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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 FreeO₂ Post-Op trial is a prospective, multicenter, randomized, controlled trial that evaluates the clinical impact of automated O₂ administration vs. conventional O₂ 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 O₂ administration) or *FreeO₂* group (automated closed-loop O₂ 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 SpO₂ = 88-92% for COPD and 92-96% for non-COPD patients. Secondary outcomes are the nursing workload assessed by the number of manual O₂ flow adjustments, the time spent with severe desaturation (SpO₂ <85%) and hyperoxia area (SpO₂ > 98%), the time spent in a hyperoxia area (SpO₂ > 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

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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.

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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 O₂ flows is difficult to achieve in clinical practice and time-consuming.[9]

The FreeO₂ 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. FreeO₂ is a closed-loop device that automates oxygen administration to spontaneously breathing patients, in response to pulse oximetry (SpO₂) continuous measurements.[10] Automated O₂ administration allows to maintain constant SpO₂ within a pre-determined range using variable O₂ flows, as opposed to manual O₂ administration where the flow is kept constant, with variable SpO₂ values. In preterm infants receiving mechanical ventilation, automated O₂ control results in more time spent within the intended SpO₂ target.[11-13] In a healthy adult model with induced hypoxemia, such a system was more efficient to maintain SpO₂ within the oxygenation target, while ensuring a significant reduction of hypoxemia and hyperoxia periods, as compared to constant O₂ 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 FreeO₂ system, using artificial intelligence closed-loop

adjustments and predictive analytics, will thus be 1- to perform frequent and rapid O₂ 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 O₂ flow that may be potentially deleterious (hypercapnia worsening, coronary and/or cerebral arteries vasoconstriction...).

Objectives

The FreeO₂ Post-Op trial aims to evaluate the clinical impact of automated O₂ administration vs conventional O₂ therapy in terms of oxygenation and hypoxemia prevention after major abdominal or thoracic surgeries.

Trial design

The FreeO₂ 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 O₂ administration) or *FreeO₂* group (automated closed-loop O₂ administration).

METHODS: PATIENTS, INTERVENTIONS AND OUTCOMES

Study setting

The FreeO₂ 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 FreeO₂ 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/m², 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 FreeO₂ 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 PaCO₂ > 55 mm Hg (if measured), necessity of an O₂ flow less than 15 L/min to maintain a SpO₂ 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 *FreeO₂* 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 O₂ administration is performed using the FreeO₂ system (Oxynov Inc., Québec, QC, Canada) that is set to maintain SpO₂ between 92-96% for non-COPD patients or between 88-92% for COPD patients. FreeO₂ is equipped with a SpO₂ monitor and an electronically-controlled valve that automatically adjusts O₂ 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 SpO₂ target.[14] Conventional O₂ is administered using manual flowmeters, according to standard procedures. All participating units were encouraged to use the same standardized SpO₂ target as in the automated O₂ administration group, as recommended in international guidelines.[1,2] In both arms, oxygen can be administered either using nasal prongs for low flow (O₂ < 6 L/min), or standard face mask in all cases (O₂ = 0-20 L/min).

Continuous oximetry recordings are performed in each group during the 3 days of the study, using the FreeO₂ 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 FreeO₂ group, the FreeO₂ will be used both for oxygen administration and for recording. In

the Standard group, the FreeO₂ 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 *FreeO₂*), patients will be connected to the FreeO₂ system to enable continuous oximetry recordings of one SpO₂ 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 *FreeO₂* group.

The target zone of oxygen saturation is SpO₂ = 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 O₂ flow adjustments and airway management procedures (twice daily assessment); time spent with severe desaturation (SpO₂<85%); time spent with hyperoxia (SpO₂> 98%); oxygen consumption measured at the end of administration;. All data related to oxygenation will be recorded in both groups using the FreeO₂ 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 FreeO₂ 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 (FreeO₂) 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 *FreeO₂* 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 FreeO₂ 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 SpO₂ 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 FreeO₂ 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 FreeO₂ 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 FreeO₂ 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 acceptance 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 O₂ 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 O₂ 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 pharmacologic 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 (FreeO₂ 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 FreeO₂. [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 O₂ 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 O₂ therapy tends to reduce but not abolish the occurrence of desaturation,[34] given the fact that only point checks are made to adjust O₂ flow to actual patients' needs.

It has also been demonstrated that the duration of O₂ therapy was an independent risk factor for developing postoperative respiratory complications. Patients who require O₂ 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 O₂ 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 O₂ 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 O₂ 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 O₂ administration was found superior to manual O₂ administration to improve the time spent within oxygenation targets, with a between-group difference of 29%,[10] as already observed in other studies on O₂ automated administration.[53,54] In L'Her et al study, patients experienced less time with hypoxemia and hyperoxia in the FreeO₂ group.[10] When receiving automated oxygen, partial or complete oxygen weaning was more frequent during initial care, as compared to standard manual O₂ administration.

