generation

A computer-generated randomization is performed in the post-recovery room, within a one-hour delay after endotracheal extubation. It is performed using random blocks in a 1:1 ratio, with the use of a centralized web-based management system (Clinfile). Stratification is performed either according to the study center and a medical history of COPD. After randomization, treatment is to be initiated within less than one hour.

Blinding

Although the individual study assignments of the patients will not be masked, the coordinating center and all the investigators will remain unaware of the study group outcomes until the data will be locked.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

At the time of enrolment, physiological characteristics, coexisting medical conditions, surgery and anesthetics characteristics, and oxygen flow rates are recorded. In both groups, pulse oximetry, respiratory and heart rate, are continuously monitored using a dedicated software enabling data extraction from the FreeO_2 device. Each hour during the first 3 hours following randomization and daily during the following 3 days, all standard clinical parameters are collected. Evolution and clinical outcomes are monitored at Day 28.

Data are collected and recorded on an e-CRF by a trained investigator or research assistant at each centre. A blank copy of the e-CRF can be printed from the e-CRF; this enables the investigator or research assistant to fill it out with the data of the included patients, which will thereby be captured. Once data collection has been completed, the investigator or research assistant shall sign and date the copy. This document will constitute an integral part of the patient's medical records; as such, it shall be retained permanently. Data recorded in the e-CRF that originate in source documents must be consistent with each other; if they are not, the differences have got to be justified and documented.

Statistical methods

All the analyses will be performed by the study statistician, in accordance with the *International Conference on Harmonisation and Good Clinical Practice guidelines*.[23] A predefined statistical analysis plan will be followed. The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion and exclusion criteria for each patient. All the analyses will be conducted by the biostatistics department of the *Centre d'Investigation Clinique* from Brest University Hospital (CIC INSERM 1412) using SAS, V.9.3 statistical software (SAS Institute, Cary, North Carolina, USA). A two-tailed P value equal or less than 0.05 will be considered as statistically significant.

Descriptive analysis of patient groups at baseline

The continuous variables will be analyzed using standard parameters (median, interquartile ranges and extreme values, or mean and SD), while indicating the number of missing data. The category variables will be presented in the form of absolute frequency and percentage, in each treatment group.

The criteria of subject selection will be verified based on the data recorded in the electronic case reports. Falsely included subjects such as those lost to follow-up will be described. Deviations from the protocol will be described and analyzed on a case-by-case basis.

Analysis pertaining to the main criteria of evaluation

The percentages of time within the considered SpO_2 range will be compared between the two groups by means of a variance analysis, according to stratification.

Analysis pertaining to the secondary criteria of evaluation

Secondary criteria of evaluation will be compared between the two treatment groups by means of the Student's t-test (or the Mann–Whitney U test, if necessary) for continuous quantitative variables and by means of the X2 test (or Fisher's exact test) for qualitative variables.

METHODS: MONITORING

Data monitoring

Before starting patient enrolment, all physicians and other healthcare workers in the ICU attend formal training sessions on the study protocol and data collection.

An investigator at each center is responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the e-CRF. Research assistants regularly monitor all the centers on site to check adherence to the protocol and the accuracy of the data recorded.

Harms

The investigator is allowed to temporarily, or permanently discontinue the participation of a patient in the study for any reason that would optimally serve the interests of the subject, particularly in case of serious adverse events suspected to be associated with the type of oxygenation method that is used.

Auditing

The trial is overseen by a steering committee and an independent safety monitoring board composed of three independent experts (Jean-Pierre Frat, Christophe Guitton, Alain Mercat). All centers are monitored by the promotor to check adherence to the protocol, and accuracy of recorded data. An investigator at each center is responsible for enrolling patients and ensuring adherence to the protocol. Research assistants at each center are responsible for patients' follow-up, and for completing the electronic case-report form.

ETHICS AND DISSEMINATION

Consent or assent

The patient is included after having provided a written informed consent to the investigator according to the decision of the central ethics committee. If the patient is not able to understand the information given, he/she can be included if the same procedure is completed with a next of kin. After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.

Patient and public involvement

Patients and the public were not involved in the design or conduct of the study. There is no plan to disseminate the results to study participants.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The FreeO_2 PostOp study is an investigator-initiated trial funded by the French Ministry of Health obtained in 2014 from a regional hospital clinical research programme (*Programme Hospitalier de Recherche Clinique Interrégional HUGO 2014*). A scientific committee including ELH, FL, and EN conceived, drafted and wrote the project. All other authors of the current manuscript are the investigators in the different centers. The study is promoted by the University Hospital of Brest.

ELH and FL are the inventors of the $FreeO_2$ device and founded Oxynov Inc. to develop the commercial device. The firm Oxynov Inc. provides the automated oxygen therapy equipment to all the participating centers but has no other involvement in the study.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicize and explain the research to clinicians, commissioners and service users.

DISCUSSION

In postoperative patients, pulmonary function is markedly altered both by general anesthesia, mechanical ventilation and surgery. Postoperative respiratory complications following surgery are the second most frequent complications after surgery [19] and considered as a major cause of morbidity and mortality. [17,24,25] The $FreeO_2$ PostOp trial is the first clinical evaluation of automated oxygen titration in patients undergoing major abdominal or thoracic surgeries. The objectives of the study are to compare the oxygenation parameters (time in the oxygenation target, time with hypoxemia and with hyperoxia) with usual oxygen therapy and automated oxygen titration and weaning.

Risk and consequences of hypoxemia

There is a good level of evidence and good acceptation by the medical community that hypoxemia is harmful,[26] especially in adult patients with myocardial ischemia,[27] neuro-trauma.[28] Data also suggests that even short periods of hypoxemia may promote significant negative hemodynamic effects.[29] In an animal model, right ventricular dilation was observed with only 2 hours of daily hypoxemia.[30]

During the postoperative period, the occurrence of marked oxygen desaturation related to periodic apnea and hypoventilation for several hours has been recognized for a long time,[31,32] with potentially severe consequences such as myocardial ischemia.[33] The incidence of hypoxemia is high in the recovery room (10-50%),[20] and up to 50% of postoperative patients will demonstrate episodic hypoxemia in the absence of O_2 therapy.[34,35] It has also been shown that desaturation episodes are more frequent on the first night after surgery, but may also worsened 3-5 days postoperatively, especially in patients with obstructive sleep apnea.[36-38]

Pathophysiology of these O_2 desaturations is complex but may be due either to the patient's condition itself (advanced age, COPD, diabetes, obesity…), respiratory mechanics modifications (reduction of functional residual capacity, atelectasis, thoracoabdominal compliance decrease), but also to the use of pharmaceutic agents that are given during surgery (anesthetics and neuromuscular blocking drugs), or those that are given to relief postoperative pain (opioids and sedatives).[32]

Our hypothesis is that desaturations will be reduced with the automated oxygen titration (FreeO_2 group), as the oxygen flow is titrated every second and that desaturations will immediately lead to increasing of oxygen flowrate. In previous studies comparing manual and automated oxygen administration, it was demonstrated that time with hypoxemia was reduced with FreeO_2.[10,15] However, no data are available during the postoperative care.

