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Automated closed-loop vs. standard manual oxygen administration after major abdominal or thoracic surgery: an international multicentre randomised controlled study.

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ABSTRACT

Introduction Hypoxaemia and hyperoxaemia may occur after surgery, with related complications. This multicentre and randomised trial evaluated the impact of automated closed-loop oxygen administration after high-risk abdominal or thoracic surgeries in terms of optimising the SpO_2 time within target range.

Methods After extubation, patients with an intermediate to high risk for postoperative pulmonary complications were randomised to *Standard* or *Automated* closed-loop oxygen administration. The primary outcome was the percentage of time within the oxygenation range, during a three-day frame. The secondary outcomes were the time with hypoxaemia and hyperoxaemia under oxygen.

Results Among the 200 patients, time within range was higher in the *Automated* group, both initially (≤3-hours; 91.4±13.7 vs. 40.2±35.1 % of time; difference +51.0% [CI95% -42.8;59.2]; p<0.0001) and during the three-day period (94.0±11.3 vs. 62.1±23.3 % of time; difference +31.9% [CI95% 26.3;37.4]; p<0.0001). Periods of hypoxaemia were reduced in the *Automated* group (≤3 days; 32.6±57.8 [1.2±1.9%] vs. 370.5±594.3 min [5.0±11.2%]; difference -10.2% [CI95% -13.9;-6.6]; p<0.0001), as well as hyperoxaemia under oxygen (≤3 days; 5.1±10.9 [4.8±11.2%] vs. 177.9±277.2 min [27.0±23.8%]; difference -22.0% [CI95% -27.6;-16.4]; p<0.0001). Kaplan-Meier analysis depicted a significant difference in terms of hypoxaemia (P=0.01) and severe hypoxaemia (P=0.0003) occurrence between groups in favour of the *Automated* group. Twenty-five patients experienced hypoxaemia for more than 10% of the entire monitoring time during the 3 days within the *Standard* group, as compared to the *Automated* group (p<0.0001).

Conclusion *Automated* closed-loop oxygen administration promotes greater time within the oxygenation target, as compared to *Standard* manual administration, thus reducing the occurrence of hypoxaemia and hyperoxaemia.

Trial registration: clinicaltrials.gov identifier NCT02546830

Keywords: oxygen therapy, postoperative complications, thoracic surgery, abdominal surgery, hypoxaemia, hyperoxaemia

INTRODUCTION

Current standards for prescribing oxygen recommend providing adequate flows to correct hypoxaemia and avoid hyperoxaemia.[1,2] While the deleterious effects of hypoxaemia are well-known, the potential harmful effects of hyperoxaemia are underappreciated; hyperoxaemia 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, is time-consuming [9] and O_2 therapy is thus commonly administered with poor adherence to treatment recommendations.

The FreeO_2 system is an innovative device, developed in collaboration between researchers at university hospitals in Brest (France) and Québec (Canada) and Oxynov Inc., an R&D spin-off from Laval University in Québec. FreeO_2 is a closed-loop device that automates oxygen administration to spontaneously breathing patients, in response to continuous pulse oximetry (SpO_2) measurements.[10] Automated O_2 administration can 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 healthy adults with induced hypoxaemia, such a system was more efficient to maintain SpO_2 within the oxygenation target, while ensuring a significant reduction in hypoxaemia and hyperoxaemia periods, as compared to constant O_2 flows.[14] Its efficacy in terms of optimising the SpO_2 time within target range has also been validated in hospitalised 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 hypoxaemia may be high while considering patient clinical status (obstructive sleep apnoea, restrictive pathologies related to obesity, frequent co-morbidities), the type of surgery and anaesthesia, and the fact that patients are frequently given opioid treatment postoperatively.[16-22] The prevalence of postoperative hypoxaemia is often underestimated, and there remains a significant number of patients who still develop respiratory complications following extubation, thereby suggesting that there is room for improvement in these patients. Oxygen therapy is almost invariably applied after elective extubation using low-flow devices to correct oxygenation

impairment, but may not always prevent the postoperative deterioration in respiratory function. Hypoxaemia may occur either during the immediate postoperative period (it is therefore mainly related to surgery or anaesthesia) or may be delayed up to 3 days without a clear trigger or underlying pathology. If the PaO_2 is increased excessively, it may also lead to hyperoxaemia-mediated vasoconstriction in almost all vascular beds, including coronary arteries, and promote atelectasis formation.[23]