As automated closed-loop O₂ 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 SpO₂. However, this would not enable continuous oxygenation monitoring up to 3-days. Moreover, only continuous of non-averaged SpO₂ values do enable precise and rapid adjustments of the O₂ 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 FreeO₂ PostOp will also represent the largest prospective study comparing two oxygenation strategies over such a period in the postoperative setting.

In conclusion, the FreeO₂ PostOp trial is a pragmatic RCT designed to test the hypothesis that automated closed-loop O₂ administration is superior to standard manual O₂ administration, during the postoperative care of patients with major abdominal or thoracic surgery. To the

best of our knowledge, the FreeO₂ PostOp trial is the first to evaluate the usefulness of automated closed-loop O₂ administration after extubation in such an indication.

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REFERENCES

- 1- O'Driscoll BR, Howard LS, Earis J, et al. BTS guidelines for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017; 72: i1-i90.
- 2- GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2016.
<http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016>
Date last accessed: March 30, 2018.
- 3- Abdo WF, Heunks LMA. Oxygen-induced hypercapnia in COPD: myths and facts. *Crit Care* 2012; 16: 323.
- 4- Aubier M, Murciano D, Miloc-Emili J et al. Effects of the administration of O₂ on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis* 1980; 122: 747-754.
- 5- Austin MA, Wills KE, Blizzard L et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomized controlled trial. *BMJ* 2010; 341: c5642.
- 6- Wijesinghe M, Perrin K, Ranchord A, et al. Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart* 2009; 95: 198-202.
- 7- Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J* 2009; 158: 371-317.
- 8- Floyd TF, Clark JM, Gelfand R, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. *J Appl Physiol* 2003; 95: 2453-2461.

- 9- Mok W, Wang W, Cooper S, et al. Attitudes towards vital signs monitoring in the detection of clinical deterioration: scale development and survey ward nurses. *Int J Qual Health Care* 2015; 27: 207-213.
- 10- L'Her E, Dias P, Gouillou M, et al. Automatic versus manual oxygen administration in the emergency department. *Eur Respir J* 2017; 50: 1602552.
- 11- Claire N, Gerhardt T, Everett R, et al. Closed-loop controlled inspired oxygen concentration for mechanically ventilated very low birth weight infants with frequent episodes of hypoxemia. *Pediatrics* 2001; 107: 1120-1124.
- 12- Claire N, Bancalari E, D'Ugard C, et al. Multicenter crossover study of automated controlled of inspired oxygen in ventilated preterm infants. *Pediatrics* 2011; 127: e76-e83.
- 13- Hallenberger A, Poets CF, Hom W, et al. Closed-loop automatic oxygen control (CLAC) in preterm infants: a randomized controlled trial. *Pediatrics* 2014; 133: e379-e385.
- 14- Lellouche F, L'Her E. Automated oxygen flow titration to maintain constant oxygenation. *Respir Care* 2012; 57: 1254-1262.
- 15- Lellouche F, Bouchard PA, Roberge M, et al. Automated oxygen titration and weaning with FreeO2 in patients with acute exacerbation of COPD: a pilot randomized trial. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1983-1990.
- 16- Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modeling strategy based on available data. *Lancet* 2008; 372: 139-144.
- 17- Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 2005; 242: 326-341.

- 18-Shander A, Fleisher LA, Barie PS, et al. Clinical and economic burden of postoperative complications: patient safety summit on definition, risk-reducing interventions, and preventive strategies. Crit Care Med 2011; 39: 2163-2172.
- 19-Arozullah AM, Daley J, Henderson WG, et al. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg 2000; 232: 242-253.
- 20-Lawrence VA, Dhanda R, Hilsenbeck SG, et al. Risk of pulmonary complications after elective abdominal surgery. Chest 1996; 110: 744-750.
- 21-Lindberg P, Gunnarsson L, Tokics L, et al. Atelectasis and lung function in the postoperative period. Acta Anaesthesiol Scand 1992; 36: 546-553.
- 22-Mazo V, Sabaté S, Canet J, et al. Prospective external validation of a predictive score for postoperative pulmonary complications. Anesthesiology 2014; 121: 219-231.
- 23-International council for harmonization of technical requirements for pharmaceuticals for human use. Guidelines for good clinical practice – R2 November 2016.
- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf Date last accessed: March 30, 2018.
- 24-Karcz M, Papadakos PJ. Respiratory complications in the postanesthesia care unit: a review of pathophysiological mechanisms. Can J Respir Ther 2013; 49: 21-29.
- 25-Serpa Neto A, Hemmes SN, Barbas CS, et al. Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. Lancet respir med 2014; 2: 1007-1015.

26-Bateman NT, Leach RM. ABC of oxygen. Acute oxygen therapy. BMJ 1998; 317: 798-801.