Automated weaning of oxygen

Oxygen supplementation has initially been promoted to decrease postoperative hypoxemia, even if it is also known that it will not have any effect on the overall number of central or obstructive apnea, neither atelectasis.[31] Not all patients will benefit from systematic O_2 administration,[39] but probably only specific patients with a high-risk profile, especially those following long duration and major thoracic or abdominal surgery.[40-42] Moreover, standard continuous O_2 therapy tends to reduce but not abolish the occurrence of desaturation,[34] given the fact that only point checks are made to adjust O_2 flow to actual patients' needs.

It has also been demonstrated that the duration of O_2 therapy was an independent risk factor for developing postoperative respiratory complications. Patients who require O_2 for

≥75% of recovery room time (or greater than 90 min) appear to be at greater risk of developing respiratory complications.[43] This fact may suggest that some patients are not adequately screened for risk factors such as OSA by standard pre-anesthesia testing, and that a device dedicated to continuous monitoring of O_2 administration (either alarms on duration and flow variations) may help to detect such high-risk patients. The increased resource utilization in patients with longer oxygen therapy requirement in the recovery room likely reflects the increase in occurrence of pulmonary respiratory complications requiring invasive and non-invasive ventilatory support, especially on the day of surgery.

In L'Her et al study, it was shown that the partial or complete oxygen weaning was significantly increased with automated oxygen titration in comparison with standard oxygen administration, in patients managed in the emergency department during 3 hours.[10]

In the specific setting of post-operative patients, the reduction of the weaning time may improve the efficiency of the turn-over of the patients in the recovery room.

Risk and consequences of hyperoxemia

Few studies have promoted the utilization of hyperoxia during and after colo-rectal surgery to reduce wound infection [44] but this is not recommended in routine, given controversial data.[45-47] In a post-hoc analysis of the PROXI trial, the authors even pointed out the potential risks of acute coronary syndromes associated with perioperative hyperoxia.[48] The pathophysiological risks associated with hyperoxia are described for a long time, especially in COPD patients.[4] The first recommendation to adjust oxygen flow rates in order to reduce the risks of hyperoxia was published in the early 60's,[49] and several more recent guidelines have reiterated similar recommendations.[1,2] The recent demonstration in a large randomized controlled trial of an increased mortality for ICU patients assigned to a standard O_2 therapy practice, as compared to a more conservative one (absolute risk reduction 0.086 [95% CI, 0.017-0.150]; p=0.01) has revived the debate about potential harm of excessive oxygen therapy in an unselected patients' population.[50] Adverse effects of hyperoxia could be mediated through a higher oxidative stress, but also increased coronary [6,7] and cerebral arteries resistances,[8] all being associated with a potential clinical impact.[51,52] Such potential adverse events related to hyperoxia clearly mandates attention in avoiding unnecessary O_2 administration. It was demonstrated in two randomized trials from our team,[10,15] that time with hyperoxia could be reduced with

automated oxygen titration, and the hypothesis of the present study is that this problem will also be reduced after thoracic or abdominal surgeries.

Clinical data with automated oxygen titration

Several systems have been developed to titrate oxygen flow rate in neonates and in adult patients.[10,14] In a previous RCT on adult patients admitted to the ED for acute hypoxemic respiratory failure, the use of automated O_2 administration was found superior to manual O_2 administration to improve the time spent within oxygenation targets, with a between-group difference of 29%,[10] as already observed in other studies on O_2 automated administration.[53,54] In L'Her et al study, patients experienced less time with hypoxemia and hyperoxia in the FreeO_2 group.[10] When receiving automated oxygen, partial or complete oxygen weaning was more frequent during initial care, as compared to standard manual O_2 administration.

As automated closed-loop O_2 administration is not the standard of care for postoperative patients, we did not design this study as a non-inferiority study but rather as a superiority study. One limitation of the study is that investigators are aware of the inclusion group, and blinding is difficult in studies with respiratory support. However, given the characteristics of the two strategies under evaluation, a double-blind trial was not possible. Second, the assessment of the oxygenation status could be considered as more precise by analyzing blood gas sample rather than SpO_2. However, this would not enable continuous oxygenation monitoring up to 3-days. Moreover, only continuous of non-averaged SpO_2 values do enable precise and rapid adjustments of the O_2 flow, in response to exact patients' needs.
Noteworthy, all patients in both groups will be continuously monitored using the same oximeter, which may represent a strength of this study; therefore, the FreeO_2 PostOp will also represent the largest prospective study comparing two oxygenation strategies over such a period in the postoperative setting.

In conclusion, the FreeO_2 PostOp trial is a pragmatic RCT designed to test the hypothesis that automated closed-loop O_2 administration is superior to standard manual O_2 administration, during the postoperative care of patients with major abdominal or thoracic surgery. To the

best of our knowledge, the FreeO_2 PostOp trial is the first to evaluate the usefulness of automated closed-loop O_2 administration after extubation in such an indication.

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Footnotes

Contributors E-LH and F-L designed this study, drafted the manuscript of the protocol and critically revised the manuscript. E-LH, S-J, D-V, C-J, B-H, E-F, T-K, V-P, PA-B, and F-L participated in the conduct of the study. M-G and E-N participated in the protocol methodological assessment and statistical plan. All authors read and approved the final manuscript.

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Disclaimer The sponsors have no role in the study design and conduct; the collection, management, analysis and interpretation of the data; or the preparation and approval of the manuscript.