The potential interest of the FreeO_2 system, using artificial intelligence, closed-loop adjustments and predictive analytics, is 1. to perform 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 continuous data recording in isolated clinical settings (*i.e.* non-ICU surgical ward) in order to detect at a very early stage clinical deterioration through the integration and fusion of information; and 3. to avoid the maintenance of unnecessarily high O_2 flow that may be deleterious.

The *FreeO_2 Post-Op* trial aimed to evaluate the clinical impact of automated closed-loop vs. standard manual O_2 administration in terms of oxygenation, after major abdominal or thoracic surgeries. We hypothesised that automated O_2 administration would promote better adherence to clinical guidelines than conventional therapy, thus optimising the SpO_2 time within the target range for up to 3 days following surgery.

METHODS

Study design

The $FreeO_2$ PostOp international, multicentre, randomised, controlled trial was funded by the French ministry of health (*Programme Hospitalier de Recherche Clinique Interrégional HUGO 2012-199*) and promoted by Brest University Hospital. The trial was overseen by a steering committee and safety monitoring board, composed of three independent experts. The Institutional Review Board of Brest University Hospital approved the trial for all French centres, and the institutional review board from the Québec Heart and Lung Institute (Canada) approved the trial for their own centre. The $FreeO_2$ Post-Op study was conducted in accordance with the declaration of Helsinki and registered on September 11, 2015 at ANSM (IDRCB2014-A00615-42) and Clinicaltrials (NCT02546830).

The $FreeO_2$ PostOp study took place at five university hospitals in France and Canada (Brest, Clermont-Ferrand, Montpellier, Poitiers, Québec). First patient inclusion was performed on January 2016 and last inclusion on September 2018. All centres were regularly monitored to check adherence to the protocol and accuracy of the recorded data. An investigator at each centre was responsible for enrolling patients and ensuring adherence to the protocol. Research assistants were responsible for patient follow-up and for completing the electronic case report form. Although assignment to the study could not be blinded, all clinicians in charge of the patients remained unaware of the study outcomes, *i.e.* while clinicians were aware of the O_2 flow and SpO_2 values modifications (in the Automated group, simply while looking at the device's screen), they were not constantly looking at the device during the three-day monitoring frame, and thus could not be aware of all O_2 flow modifications and SpO_2 time within the target range in both groups over time.

Patients

To be eligible, adult patients (≥ 18 years) were to be screened for scheduled abdominal or thoracic surgery during the anaesthesia consultation and to be considered as requiring general anaesthesia with an expected duration of two hours or more in the participating

centres. Patients had to present an intermediate to high risk for postoperative pulmonary complications, with an ARISCAT risk score ≥26.[24]

Informed consent was signed by the patient before the surgery. Figure 1 shows the flow chart diagram of the FreeO_2 PostOp study.

Patients fulfilling one or more of the following criteria were excluded: patients with a body mass index ≥35 kg/m^2, patients with obstructive sleep apnoea and pregnant patients to provide a relatively homogenous study population and avoid potential confounding factors in the interpretation.

Randomisation and masking

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

Computer-generated randomisation was performed within a maximal one-hour delay following endotracheal extubation in the recovery room. It was performed using random blocks in a 1:1 ratio, with the use of a centralised web-based management system (Clinfile, Multihealth, Velisy Villacoublay, France). Patients were assigned to standard manual oxygen administration (*Standard*) or to automated closed-loop oxygen administration (*Automated*). Stratification was performed either according to the study centre and a medical history of COPD. After randomisation, treatment was initiated within one hour.