27-Galatius-Jensen S, Hansen J, Rasmussen V, et al. Nocturnal hypoxaemia after myocardial infarction: association with nocturnal myocardial ischaemia and arrhythmias. Br Heart J 1994; 72: 23-30.

28-DeWitt DS, Prough DS. Blast-induced brain injury and posttraumatic hypotension and hypoxemia. J Neurotrauma 2009; 26: 877-887.

29-Selinger SR, Kennedy TP, Buescher P, et al. Effects of removing oxygen from patients with chronic obstructive disease. Am Rev Respir Dis 1987; 136: 85-91.

30-Nattie EE, Doble EA. Threshold of intermittent hypoxia-induced right ventricular hypertrophy in the rat. Respir Physiol 1984; 56: 253-259.

31-Jones JG, Jordan C, Scudder C, et al. Episodic postoperative oxygen desaturation: the value of added oxygen. J R Soc Med 1985; 78: 1019-1022.

32-Catley DM, Thornton C, Jordan C, et al. Pronounced, episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. Anesthesiology 1985; 63: 20-28.

33-Gögenur I, Rosenberg-Adamsen S, Lie C, et al. relationship between nocturnal hypoxaemia, tachycardia and myocardial ischaemia after major abdominal surgery. Br J Anaesth 2004; 93: 333-338.

34-Canet J, Ricos M, Vidal F. Early postoperative arterial oxygen desaturation. Determining factors and response to oxygen therapy. Anesth Analg 1989; 69: 207-212.

- 35-Ramanchandran SK, Nafiu OO, Ghaferi A, et al. Independent predictors and outcomes of unanticipated early postoperative tracheal intubation after nonemergent, noncardiac surgery. *Anesthesiology* 2011; 115: 44-53.
- 36-Gögenur I, Wildschiotz G, Rosenberg J. Circadian distribution of sleep phases after major abdominal surgery. *Br J Anaesth* 2008; 100: 45-49.
- 37-Chung F, Liao P, Elsaid H, et al. Factors associated with postoperative exacerbation of sleep-disordered breathing. *Anesthesiology* 2014; 120: 299-311.
- 38-Rosenberg J, Wildschiodtz G, Pedersen MH, et al. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. *Br J Anaesth* 1994; 72: 145-150.
- 39- Gift AG, Stanik J, Karpenik J, et al. Oxygen saturation in postoperative patients at low risk for hypoxemia: is oxygen therapy needed? *Anesth Anal* 1995; 80: 368-372.
- 40-Pedersen T, Viby-Mogensen J, Ringsted C. Anaesthetic practice and postoperative pulmonary complications. *Acta Anaesthesiol Scand* 1992; 36: 812-818.
- 41-Mathew JP, Rosenbaum SH, O'Connor T, et al. Emergency tracheal intubation in the postoperative care unit: physician error or patient disease? *Anesth Analg* 1990; 71: 691-697.
- 42-Smetana GW, Lawrence VA, Cornell JE, et al. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. *Ann Intern Med* 2006; 144: 581-595.
- 43-Ramachandran SK, Thompson A, Pandit JJ, et al. Retrospective observational evaluation of postoperative oxygen saturation levels and associated postoperative respiratory complications and hospital resource utilization. *PloS one* 2017; 12:e0175408.

44-Greif R, Akça O, Horn EP, et al. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000 ; 342: 161-167.

45-Meyhoff CS, Wetterslev J, Jorgensen LN, et al. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA* 2009; 302: 1543-1550.

46-Togioka B, Galvagno S, Sumida S, et al. The role of perioperative high inspired oxygen therapy in reducing surgical site infection: a meta-analysis. *Anesth Analg* 2012; 114: 334-342.

47-Wetterslev J, Meyhoff CS, Jørgensen LN, et al. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. *Cochrane Database Syst Rev* 2015 Jun 25;(6):CD008884.

48-Fonnes S, Gögenur I, Sondergaard ES, et al. Perioperative hyperoxia – Long-term impact on cardiovascular complications after abdominal surgery, a post-hoc analysis of the PROXI trial.

49-Campbell EJ. The J. Burns Amberson Lecture. The management of acute respiratory failure in chronic bronchitis and emphysema. *Am Rev Respir Dis* 1967 ; 96 : 626-639.

50-Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit : the Oxygen-ICU randomized clinical trial. *JAMA* 2016; 316 : 1583-1589.

51-Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation* 2015; 131: 2143-2150.

52-Damiani E, Adrario E, Girardis M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. *Crit Care* 2014; 18: 711.

53-Cirio S, Nava S. Pilot study of a new device to titrate oxygen flow in hypoxic patients on long-term oxygen therapy. *Respir Care* 2011; 56: 429-434.

54-Rice KL, Schmidt MF, Buan JS, et al. AccuO2 oximetry-driven oxygen-conserving device versus fixed-dose oxygen devices in stable COPD patients. *Respir Care* 2011; 56: 1901-1905.