Competing interests E-LH reports lecture fees and travel expenses for lectures given at academic meetings from GE Healthcare, Sedana Medical, Smiths Medical, Air Liquide Medical Systems. ELH and FL are the inventors of the FreeO_2 device and founded Oxynov Inc. to develop the commercial device. The firm Oxynov Inc. provides the automated oxygen therapy equipment to all the participating centers but has no other involvement in the study.

Patient consent Obtained.

Ethics approval The Institutional Review Board of the University Hospital of Brest (France) approved the trial for all French centers (IDRCB RB14-060). The institutional review board from the Québec Heart and Lung Institute (Canada) approved the trial for their own center.. Any protocol modification will be submitted for review and approval by the ethics committee. The FreeO_2 Post-Op study is conducted in accordance with the declaration of Helsinki and was registered on September 11, 2015 at http://www.clinicaltrials.gov with trial identification number NCT02546830. First patient inclusion was performed on January 14th of 2016.

Provenance and peer review Not commissioned; externally peer reviewed.

Article Summary

- Hypoxemia may occur either during the immediate postoperative period, or may be delayed up to 3-days.

- While deleterious effects of hypoxemia are well known, the potential harmful effects of hyperoxia are underappreciated.

- Precise control of O_2 flows is difficult to achieve in clinical practice and time-consuming.

- The FreeO_2 PostOp trial is the first clinical evaluation of automated oxygen titration in patients undergoing major abdominal or thoracic surgeries.

- Strengths and limitations: the study is powered to demonstrate benefits of automated oxygen titration and weaning in term of oxygenation in major thoracic and abdominal surgery; our results will not be transposable to other surgery types.

Figures Legends

Figure 1: Study design of the FreeO_2 PostOp study

Inclusion is performed during the anesthesia consultation, prior to a scheduled major surgery (≥ 2-hours duration; ARISCAT score ≥ 26). Eligibility criteria are verified and the patient needs to sign the informed consent. Randomization is performed no later than 1-hour following extubation in the recovery room. Clinical data will be recorded each hour during the first 3-hours of care and twice daily for up to 3-days. Continuous SpO_2 recording will be performed in each randomization groups for up to 3-days. Outcome parameters will be assessed at day 28.

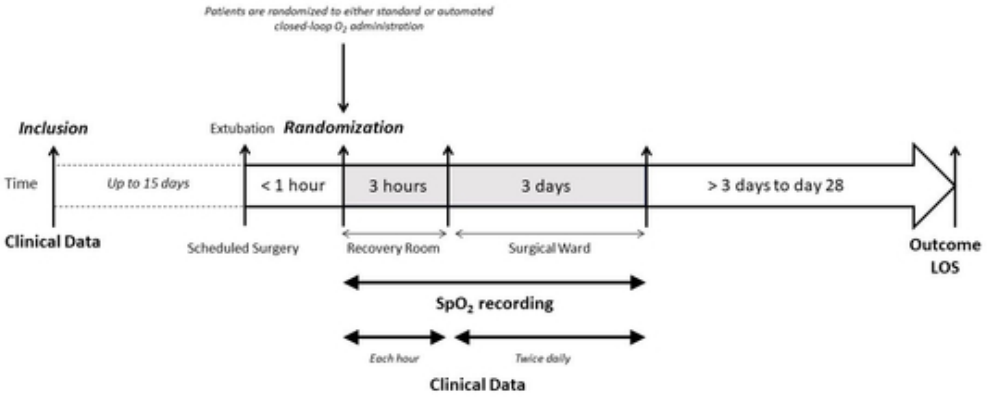
LOS: length-of-stay (days); SpO_2: pulse oximetry (%).

Figure 2: Consort diagram of the FreeO_2 PostOp study

Randomization will be performed after verification of the eligibility criteria and it will be stratified according to the presence of a medical history of COPD. For non-COPD patients the target will be a SpO_2 range = 92-96%; for COPD patients the target will be a SpO_2 range = 88-92%.

Patients will be assigned either to standard continuous O_2 administration (*Standard*: manual adjustment), or automated closed-loop O_2 administration (*FreeO_2*: automated adjustment, up to each second); in both groups, continuous SpO_2 recordings will be performed during up to 3 days according to the FreeO_2 system.

SpO_2: pulse oximetry (%).



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LOS: length-of-stay (days); SpO2: pulse oximetry (%).

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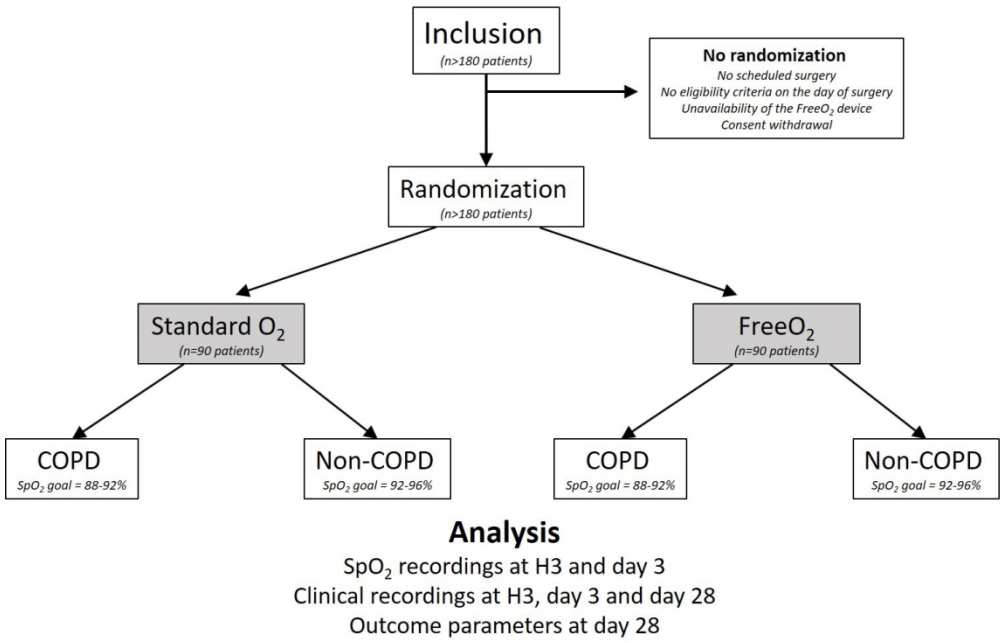

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SpO2: pulse oximetry (%).