Although the individual study assignments of the patients were not masked, the coordinating centre and all the investigators remained unaware of the study group outcomes until the data were locked. Before locking the database and after trial completion, the review board checked data and decided which patients could be included in the intention-to-treat analysis in accordance with the Good Clinical Practice Guidelines. An adjudication committee, who was unaware of the study groups, extracted pulse oximetry

curves and values and reviewed all the data to analyse the events occurring during the procedure in order to verify patient safety. The complete methodology of the study has been published previously.[25]

Procedures

The maximal study participation was 3 days. The study was stopped before 3 days if the patient was to be discharged from hospital earlier.

Automated O_2 was administered using the FreeO_2 system (Oxynov Inc., Québec, QC, Canada) that was set to maintain SpO_2 between 92-96% for non-COPD patients or between 88-92% for COPD patients, as recommended by international guidelines.[1,2]. FreeO_2 is equipped with a SpO_2 monitor and an electronically-controlled valve that automatically adjusts oxygen flows from 0 to 20 L/min on a per second basis, with a precision of 0.1 L/min, according to a closed-loop algorithm in order to reach the predetermined SpO_2 target.[14] *Standard* oxygen was administered using manual flowmeters, according to standard clinical procedures. All participating units were encouraged to use the same standardised SpO_2 target. In both arms, oxygen was administered either using nasal prongs for low flow (O_2<6 L/min) in case of clinical stability, or an open face mask for low or medium flow. On a routine basis, we advocated the use of face masks for all patients, in order being able to deliver either low to medium flow, or transient increases in response to patient needs, especially in response to efforts.

To accurately determine the incidence and severity of postoperative SpO_2 variations, continuous oximetry recordings were performed in each group during the entire study, using the FreeO_2 monitoring system at 1 Hz (One SpO_2 value per second) and connected to Nonin© 6000 CA flexible adult single-use digital sensors. The position of the sensors was checked at least every 12 hours.

Considering the variety of pathological cases for patients requiring surgery, medical treatment (*i.e.* fluid administration, prophylactic antibiotics and postoperative pain management), including respiratory support, was determined by the attending physicians based on a clinical needs assessment. Medical diagnoses associated with general characteristics (e.g. COPD, cardiopathy) were determined during the anaesthesia

consultation, according to patient medical files. According to the potential risk of pulmonary complications (ARISCAT score), specific attention was paid to this point of interest.

Measurements and Outcomes

The primary outcome measure was the percentage of time spent within the SpO_2 target zone, during a three-day time frame. While continuous oximetry was recorded in both groups at a frequency of 1 Hz, even short episodes of oxygen desaturation were detected. The target zone of oxygen saturation was SpO_2 = 88-92% for COPD and 92-96% for non-COPD patients; this target zone was considered for patients receiving additional oxygen, and patients without oxygen, but higher than the range, were considered adequately treated.

Several secondary outcome measures were evaluated during a three-day time frame: nursing workload assessed by the number of manual oxygen flow adjustments; time with hypoxaemia (SpO_2 below 88% for COPD, and 92% for non-COPD), severe hypoxaemia (SpO_2<85% for all); hyperoxaemia under oxygen (SpO_2> 98%), and the first occurrence of a clinically significant hypoxaemia and severe hypoxaemia event, defined as the occurrence of such an event for at least 30 seconds.

Other outcome measures were assessed during a maximal 28-day time frame: duration of oxygen administration during hospitalisation, number of complications related to oxygen administration, frequency of use of ventilation (invasive or non-invasive), duration of hospitalisation and survival rate.

Statistical methods

Based on previous studies, we estimated 85% of time within the oxygenation range with the automated closed-loop oxygen administration system ($FreeO_2$) and a standard deviation equal to or greater than 30%. Thus, a total number of 200 patients was needed to demonstrate a 15% decrease in the absolute difference between the *Standard* and *$FreeO_2$* groups.

All analyses were performed by an independent statistician, on an intention-to-treat basis using SAS V.9.4 statistical software (SAS Institute, Cary, North Carolina, USA). Continuous variables were analysed using standard parameters (median, interquartile ranges and

extreme values, or mean and SD), while categorical variables were analysed in the form of absolute frequency and percentage. The main criteria of evaluation (percentage of time within the considered SpO_2 range) was compared between the two groups by means of variance analysis, according to stratification. Secondary criteria of evaluation were 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 χ^2 test (or Fisher's exact test) for qualitative variables. The probability of a significant hypoxaemia episode occurring within groups was compared using the Kaplan-Meier estimate and the Log-Rank test. A two-tailed P value equal or less than 0.05 was considered statistically significant.