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 FreeO₂ 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 FreeO₂ 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 O₂ flows is difficult to achieve in clinical practice and time-consuming.
- The FreeO₂ 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 FreeO₂ 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 SpO₂ 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); SpO₂: pulse oximetry (%).

Figure 2: Consort diagram of the FreeO₂ 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 SpO₂ range = 92-96%; for COPD patients the target will be a SpO₂ range = 88-92%.

Patients will be assigned either to standard continuous O₂ administration (*Standard*: manual adjustment), or automated closed-loop O₂ administration (*FreeO₂*: automated adjustment, up to each second); in both groups, continuous SpO₂ recordings will be performed during up to 3 days according to the FreeO₂ system.

SpO₂: pulse oximetry (%).

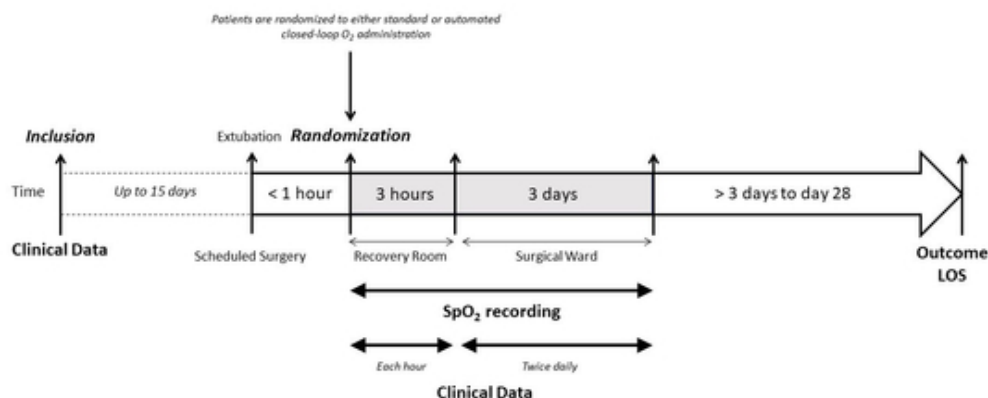


Figure 1: Study design of the FreeO2 PostOp study

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 SpO₂ 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); SpO₂: pulse oximetry (%).

45x25mm (300 x 300 DPI)

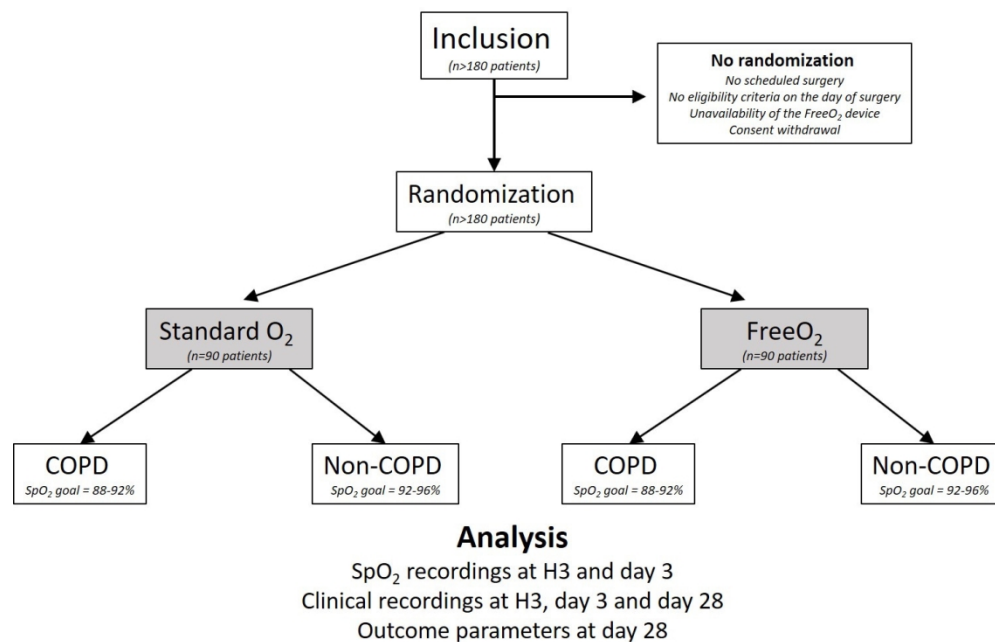


Figure 2: Consort diagram of the FreeO2 PostOp study

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 SpO₂ range = 92-96%; for COPD patients the target will be a SpO₂ range = 88-92%.

Patients will be assigned either to standard continuous O₂ administration (Standard: manual adjustment), or automated closed-loop O₂ administration (FreeO₂: automated adjustment, up to each second); in both groups, continuous SpO₂ recordings will be performed during up to 3 days according to the FreeO₂ system. SpO₂: pulse oximetry (%).