128x83mm (300 x 300 DPI)

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Automated oxygen administration vs. conventional oxygen therapy after major abdominal or thoracic surgery: study protocol for an international multicenter randomized controlled study

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Automated oxygen administration vs. conventional oxygen therapy after major abdominal or thoracic surgery: study protocol for an international multicenter randomized controlled study.

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ABSTRACT

Introduction

Hypoxemia and hyperoxia may occur after surgery with potential related complications. The FreeO_2 Post-Op trial is a prospective, multicenter, randomized, controlled trial that evaluates the clinical impact of automated O_2 administration vs. conventional O_2 therapy after major abdominal or thoracic surgeries. The study is powered to demonstrate benefits of automated oxygen titration and weaning in term of oxygenation, which is an important surrogate for complications after such interventions.

Methods and Analysis

After extubation, patients are randomly assigned to the *Standard* (manual O_2 administration) or *FreeO_2* group (automated closed-loop O_2 administration). Stratification is performed for the study center and a medical history of COPD. Primary outcome is the percentage of time spent in the target zone of oxygen saturation, during a 3-days time frame. In both groups, patients will benefit from continuous oximetry recordings. The target zone of oxygen saturation is SpO_2 = 88-92% for COPD and 92-96% for non-COPD patients. Secondary outcomes are the nursing workload assessed by the number of manual O_2 flow adjustments, the time spent with severe desaturation (SpO_2 <85%) and hyperoxia area (SpO_2> 98%), the time spent in a hyperoxia area (SpO_2> 98%), the oxygen consumption, the duration of oxygen administration during hospitalization, the frequency of use of mechanical ventilation (invasive or noninvasive), the duration of the post-recovery room stay, the hospitalization length of stay and the survival rate.

Ethics and Dissemination

The Institutional Review Board of the University Hospital of Brest (France) approved the trial for all French centers (IDRCB RB14-060), and the institutional review board from the Québec Heart and Lung Institute (Canada) approved the trial for their own center. The results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Trial registration: clinicaltrials.gov identifier NCT02546830

Keywords: oxygen therapy, postoperative complications, thoracic surgery, abdominal surgery, hypoxemia, hyperoxia

Strengths and limitations:

- The FreeO_2 PostOp trial is the first and largest clinical evaluation of automated oxygen titration over standard of care in patients undergoing major surgeries;
- As automated oxygen titration is not the standard of care for postoperative patients, the study was designed as a superiority study;
- The use of continuous and non-averaged SpO_2 values monitoring in all groups of patients enables precise oxygenation evaluation during the entire study period;
- One limitation of the study is that investigators are aware of the inclusion group, while blinding is difficult in studies with respiratory support;
- Second limitation could be that the oxygenation status assessment would have been more precise using arterial blood gases.

INTRODUCTION

Background and Rationale

Current standards for prescribing oxygen recommend providing adequate flows to correct hypoxemia and avoid hyperoxia.[1,2] While deleterious effects of hypoxemia are well known, the potential harmful effects of hyperoxia are underappreciated. Yet, hyperoxia may increase mortality in severe COPD patients [3-5] and may cause cardiac and neurological adverse toxicities in certain situations.[6-8] Precise control of O_2 flows is difficult to achieve in clinical practice and time-consuming.[9]

The FreeO_2 system (Oxynov Inc. Québec, Qc, Canada) is an innovative device, developed in collaboration between our researchers from Brest-France, Québec-Canada University Hospitals and Oxynov Inc. a R&D Spin-off from Laval University-Québec. FreeO_2 is a closed-loop device that automates oxygen administration to spontaneously breathing patients, in response to pulse oximetry (SpO_2) continuous measurements.[10] Automated O_2 administration allows to maintain constant SpO_2 within a pre-determined range using variable O_2 flows, as opposed to manual O_2 administration where the flow is kept constant, with variable SpO_2 values. In preterm infants receiving mechanical ventilation, automated O_2 control results in more time spent within the intended SpO_2 target.[11-13] In a healthy adult model with induced hypoxemia, such a system was more efficient to maintain SpO_2 within the oxygenation target, while ensuring a significant reduction of hypoxemia and hyperoxia periods, as compared to constant O_2 flows.[14] Its efficacy has also been validated in hospitalized COPD patients,[15] or during the early emergency care of patients with acute respiratory distress.[10]

Following major abdominal or thoracic surgery, the risk of hypoxemia may be high while considering patients' clinical status (OSA, restrictive pathologies related to obesity, frequent co-morbidities), the type of surgery and anesthesia.[16-21] Hypoxemia may occur either during the immediate postoperative period (they are mainly related to surgery or anesthesia) or may be delayed up to 3-days without clear trigger or underlying pathologies. The potential interest of the FreeO_2 system, using artifical intelligence closed-loop adjustments and predictive analytics, will thus be 1- to perform frequent and rapid O_2

adjustments in response to oxygenation condition variations (up to each second), or to any physiological condition changes (movement, speech, eating, toilet); 2- to enable remote monitoring and data recording in isolated clinical settings (*i.e.* non-ICU surgical ward), in order to detect clinical deterioration at a very early stage through integration and fusion of informations; 3- to avoid maintenance of un-necessary high O_2 flow that may be potentially deleterious (hypercapnia worsening, coronary and/or cerebral arteries vasoconstriction…).

Objectives

The aim of the study is to assess the use feasibility of the FreeO_2 system so as to deliver automatically oxygen in the post anesthesia care unit in a patient population admitted for major abdominal and thoracic surgery. Our hypothesis is that the FreeO_2 system will provide a better control of the oxygen saturation and reduce postoperative hypoxemia.

Trial design

The FreeO_2 PostOp study is an investigator-initiated, prospective, multicenter, randomized, control, open trial on medical devices comparing two strategies of oxygen therapy following major surgeries with either standard treatment or automated closed-loop oxygenation. Patients are randomly assigned to the *Standard* (manual O_2 administration) or *FreeO_2* group (automated closed-loop O_2 administration).