RESULTS

Patients

The time course of patient participation is detailed within the Supplementary Appendix, Figure S1. Two hundred patients were randomised to either the *Standard* (n=103) or the *Automated* group (n=97) (Figure 1). No patients were excluded due to unavailable pulse oximetry signal solely, but rather to medical condition deterioration. Patient demographics, physiological characteristics and comorbidities were well-balanced in between groups (Table 1). Principal outcome parameters could be measured in only 169 patients (84.5%) due to recording problems and SpO_2 signal loss over the time frame (83.5 and 85.6% in the *Standard* and *Automated* group respectively).

Oxygenation parameters and primary outcome

Oxygenation parameters results are provided within Table 2, either for the short-term (≤3-hours) and the long-term (≤3 days) period (see also Figures 3 and 4 for illustration). Time within range was higher in the *Automated* group, either during the short-term (≤3-hours; 91.4±13.7 vs. 40.2±35.1 % of time; adjusted difference +51.0 of % points [CI 95% -42.8; 59.2]; p<0.0001) or the long-term period (≤3 days; 94.0±11.3 vs. 62.1±23.3 % of time; adjusted difference +31.9% of % points [CI 95% 26.3; 37.4]; p<0.0001). Periods of hypoxaemia were reduced in the *Automated* group (≤3 days; 32.6±57.8 [1.2±1.9%] vs. 370.5±594.3 min [5.0±11.2%]; adjusted difference -10.2% of % points [CI 95% -13.9; -6.6]; p<0.0001), as well as hyperoxaemia under oxygen (≤3 days; 5.1±10.9 [4.8±11.2%] vs. 177.9±277.2 min [27.0±23.8%]; adjusted difference -22.0% of % points [CI 95% -27.6; -16.4]; p<0.0001).

In the *Standard* group, up to 25 patients experienced hypoxaemia for more than 10% of time during the 3 days of recording, while this adverse event was not observed for patients assigned to the *Automated* group (p<0.0001) (Table 3).

A significant difference in terms of hypoxaemia (P=0.01) and severe hypoxaemia (P=0.0003) occurrence was observed between groups, always in favour of the *Automated* group (Figure 2).

Secondary outcomes

Secondary outcomes results are provided within Table 4.

Mean oxygen flow was not different in between groups, but flow variations >50% were more frequent in the *Automated* group (39 vs. 19.5% patients; p<0.001), as well as weaning in the recovery room (14.1 vs. 4.3% patients; p<0.001) (Table 2). Oxygen was still prescribed after Day 3 in 34 (33.3%) vs. 17 (18.3%) patients in the *Standard* and *Automated* group, respectively (p=0.01).

No difference was observed in between groups, either in terms of any other type of adverse event, respiratory assistance needs (11 vs. 10 patients; p=0.89) nor in terms of the length of stay (13.3 ± 11.3 vs. 12.5 ± 12.4 days; P=0.7) in the *Standard* and *Automated* group, respectively.

DISCUSSION

The FreeO_2 PostOp trial was a pragmatic international multicentre randomised clinical trial designed to test the hypothesis that *Automated* closed-loop O_2 administration is superior to *Standard* manual oxygen administration in patients recovering from high-risk abdominal or thoracic surgery. To the best of our knowledge, this is the first study to investigate the usefulness of *Automated* oxygen administration in such an indication. *Automated* oxygen administration was demonstrated to increase time within the oxygenation range following high-risk surgery, as compared to *Standard* oxygen administration. There was also a significant decrease in the occurrence of hypoxaemia and hyperoxaemia for patients assigned to the *Automated* group.