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Primary Subject Heading:	Respiratory medicine
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Manuscripts

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 FreeO₂ Post-Op trial is a prospective, multicenter, randomized, controlled trial that evaluates the clinical impact of automated O₂ administration vs. conventional O₂ 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 O₂ administration) or *FreeO₂* group (automated closed-loop O₂ 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 SpO₂ = 88-92% for COPD and 92-96% for non-COPD patients. Secondary outcomes are the nursing workload assessed by the number of manual O₂ flow adjustments, the time spent with severe desaturation (SpO₂ <85%) and hyperoxia area (SpO₂ > 98%), the time spent in a hyperoxia area (SpO₂ > 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

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Strengths and limitations:

- The FreeO₂ 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 SpO₂ 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 O₂ flows is difficult to achieve in clinical practice and time-consuming.[9]

The FreeO₂ 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. FreeO₂ is a closed-loop device that automates oxygen administration to spontaneously breathing patients, in response to pulse oximetry (SpO₂) continuous measurements.[10] Automated O₂ administration allows to maintain constant SpO₂ within a pre-determined range using variable O₂ flows, as opposed to manual O₂ administration where the flow is kept constant, with variable SpO₂ values. In preterm infants receiving mechanical ventilation, automated O₂ control results in more time spent within the intended SpO₂ target.[11-13] In a healthy adult model with induced hypoxemia, such a system was more efficient to maintain SpO₂ within the oxygenation target, while ensuring a significant reduction of hypoxemia and hyperoxia periods, as compared to constant O₂ 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 FreeO₂ system, using artificial intelligence closed-loop adjustments and predictive analytics, will thus be 1- to perform frequent and rapid O₂

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 O₂ 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 FreeO₂ 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 FreeO₂ system will provide a better control of the oxygen saturation and reduce postoperative hypoxemia.

Trial design

The FreeO₂ 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 O₂ administration) or *FreeO₂* group (automated closed-loop O₂ administration).

METHODS: PATIENTS, INTERVENTIONS AND OUTCOMES

Study setting

The FreeO₂ 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 FreeO₂ 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/m², 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 FreeO₂ 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 PaCO₂ > 55 mm Hg (if measured), necessity of an O₂ flow less than 15 L/min to maintain a SpO₂ 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 *FreeO₂* 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 O₂ administration is performed using the FreeO₂ system (Oxynov Inc., Québec, QC, Canada) that is set to maintain SpO₂ between 92-96% for non-COPD patients or between 88-92% for COPD patients. FreeO₂ is equipped with a SpO₂ monitor and an electronically-controlled valve that automatically adjusts O₂ 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 SpO₂ target.[14] Conventional O₂ is administered using manual flowmeters, according to standard procedures. All participating units were encouraged to use the same standardized SpO₂ target as in the automated O₂ administration group, as recommended in international guidelines.[1,2] In both arms, oxygen can be administered either using nasal prongs for low flow (O₂ < 6 L/min), or standard face mask in all cases (O₂ = 0-20 L/min). Continuous oximetry recordings are performed in each group during the 3 days of the study, using the FreeO₂ 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 FreeO₂ group, the FreeO₂ will be used both for oxygen administration and for recording. In the Standard group, the FreeO₂ 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 *FreeO₂*), patients will be connected to the FreeO₂ system to enable continuous oximetry recordings of one SpO₂ 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 *FreeO₂* group.

The target zone of oxygen saturation is SpO₂ = 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 O₂ flow adjustments and airway management procedures (twice daily assessment); time spent with severe desaturation (SpO₂<85%); time spent with hyperoxia (SpO₂> 98%); oxygen consumption measured at the end of administration. All data related to oxygenation will be recorded in both groups using the FreeO₂ 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 FreeO₂ 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 (FreeO₂) 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 *FreeO₂* 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 anaesthetics 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 FreeO₂ 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 SpO₂ 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 FreeO₂ 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 FreeO₂ 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 FreeO₂ 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 FreeO₂ 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 acceptance 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 O₂ 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 O₂ 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 pharmacologic agents that are given during surgery (anesthetics and neuromuscular blocking drugs), or those that are given to relieve postoperative pain (opioids and sedatives).[34]

Our hypothesis is that desaturations will be reduced with the automated oxygen titration (FreeO₂ 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 FreeO₂.^[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 O₂ 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 O₂ therapy tends to reduce but not abolish the occurrence of desaturation,^[36] given the fact that only point checks are made to adjust O₂ flow to actual patients' needs.

It has also been demonstrated that the duration of O₂ therapy was an independent risk factor for developing postoperative respiratory complications. Patients who require O₂ 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 O₂ 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 O₂ 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 O₂ 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 O₂ administration was found superior to manual O₂ administration to improve the time spent within oxygenation targets, with a between-group difference of 29%,[10] as already observed in other studies on O₂ automated administration.[55,56] In L'Her et al study, patients experienced less time with hypoxemia and hyperoxia in the FreeO₂ group.[10] When receiving automated oxygen, partial or complete oxygen weaning was more frequent during initial care, as compared to standard manual O₂ administration.