METHODS: PATIENTS, INTERVENTIONS AND OUTCOMES

Study setting

The FreeO_2 PostOp study is taking place in 5 different university hospitals in France and Canada (Brest, Clermont-Ferrand, Montpellier, Poitiers, Québec). The Institutional Review Board of the University Hospital of Brest (France) approved the trial for all French centers (IDRCB RB14-060). The institutional review board from the Québec Heart and Lung Institute (Canada) approved the trial for their own center. The FreeO_2 Post-Op study is conducted in accordance with the declaration of Helsinki and was registered on September 11, 2015 at http://www.clinicaltrials.gov with trial identification number NCT02546830. First patient inclusion was performed on January 14th of 2016. The entire study will be performed in accordance with the *International Conference on Harmonisation and Good Clinical Practice guidelines*.[22]

Eligibility criteria

Inclusion criteria

To be included, adult patients (≥ 18 years) may be screened for scheduled abdominal or thoracic surgery during the anesthesia consultation and be considered as requiring general anesthesia with an expected duration of two hours or more in the participating centers.
Patients with intermediate to high risk for postoperative pulmonary complications following abdominal surgery with general anesthesia are eligible for participation. To identify such patients, the ARISCAT risk score will be used.[23] An ARISCAT risk score ≥ 26 is associated with an intermediate to high risk for postoperative pulmonary complications.
Informed consent is to be signed before the surgery. (Figure 1).

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: life-threatening condition requiring an unplanned emergent surgery, lack of informed consent prior to

randomization, non-adult patients (age <18 years), patients with a body mass index ≥35 kg/m^2, patients with obstructive sleep apnea, pregnant or lactating women, perturbed or non-cooperative patients, to provide a relatively homogenous study population and avoid potential confounding factors in the interpretation.

Randomization criteria

Patients will be randomized if they fulfill all the following criteria: availability of the FreeO_2 prototype; absence of criteria of severity justifying the immediate utilization of ventilatory support (loss of consciousness with a Glasgow Coma Score ≤ 12, serious ventricular rhythm disorders, hemodynamic instability (SBP <80mmHg or recourse to vasopressors), cardiac or respiratory arrest, pH < 7.35 and $PaCO_2$ > 55 mm Hg (if measured), necessity of an O_2 flow less than 15 L/min to maintain a SpO_2 higher than 92%; no emergent surgery required for an adverse event; pulse oximetry signal is available.

Study intervention

Patients eligible for randomization will be randomly assigned to the *Standard* or *FreeO_2* group (Figure 2). The maximal study duration is 3 days. The study was stopped before 3 days if patient was discharge earlier from hospital or in case of discomfort while keeping nasal prongs and sensors.

Automated O_2 administration is performed using the FreeO_2 system (Oxynov Inc., Québec, QC, Canada) that is set to maintain SpO_2 between 92-96% for non-COPD patients or between 88-92% for COPD patients. FreeO_2 is equipped with a SpO_2 monitor and an electronically-controlled valve that automatically adjusts O_2 flows from 0 to 20 L/min on a per second basis, with a 0.1 L/min precision, according to a closed-loop algorithm in order to reach the predetermined SpO_2 target.[14] Conventional O_2 is administered using manual flowmeters, according to standard procedures. All participating units were encouraged to use the same standardized SpO_2 target as in the automated O_2 administration group, as recommended in international guidelines.[1,2] In both arms, oxygen can be administered either using nasal prongs for low flow (O_2 < 6 L/min), or standard face mask in all cases (O_2 = 0-20 L/min).
Continuous oximetry recordings are performed in each group during the 3 days of the study, using the FreeO_2 monitoring system connected to Nonin© 6000 CA flexible adult single-use

digital sensors. Position of the sensors is to be controlled at least every 12-hours. In the $FreeO_2$ group, the $FreeO_2$ will be used both for oxygen administration and for recording. In the Standard group, the $FreeO_2$ will be used in the recording only and the oxygen administration will be set manually.

Standard procedures

Considering the variety of pathological cases for patients attending the recovery room, medical treatment, including the other respiratory support, is determined by the attending physicians based on clinical needs assessment. All other aspects of patient care after inclusion in the study, including fluid administration, prophylactic antibiotics and postoperative pain management, are made at clinicians' discretion based on the expertise of the staff at each center and routine clinical practice.

Primary outcome measure

The primary outcome measure will be the percentage of time spent in the target zone of oxygen saturation, during a 3-days time frame. In both groups (*Standard* and *FreeO$_2$*), patients will be connected to the $FreeO_2$ system to enable continuous oximetry recordings of one SpO_2 value per second, either in the recording mode for patients assigned to the *Standard* group, or in the automated closed-loop mode for patients assigned to the *FreeO$_2$* group.

The target zone of oxygen saturation is SpO_2 = 88-92% for COPD and 92-96% for non-COPD patients.

Secondary outcome measures

Several secondary outcome measures will be evaluated during a 3-days time frame : nursing workload assessed by the number of manual O_2 flow adjustments and airway management procedures (twice daily assessment); time spent with severe desaturation (SpO_2<85%); time spent with hyperoxia (SpO_2> 98%); oxygen consumption measured at the end of administration. All data related to oxygenation will be recorded in both groups using the $FreeO_2$ device, enabling us to qualify desaturation using the Oxygen Desaturation Index at different levels (ODI2% and ODI4%).

Other outcome measures will be assessed during a maximal 28-days time frame: duration of oxygen administration during hospitalization, number of complications related to the administration of oxygen; frequency of use of ventilation (invasive or noninvasive); duration of hospitalization; survival rate.

Participant timeline

Figure 1 shows the participant timeline of the $FreeO_2$ PostOp study.

Sample size

Based on previous studies and data from the literature,[10,20] we estimated a 85% time within oxygenation range with the automated closed-loop oxygen administration system ($FreeO_2$) during the 3 days following surgery and a standard deviation equal or more than 30%. A total number of 180 patients will be needed to demonstrate a 15% decrease in absolute difference between the *Standard* and *FreeO$_2$* groups (90 patients in each group). The α risk is 5% and the β risk is 10% with a bilateral formulation. The expected duration of patient enrolment will be 3 years.

METHODS: ASSIGNMENT OF INTERVENTION

Allocation and sequence generation

A computer-generated randomization is performed in the post-recovery room, within a one-hour delay after endotracheal extubation. It is performed using random blocks in a 1:1 ratio, with the use of a centralized web-based management system (Clinfile). Stratification is performed either according to the study center and a medical history of COPD. After randomization, treatment is to be initiated within less than one hour.