Impact on hypoxaemia

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

In postoperative patients, pulmonary function is altered by general anaesthesia and surgery. Postoperative respiratory complications following surgery are the second most frequent complications [19] and considered as a major cause of morbidity and mortality.[17,24,25] In this condition, the occurrence of oxygen desaturation related to periodic apnoea and hypoventilation has been recognised for a long time,[31,32] with potentially severe consequences such as myocardial ischemia.[33] The incidence of hypoxaemia is high in the recovery room (10-50%),[20] and up to 50% of postoperative patients will demonstrate episodic hypoxaemia in the absence of O_2 therapy.[34,35] It has also been shown that desaturation episodes are more frequent during the first night following surgery, but may also be worsened 3-5 days postoperatively, especially in patients with obstructive sleep apnoea.[36-38] In a study performed on 833 patients with continuous oximetry monitoring following non-cardiac surgery, hypoxaemia was found to be common and prolonged, even in

patients without specific risk factors. [22]. The authors also pointed out the fact that conventional point-check oximetry within surgical wards may underestimate hypoxaemia incidence and severity, and postulated that point-check monitoring on aroused patients may induce SpO_2 measurements increases that might be unsustained once the stimulus is removed, thus masking oxygen desaturations.

The pathophysiology of these oxygen desaturations is rather complex, but may be due to the patient's condition itself (advanced age, COPD, diabetes, obesity), modifications in respiratory mechanics (reduction of functional residual capacity, atelectasis, thoracoabdominal compliance decrease), but also to the use of pharmaceutical agents that are given during surgery (anaesthetics and neuromuscular blocking drugs), or those that are given to relieve postoperative pain (opioids and sedatives).[32] In our study, hypoxaemia periods were shorter in the *Automated* group (adjusted difference -95 min.; P<0.0001), less frequent (Figure 3), but the incidence was also significantly lower, as 25 and 17 patients experienced hypoxaemia for more than 10% and 20% of the time, respectively, in the *Standard* group, as compared to none within the *Automated* group during the three-day period (P<0.001). It is somewhat interesting that hypoxaemia episodes within the *Standard* group occurred despite frequent hyperoxaemia within the first three-hour period (Supplementary Appendix, Figure S2). These hypoxaemia episodes remained frequent during the 3 days following surgery (Supplementary Appendix, Figure S3), probably because of underlying patient pathologies and the use of opioid analgesics.

Impact on hyperoxaemia

It has been demonstrated in two randomised trials by our team [10,15] that time with hyperoxaemia could be reduced with automated closed-loop oxygen administration, and we initially hypothesised that this problem would also be reduced after thoracic or abdominal surgeries.

Within our study, supplemental oxygen was overwhelmingly used during the immediate postoperative phase, thus promoting excessive hyperoxaemia (adjusted difference of time within range +51% [42.8;59.2]; P<0.0001) without suppression of hypoxaemia periods in the

Standard group. Such overoxygenation is very frequent in most patients within the recovery room, even in COPD patients, and oxygen flow adjustments in response to SpO2 values are quite few (Figure 4).

Few studies have promoted the utilisation of hyperoxaemia for colo-rectal surgery, in order 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 hyperoxaemia.[48] The pathophysiological risks associated with hyperoxaemia have been recognised for a long time, especially in COPD patients.[4] The first recommendation to adjust oxygen flow rates in order to reduce the risks of hyperoxaemia was published in the early 1960s,[49] and several more recent guidelines have reiterated similar recommendations.[1,2] The recent demonstration in a large randomised controlled trial of increased mortality in ICU patients assigned to 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 the potential harm of excessive oxygen therapy in an unselected patient population.[50] Adverse effects of hyperoxaemia could be mediated through higher oxidative stress, but also increased coronary [6,7] and cerebral artery resistance,[8] which are all associated with a potential clinical impact.[51,52] Another side effect of oxygen is caused by gas absorption, which is a known mechanism of atelectasis formation. While several other observational studies have supported similar benefits when avoiding hyperoxaemia and liberal oxygen use,[53,54] the recent ICU-ROX and $LOCO_2$ trials,[55,56] however, depicted conflicting results without clear evidence of any benefit of avoiding hyperoxaemia, but rather potential harm related to a low SpO_2 value.