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As automated closed-loop O₂ 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 SpO₂. However, this would not enable continuous oxygenation monitoring up to 3-days. Moreover, only continuous of non-averaged SpO₂ values do enable precise and rapid adjustments of the O₂ 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 FreeO₂ PostOp will also represent the largest prospective study comparing two oxygenation strategies over such a period in the postoperative setting.

In conclusion, the FreeO₂ PostOp trial is a pragmatic RCT designed to test the hypothesis that automated closed-loop O₂ administration is superior to standard manual O₂ administration, during the postoperative care of patients with major abdominal or thoracic surgery. To the best of our knowledge, the FreeO₂ PostOp trial is the first to evaluate the usefulness of automated closed-loop O₂ administration after extubation in such an indication.

REFERENCES

- 1- O'Driscoll BR, Howard LS, Earis J, et al. BTS guidelines for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017; 72: i1-i90.
- 2- GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2016. <http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016>
Date last accessed: March 30, 2018.
- 3- Abdo WF, Heunks LMA. Oxygen-induced hypercapnia in COPD: myths and facts. *Crit Care* 2012; 16: 323.
- 4- Aubier M, Murciano D, Miloc-Emili J et al. Effects of the administration of O₂ on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis* 1980; 122: 747-754.
- 5- Austin MA, Wills KE, Blizzard L et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomized controlled trial. *BMJ* 2010; 341: c5642.
- 6- Wijesinghe M, Perrin K, Ranchord A, et al. Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart* 2009; 95: 198-202.
- 7- Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J* 2009; 158: 371-317.
- 8- Floyd TF, Clark JM, Gelfand R, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. *J Appl Physiol* 2003; 95: 2453-2461.

9- Mok W, Wang W, Cooper S, et al. Attitudes towards vital signs monitoring in the detection of clinical deterioration: scale development and survey ward nurses. *Int J Qual Health Care* 2015; 27: 207-213.

10- L’Her E, Dias P, Gouillou M, et al. Automatic versus manual oxygen administration in the emergency department. *Eur Respir J* 2017; 50: 1602552.

11- Claire N, Gerhardt T, Everett R, et al. Closed-loop controlled inspired oxygen concentration for mechanically ventilated very low birth weight infants with frequent episodes of hypoxemia. *Pediatrics* 2001; 107: 1120-1124.

12- Claire N, Bancalari E, D’Ugard C, et al. Multicenter crossover study of automated controlled of inspired oxygen in ventilated preterm infants. *Pediatrics* 2011; 127: e76-e83.

13- Hallenberger A, Poets CF, Hom W, et al. Closed-loop automatic oxygen control (CLAC) in preterm infants: a randomized controlled trial. *Pediatrics* 2014; 133: e379-e385.

14- Lellouche F, L’Her E. Automated oxygen flow titration to maintain constant oxygenation. *Respir Care* 2012; 57: 1254-1262.

15- Lellouche F, Bouchard PA, Roberge M, et al. Automated oxygen titration and weaning with FreeO2 in patients with acute exacerbation of COPD: a pilot randomized trial. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1983-1990.

16- Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modeling strategy based on available data. *Lancet* 2008; 372: 139-144.

17- Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 2005; 242: 326-341.

- 18-Shander A, Fleisher LA, Barie PS, et al. Clinical and economic burden of postoperative complications: patient safety summit on definition, risk-reducing interventions, and preventive strategies. *Crit Care Med* 2011; 39: 2163-2172.
- 19-Arozullah AM, Daley J, Henderson WG, et al. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. *Ann Surg* 2000; 232: 242-253.
- 20-Lawrence VA, Dhanda R, Hilsenbeck SG, et al. Risk of pulmonary complications after elective abdominal surgery. *Chest* 1996; 110: 744-750.
- 21-Lindberg P, Gunnarsson L, Tokics L, et al. Atelectasis and lung function in the postoperative period. *Acta Anaesthesiol Scand* 1992; 36: 546-553.
- 22-International council for harmonization of technical requirements for pharmaceuticals for human use. Guidelines for good clinical practice – R2 November 2016.
- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf Date last accessed: August 7, 2018.
- 23-Mazo V, Sabaté S, Canet J, et al. Prospective external validation of a predictive score for postoperative pulmonary complications. *Anesthesiology* 2014; 121: 219-231.
- 24-Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 2013; 158: 200-207.
- 25-Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomized trials. *BMJ* 2010; 340: c332.

26-Karcz M, Papadakos PJ. Respiratory complications in the postanesthesia care unit: a review of pathophysiological mechanisms. *Can J Respir Ther* 2013; 49: 21-29.