Blinding

Although the individual study assignments of the patients will not be masked, the coordinating center and all the investigators will remain unaware of the study group outcomes until the data will be locked.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

At the time of enrolment, physiological characteristics, coexisting medical conditions, surgery and anesthetics characteristics, and oxygen flow rates are recorded. In both groups, pulse oximetry, respiratory and heart rate, are continuously monitored using a dedicated software enabling data extraction from the FreeO_2 device. Each hour during the first 3 hours following randomization and daily during the following 3 days, all standard clinical parameters are collected. Evolution and clinical outcomes are monitored at Day 28.

Data are collected and recorded on an e-CRF by a trained investigator or research assistant at each centre. A blank copy of the e-CRF can be printed from the e-CRF; this enables the investigator or research assistant to fill it out with the data of the included patients, which will thereby be captured. Once data collection has been completed, the investigator or research assistant shall sign and date the copy. This document will constitute an integral part of the patient's medical records; as such, it shall be retained permanently. Data recorded in the e-CRF that originate in source documents must be consistent with each other; if they are not, the differences have got to be justified and documented.

Statistical methods

All the analyses will be performed by the study statistician.

A predefined statistical analysis plan will be followed. The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion and exclusion criteria for each patient. All the analyses will be conducted by the biostatistics department of the *Centre d'Investigation Clinique* from Brest University Hospital (CIC INSERM 1412) using SAS, V.9.3 statistical software (SAS Institute, Cary, North Carolina, USA). A two-tailed P value equal or less than 0.05 will be considered as statistically significant.

Descriptive analysis of patient groups at baseline

The continuous variables will be analyzed using standard parameters (median, interquartile ranges and extreme values, or mean and SD), while indicating the number of missing data. The category variables will be presented in the form of absolute frequency and percentage, in each treatment group.

The criteria of subject selection will be verified based on the data recorded in the electronic case reports. Falsely included subjects such as those lost to follow-up will be described. Deviations from the protocol will be described and analyzed on a case-by-case basis.

Analysis pertaining to the main criteria of evaluation

The percentages of time within the considered SpO_2 range will be compared between the two groups by means of a variance analysis, according to stratification.

Analysis pertaining to the secondary criteria of evaluation

Secondary criteria of evaluation will be compared between the two treatment groups by means of the Student's t-test (or the Mann–Whitney U test, if necessary) for continuous quantitative variables and by means of the X2 test (or Fisher's exact test) for qualitative variables.

METHODS: MONITORING

Data monitoring

Before starting patient enrolment, all physicians and other healthcare workers in the ICU attend formal training sessions on the study protocol and data collection.

An investigator at each center is responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the e-CRF. Research assistants regularly monitor all the centers on site to check adherence to the protocol and the accuracy of the data recorded.

Harms

The investigator is allowed to temporarily, or permanently discontinue the participation of a patient in the study for any reason that would optimally serve the interests of the subject, particularly in case of serious adverse events suspected to be associated with the type of oxygenation method that is used.

Auditing

The trial is overseen by a steering committee and an independent safety monitoring board composed of three independent experts (Jean-Pierre Frat, Christophe Guitton, Alain Mercat). All centers are monitored by the promotor to check adherence to the protocol, and accuracy of recorded data. An investigator at each center is responsible for enrolling patients and ensuring adherence to the protocol. Research assistants at each center are responsible for patients' follow-up, and for completing the electronic case-report form.

ETHICS AND DISSEMINATION

The French national agency for drug and biomedical devices security (ANSM) approved the use of the FreeO_2 device within this study on the 5th of August 2014. The Institutional Review Board of the University Hospital of Brest, France (CPP Ouest 6 -845) approved the trial for all French centers on the 2nd of February 2015 (IDRCB RB14-060). The main modification of the protocol was made after obtaining CE marking for the device (Protocol version #3), other amendments were related to investigators changes and an extension of the study length (final version: #5). The study sponsor notified all amendments to investigators. The institutional review board from the Québec Heart and Lung Institute (Canada) approved the trial for their own center.

Consent or assent

The patient is included after having provided a written informed consent to the investigator according to the decision of the central ethics committee. If the patient is not able to understand the information given, he/she can be included if the same procedure is completed with a next of kin. After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.

Patient and public involvement

Patients and the public were not involved in the design or conduct of the study. There is no plan to disseminate the results to study participants.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The $FreeO_2$ PostOp study is an investigator-initiated trial funded by the French Ministry of Health obtained in 2014 from a regional hospital clinical research programme (*Programme Hospitalier de Recherche Clinique Interrégional HUGO 2014*). A scientific committee including ELH, FL, and EN conceived, drafted and wrote the project. All other authors of the current manuscript are the investigators in the different centers. The study is promoted by the University Hospital of Brest.

ELH and FL are the inventors of the $FreeO_2$ device and founded Oxynov Inc. to develop the commercial device. The firm Oxynov Inc. provides the automated oxygen therapy equipment to all the participating centers but has no other involvement in the study.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

The protocol is reported according to the SPIRIT guidelines.[24] Findings will be submitted to peer-reviewed journals and presented at local, national and international meetings and conferences according to CONSORT guidelines.[25] to publicize and explain the research to clinicians, commissioners and service users.

Authorship eligibility guidelines will take into account participation to the protocol design and writing, final analysis of the results, patients' recruitment, and final manuscript revision.

DISCUSSION

In postoperative patients, pulmonary function is markedly altered both by general anesthesia, mechanical ventilation and surgery. Postoperative respiratory complications following surgery are the second most frequent complications after surgery [19] and considered as a major cause of morbidity and mortality. [17,26,27] The FreeO_2 PostOp trial is the first clinical evaluation of automated oxygen titration in patients undergoing major abdominal or thoracic surgeries. The objectives of the study are to compare the oxygenation parameters (time in the oxygenation target, time with hypoxemia and with hyperoxia) with usual oxygen therapy and automated oxygen titration and weaning.