Even if debated, the potential physiological adverse events,[6-8,57-59] related to hyperoxaemia clearly mandates attention in avoiding unnecessary oxygen administration, *i.e.* not administering oxygen when the SpO_2 is 96% or greater, and not starting oxygen when the SpO_2 is 92% or 93% [60,61]. The DETO2X-AMI randomised trial in patients with acute myocardial infarction provides definitive evidence for a lack of benefit for supplemental oxygen therapy in patients with acute myocardial infarction who have a normal SpO_2 value [62].

Automated weaning of oxygen

Oxygen supplementation is almost invariably applied after elective extubation to correct oxygenation impairment and to decrease the occurrence of postoperative hypoxaemia, even if it is also well-known that it will not have any effect on the overall number of central or obstructive apnoea, neither atelectasis.[31] All patients will not benefit from systematic oxygen administration following endotracheal extubation [39], but probably those with a high-risk profile, especially following long duration and major thoracic or abdominal surgery, such as the patients that were recruited within our study.[40-42] Moreover, standard continuous oxygen administration reduces but does not abolish the occurrence of desaturation,[34] given the fact that solely SpO_2 point checks are made to adjust oxygen flow to actual patient needs, thus missing the occurrence of transient hypoxaemia.

It has also been demonstrated that the duration of oxygen therapy is an independent risk factor for developing postoperative respiratory complications. Patients who require oxygen for ≥75% of recovery room time (or greater than 90 min) appear to be at a greater risk of developing respiratory complications.[43] This fact may suggest that some patients are not adequately screened for risk factors such as obstructive sleep apnoea by standard pre-anaesthesia testing, and that a device dedicated to continuous monitoring of oxygen administration (alarms on oxygen administration duration and flow variations) may help to detect such high-risk patients. The increased resource utilisation in patients with longer oxygen therapy requirements in the recovery room likely reflects the increase in the occurrence of pulmonary respiratory complications requiring invasive and non-invasive ventilatory support, especially on the day of surgery. Unfortunately, our study was not

powered to enable such outcome impact evaluation. In a study by L'Her *et al.* that was performed within the emergency department environment, it was shown that the partial or complete oxygen weaning was significantly increased with *Automated* oxygen titration in comparison with *Standard* oxygen administration.[10]

In the specific setting of post-operative patients, a reduction in weaning time may improve the efficiency of the turn-over of the patients in the recovery room. However, one may not forget that patient monitoring and treatment with *Automated* closed-loop administration during the entire three-day period following these high-risk surgeries may also be beneficial, while it may significantly decrease the occurrence of significant hypoxaemia.

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 emergency department for acute hypoxemic respiratory failure, the use of automated oxygen 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 oxygen automated administration.[63,64] In a study by L'Her *et al.* that was performed in the stabilisation units of emergency departments, patients experienced less time with hypoxaemia and hyperoxaemia 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. Considering safety issues, the *Automated* system continuously adjusts the oxygen flow in response to patient needs, and these O_2 flow variations are continuously visualised on the screen. While the closed-loop system requires continuous SpO_2 monitoring to adjust the flow, this means that, on a routine basis, the patient is monitored for SpO_2, O_2 flow, respiratory rate and heart rate;[65] each of these parameters are monitored using adjustable alarm levels to standards or individualised goals, and deviation from the range is either visualised by lights and/or sounds. Furthermore, all trends for these parameters can be visualised and downloaded.

Study limitations

The first limitation of the study is that investigators were aware of the inclusion group, as blinding was difficult for technical reasons. As stated within the Methods, all participating units were encouraged to use the same oxygenation target in both groups, and staffing levels were equivalent. Within the recovery room, O_2 flow was regulated by anaesthesiology wards, and within the surgical ward it was regulated by general nurses, according to the physician's prescription. However, because patients in the *Standard* group were also monitored with the FreeO_2 device in recording mode, one cannot ensure that patients were not monitored more closely than in routine, especially within surgical wards. Such bias was the only technical way to ensure continuous oximetry recordings with the same sampling rate (1 Hz). However, such bias may only have decreased the potential to identify a difference in between groups (i.e. to decrease the benefits of *Automated* closed-loop oxygen administration), while a significant difference was demonstrated. Second, the assessment of oxygenation status could be considered more precise by analysing blood gas samples rather than SpO_2. However, this would not enable continuous oxygenation monitoring for up to 3 days. Moreover, only continuous of non-averaged SpO_2 values enable precise and rapid adjustments of the oxygen flow in response to exact patient needs. Of note, all patients in both groups were continuously monitored using the same oximeter, which may represent a strength of this study; therefore, the FreeO_2 PostOp study represents the largest prospective study comparing two oxygenation strategies over such a period in the postoperative setting. Third, our study was not powered for major respiratory complications nor with the modification of other adverse outcomes. However, while hypoxaemia is widely thought to be harmful, such differences in terms of time within the oxygenation range might be considered as beneficial.