27-Serpa Neto A, Hemmes SN, Barbas CS, et al. Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. *Lancet Respir Med* 2014; 2: 1007-1015.

28-Bateman NT, Leach RM. ABC of oxygen. Acute oxygen therapy. *BMJ* 1998; 317: 798-801.

29-Galatius-Jensen S, Hansen J, Rasmussen V, et al. Nocturnal hypoxaemia after myocardial infarction: association with nocturnal myocardial ischaemia and arrhythmias. *Br Heart J* 1994; 72: 23-30.

30-DeWitt DS, Prough DS. Blast-induced brain injury and posttraumatic hypotension and hypoxemia. *J Neurotrauma* 2009; 26: 877-887.

31-Selinger SR, Kennedy TP, Buescher P, et al. Effects of removing oxygen from patients with chronic obstructive disease. *Am Rev Respir Dis* 1987; 136: 85-91.

32-Nattie EE, Doble EA. Threshold of intermittent hypoxia-induced right ventricular hypertrophy in the rat. *Respir Physiol* 1984; 56: 253-259.

33-Jones JG, Jordan C, Scudder C, et al. Episodic postoperative oxygen desaturation: the value of added oxygen. *J R Soc Med* 1985; 78: 1019-1022.

34-Catley DM, Thornton C, Jordan C, et al. Pronounced, episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; 63: 20-28.

- 35-Gögenur I, Rosenberg-Adamsen S, Lie C, et al. relationship between nocturnal hypoxaemia, tachycardia and myocardial ischaemia after major abdominal surgery. *Br J Anaesth* 2004; 93: 333-338.
- 36-Canet J, Ricos M, Vidal F. Early postoperative arterial oxygen desaturation. Determining factors and response to oxygen therapy. *Anesth Analg* 1989; 69: 207-212.
- 37-Ramanchandran SK, Nafiu OO, Ghaferi A, et al. Independent predictors and outcomes of unanticipated early postoperative tracheal intubation after nonemergent, noncardiac surgery. *Anesthesiology* 2011; 115: 44-53.
- 38-Gögenur I, Wildschiotz G, Rosenberg J. Circadian distribution of sleep phases after major abdominal surgery. *Br J Anaesth* 2008; 100: 45-49.
- 39-Chung F, Liao P, Elsaid H, et al. Factors associated with postoperative exacerbation of sleep-disordered breathing. *Anesthesiology* 2014; 120: 299-311.
- 40-Rosenberg J, Wildschiodtz G, Pedersen MH, et al. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. *Br J Anaesth* 1994; 72: 145-150.
- 41- Gift AG, Stanik J, Karpenik J, et al. Oxygen saturation in postoperative patients at low risk for hypoxemia: is oxygen therapy needed? *Anesth Analg* 1995; 80: 368-372.
- 42-Pedersen T, Viby-Mogensen J, Ringsted C. Anaesthetic practice and postoperative pulmonary complications. *Acta Anaesthesiol Scand* 1992; 36: 812-818.
- 43-Mathew JP, Rosenbaum SH, O'Connor T, et al. Emergency tracheal intubation in the postoperative care unit: physician error or patient disease? *Anesth Analg* 1990; 71: 691-697.

44-Smetana GW, Lawrence VA, Cornell JE, et al. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. *Ann Intern Med* 2006; 144: 581-595.

45-Ramachandran SK, Thompson A, Pandit JJ, et al. Retrospective observational evaluation of postoperative oxygen saturation levels and associated postoperative respiratory complications and hospital resource utilization. *PloS One* 2017; 12:e0175408.

46-Greif R, Akça O, Horn EP, et al. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000 ; 342: 161-167.

47-Meyhoff CS, Wetterslev J, Jorgensen LN, et al. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA* 2009; 302: 1543-1550.

48-Togioka B, Galvagno S, Sumida S, et al. The role of perioperative high inspired oxygen therapy in reducing surgical site infection: a meta-analysis. *Anesth Analg* 2012; 114: 334-342.

49-Wetterslev J, Meyhoff CS, Jørgensen LN, et al. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. *Cochrane Database Syst Rev* 2015 Jun 25;(6):CD008884.

50-Fonnes S, Gögenur I, Sondergaard ES, et al. Perioperative hyperoxia – Long-term impact on cardiovascular complications after abdominal surgery, a post-hoc analysis of the PROXI trial. *Int J Cardiol* 2016 ; 215 : 238-243.

51-Campbell EJ. The J. Burns Amberson Lecture. The management of acute respiratory failure in chronic bronchitis and emphysema. *Am Rev Respir Dis* 1967 ; 96 : 626-639.

52-Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit : the Oxygen-ICU randomized clinical trial. *JAMA* 2016; 316 : 1583-1589.