Risk and consequences of hypoxemia

There is a good level of evidence and good acceptation by the medical community that hypoxemia is harmful,[28] especially in adult patients with myocardial ischemia,[29] neuro-trauma.[30] Data also suggests that even short periods of hypoxemia may promote significant negative hemodynamic effects.[31] In an animal model, right ventricular dilation was observed with only 2 hours of daily hypoxemia.[32]

During the postoperative period, the occurrence of marked oxygen desaturation related to periodic apnea and hypoventilation for several hours has been recognized for a long time,[33,34] with potentially severe consequences such as myocardial ischemia.[35] The incidence of hypoxemia is high in the recovery room (10-50%),[20] and up to 50% of postoperative patients will demonstrate episodic hypoxemia in the absence of O_2 therapy. [36,37] It has also been shown that desaturation episodes are more frequent on the first night after surgery, but may also worsened 3-5 days postoperatively, especially in patients with obstructive sleep apnea.[38-40]

Pathophysiology of these O_2 desaturations is complex but may be due either to the patient's condition itself (advanced age, COPD, diabetes, obesity…), respiratory mechanics modifications (reduction of functional residual capacity, atelectasis, thoracoabdominal compliance decrease), but also to the use of pharmaceutic agents that are given during surgery (anesthetics and neuromuscular blocking drugs), or those that are given to relief postoperative pain (opioids and sedatives).[34]

Our hypothesis is that desaturations will be reduced with the automated oxygen titration (FreeO_2 group), as the oxygen flow is titrated every second and that desaturations will immediately lead to increasing of oxygen flowrate. In previous studies comparing manual and automated oxygen administration, it was demonstrated that time with hypoxemia was reduced with FreeO_2.[10,15] However, no data are available during the postoperative care.

Automated weaning of oxygen

Oxygen supplementation has initially been promoted to decrease postoperative hypoxemia, even if it is also known that it will not have any effect on the overall number of central or obstructive apnea, neither atelectasis.[33] Not all patients will benefit from systematic O_2 administration,[41] but probably only specific patients with a high-risk profile, especially those following long duration and major thoracic or abdominal surgery.[42-44] Moreover, standard continuous O_2 therapy tends to reduce but not abolish the occurrence of desaturation,[36] given the fact that only point checks are made to adjust O_2 flow to actual patients' needs.

It has also been demonstrated that the duration of O_2 therapy was an independent risk factor for developing postoperative respiratory complications. Patients who require O_2 for ≥75% of recovery room time (or greater than 90 min) appear to be at greater risk of developing respiratory complications.[45] This fact may suggest that some patients are not adequately screened for risk factors such as OSA by standard pre-anesthesia testing, and that a device dedicated to continuous monitoring of O_2 administration (either alarms on duration and flow variations) may help to detect such high-risk patients. The increased resource utilization in patients with longer oxygen therapy requirement in the recovery room likely reflects the increase in occurrence of pulmonary respiratory complications requiring invasive and non-invasive ventilatory support, especially on the day of surgery.

In L'Her et al study, it was shown that the partial or complete oxygen weaning was significantly increased with automated oxygen titration in comparison with standard oxygen administration, in patients managed in the emergency department during 3 hours.[10]

In the specific setting of post-operative patients, the reduction of the weaning time may improve the efficiency of the turn-over of the patients in the recovery room.

Risk and consequences of hyperoxemia

Few studies have promoted the utilization of hyperoxia during and after colo-rectal surgery to reduce wound infection [46] but this is not recommended in routine, given controversial data.[47-49] In a post-hoc analysis of the PROXI trial, the authors even pointed out the potential risks of acute coronary syndromes associated with perioperative hyperoxia.[50] The pathophysiological risks associated with hyperoxia are described for a long time, especially in COPD patients.[4] The first recommendation to adjust oxygen flow rates in order to reduce the risks of hyperoxia was published in the early 60's,[51] and several more recent guidelines have reiterated similar recommendations.[1,2] The recent demonstration in a large randomized controlled trial of an increased mortality for ICU patients assigned to a standard O_2 therapy practice, as compared to a more conservative one (absolute risk reduction 0.086 [95% CI, 0.017-0.150]; p=0.01) has revived the debate about potential harm of excessive oxygen therapy in an unselected patients' population.[52] Adverse effects of hyperoxia could be mediated through a higher oxidative stress, but also increased coronary [6,7] and cerebral arteries resistances,[8] all being associated with a potential clinical impact.[53,54] Such potential adverse events related to hyperoxia clearly mandates attention in avoiding unnecessary O_2 administration. It was demonstrated in two randomized trials from our team,[10,15] that time with hyperoxia could be reduced with automated oxygen titration, and the hypothesis of the present study is that this problem will also be reduced after thoracic or abdominal surgeries.

Clinical data with automated oxygen titration

Several systems have been developed to titrate oxygen flow rate in neonates and in adult patients.[10,14] In a previous RCT on adult patients admitted to the ED for acute hypoxemic respiratory failure, the use of automated O_2 administration was found superior to manual O_2 administration to improve the time spent within oxygenation targets, with a between-group difference of 29%,[10] as already observed in other studies on O_2 automated administration.[55,56] In L'Her et al study, patients experienced less time with hypoxemia and hyperoxia in the FreeO_2 group.[10] When receiving automated oxygen, partial or complete oxygen weaning was more frequent during initial care, as compared to standard manual O_2 administration.

As automated closed-loop O_2 administration is not the standard of care for postoperative patients, we did not design this study as a non-inferiority study but rather as a superiority study. One limitation of the study is that investigators are aware of the inclusion group, and blinding is difficult in studies with respiratory support. However, given the characteristics of the two strategies under evaluation, a double-blind trial was not possible. Second, the assessment of the oxygenation status could be considered as more precise by analyzing blood gas sample rather than SpO_2. However, this would not enable continuous oxygenation monitoring up to 3-days. Moreover, only continuous of non-averaged SpO_2 values do enable precise and rapid adjustments of the O_2 flow, in response to exact patients' needs.
Noteworthy, all patients in both groups will be continuously monitored using the same oximeter, which may represent a strength of this study; therefore, the $FreeO_2$ PostOp will also represent the largest prospective study comparing two oxygenation strategies over such a period in the postoperative setting.

In conclusion, the $FreeO_2$ PostOp trial is a pragmatic RCT designed to test the hypothesis that automated closed-loop O_2 administration is superior to standard manual O_2 administration, during the postoperative care of patients with major abdominal or thoracic surgery. To the best of our knowledge, the $FreeO_2$ PostOp trial is the first to evaluate the usefulness of automated closed-loop O_2 administration after extubation in such an indication.

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Footnotes

Contributors E-LH and F-L designed this study, drafted the manuscript of the protocol and critically revised the manuscript. E-LH, S-J, D-V, C-J, B-H, E-F, T-K, V-P, PA-B, and F-L participated in the conduct of the study. M-G and E-N participated in the protocol methodological assessment and statistical plan. All authors read and approved the final manuscript.

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Disclaimer The sponsors have no role in the study design and conduct; the collection, management, analysis and interpretation of the data; or the preparation and approval of the manuscript.

Competing interests E-LH reports lecture fees and travel expenses for lectures given at academic meetings from GE Healthcare, Sedana Medical, Smiths Medical, Air Liquide Medical Systems. ELH and FL are the inventors of the FreeO_2 device and founded Oxynov Inc. to develop the commercial device. The firm Oxynov Inc. provides the automated oxygen therapy equipment to all the participating centers but has no other involvement in the study.

Patient consent Obtained.

Ethics approval The Institutional Review Board of the University Hospital of Brest (France) approved the trial for all French centers (IDRCB RB14-060). The institutional review board from the Québec Heart and Lung Institute (Canada) approved the trial for their own center.. Any protocol modification will be submitted for review and approval by the ethics committee. The FreeO_2 Post-Op study is conducted in accordance with the declaration of Helsinki and was registered on September 11, 2015 at http://www.clinicaltrials.gov with trial identification number NCT02546830. First patient inclusion was performed on January 14th of 2016.

Provenance and peer review Not commissioned; externally peer reviewed.

Figures Legends

Figure 1: Participant timeline of the $FreeO_2$ PostOp study

Inclusion is performed during the anesthesia consultation, prior to a scheduled major surgery (≥ 2-hours duration; ARISCAT score ≥ 26). Eligibility criteria are verified and the patient needs to sign the informed consent. Randomization is performed no later than 1-hour following extubation in the recovery room. Clinical data will be recorded each hour during the first 3-hours of care and twice daily for up to 3-days. Continuous SpO_2 recording will be performed in each randomization groups for up to 3-days. Outcome parameters will be assessed at day 28.

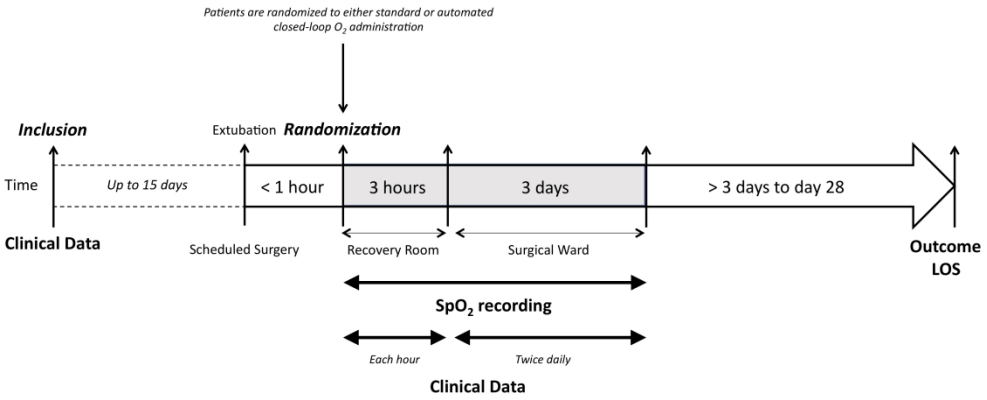
LOS: length-of-stay (days); SpO_2: pulse oximetry (%).

Figure 2: Consort diagram of the $FreeO_2$ PostOp study

Randomization will be performed after verification of the eligibility criteria and it will be stratified according to the presence of a medical history of COPD. For non-COPD patients the target will be a SpO_2 range = 92-96%; for COPD patients the target will be a SpO_2 range = 88-92%.

Patients will be assigned either to standard continuous O_2 administration (*Standard*: manual adjustment), or automated closed-loop O_2 administration (*$FreeO_2$*: automated adjustment, up to each second); in both groups, continuous SpO_2 recordings will be performed during up to 3 days according to the $FreeO_2$ system.

SpO_2: pulse oximetry (%).



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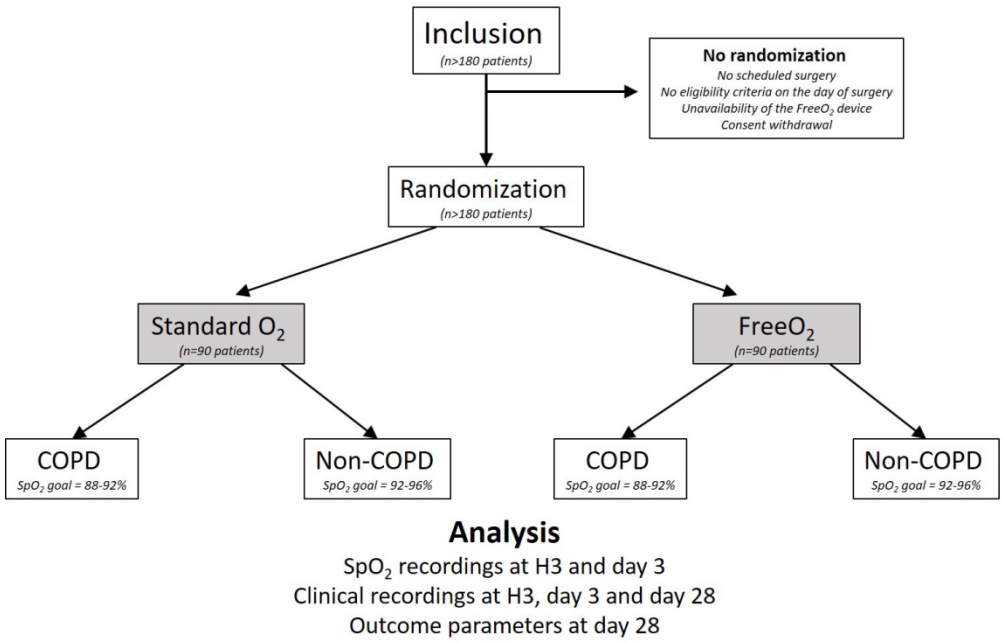

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SpO2: pulse oximetry (%).

128x83mm (300 x 300 DPI)

FreeO2 PostOp trial

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