- 53-Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation* 2015; 131: 2143-2150.
- 54-Damiani E, Adrario E, Girardis M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. *Crit Care* 2014; 18: 711.
- 55-Cirio S, Nava S. Pilot study of a new device to titrate oxygen flow in hypoxic patients on long-term oxygen therapy. *Respir Care* 2011; 56: 429-434.
- 56-Rice KL, Schmidt MF, Buan JS, et al. AccuO2 oximetry-driven oxygen-conserving device versus fixed-dose oxygen devices in stable COPD patients. *Respir Care* 2011; 56: 1901-1905.

Or peer review only

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 FreeO₂ 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 FreeO₂ 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 FreeO₂ 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 SpO₂ 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); SpO₂: pulse oximetry (%).

Figure 2: Consort diagram of the FreeO₂ 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 SpO₂ range = 92-96%; for COPD patients the target will be a SpO₂ range = 88-92%.

Patients will be assigned either to standard continuous O₂ administration (*Standard*: manual adjustment), or automated closed-loop O₂ administration (*FreeO₂*: automated adjustment, up to each second); in both groups, continuous SpO₂ recordings will be performed during up to 3 days according to the FreeO₂ system.

SpO₂: pulse oximetry (%).

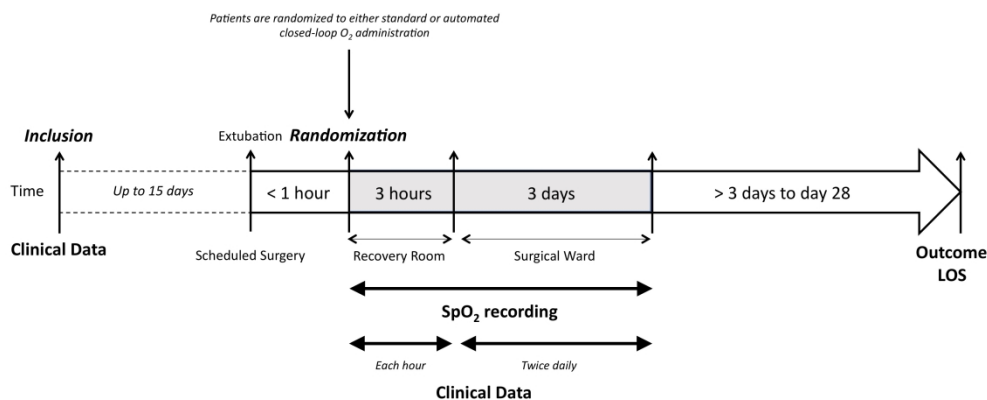


Figure 1: Participant timeline of the FreeO2 PostOp study

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 SpO₂ 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); SpO₂: pulse oximetry (%).

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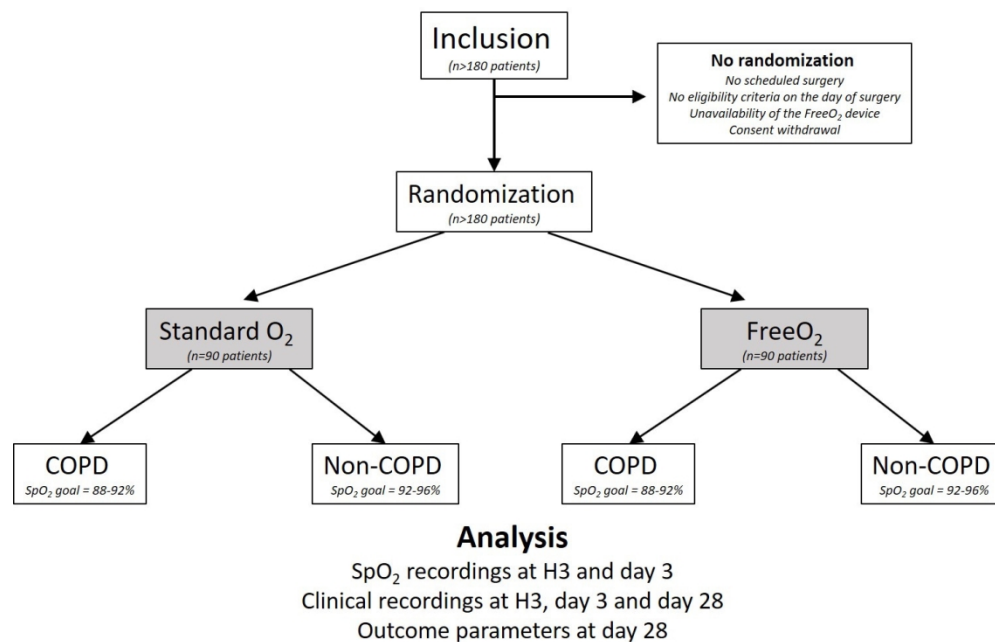


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128x83mm (300 x 300 DPI)

FreeO2 PostOp trial

SPIRIT 2013 Checklist

Section/item	Item n°	Pages
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Methods : participants, interventions and outcomes		
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Allocation		
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