In conclusion, hypoxaemia and hyperoxaemia were common and prolonged in patients recovering from high-risk surgery and assigned to *Standard* oxygen administration. *Automated* closed-loop oxygen administration promoted a greater proportion of time within the SpO_2 target range, thus avoiding prolonged periods of hypoxaemia and hyperoxaemia.

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;122:747-54.

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, WijesingheM, et al. Systematic review of studies of the effect of hyperoxemia on coronary blood flow. Am Heart J 2009;158:371-7.

8- Floyd TF, Clark JM, Gelfand R, et al. Independent cerebral vasoconstrictive effects of hyperoxemia and accompanying arterial hypocapnia at 1 ATA. J Appl Physiol 2003;95:2453-61.

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;27:207-13.

10- L'Her E, Dias P, Gouillou M, et al. Automatic versus manual oxygen administration in the emergency department. Eur Respir J 2017;50:pii1602552.

11- Claure 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;107:1120-4.

12- Claure 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;57:1254-62.

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;11:1983-90.

16- Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modeling strategy based on available date. Lancet 2008;372:139-44.

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;242:326-41.

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;39:2163-72.

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;232:242-53.

20- Lawrence VA, Dhanda R, Hilsenbeck SG, et al. Risk of pulmonary complications after elective abdominal surgery. Chest 1996;110:744-50.

21- Lindberg P, Gunnarsson L, Tokics L, et al. Atelectasis and lung function in the postoperative period. Acta Anaesthesiol Scand 1992;36:546-53.

22- Sun Z, Sessler DI, Dalton JE, et al. Postoperative Hypoxemia Is Common and Persistent: A Prospective Blinded Observational Study. Anesth Analg 2015;121:709-15.

23- Gerber D, Guensch DP, Theiler L, Erdoes G. When less is more: why extubation with less than routine 100% oxygen may be a reasonable strategy. Anesth Analg 2019;129: 1433-5.

24- Mazo V, Sabaté S, Canet J, et al. Prospective external validation of a predictive score for postoperative pulmonary complications. Anesthesiology 2014;121:219-31.

25- L'Her E, Jaber S, Verzilli D, et al. Automated oxygen administration versus conventional oxygen therapy after major abdominal or thoracic surgery: study protocol for an international multicentre randomised controlled study. BMJ Open 2019;9: e023833.

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 arrythmias. Br Heart J 1994;72:23-30.

28- DeWitt DS, Prough DS. Blast-induced brain injury and posttraumatic hypotension and hypoxemia. J Neurotrauma 2009;26:877-87.

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;56:253-9.

31- Jones JG, Jordan C, Scudder C, et al. Episodic postoperative oxygen desaturation: the value of added oxygen. J R Soc Med 1985;78:1019-22.

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;63:20-8.

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;93:333-8.

34- Canet J, Ricos M, Vidal F. Early postoperative arterial oxygen desaturation. Determining factors and response to oxygen therapy. Anesth Analg 1989;69:207-12.

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;100:45-9.

37- Chung F, Liao P, Elsaid H, et al. Factors associated with postoperative exacerbation of sleed-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;72:145-50.

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;80:368-72.

40- Pedersen T, Viby-Mogensen J, Ringsted C. Anaesthetic practice and postoperative pulmonary complications. Acta Anaesthesiol Scand 1992;36:812-8.

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;71:691-7.

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;144:581-95.

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;342:161-7.

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;302:1543-50.

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 hyperoxemia – Lont-term impact on cardiovascular complications after abdominal surgery, a post-hoc analysis of the PROXI trial. Int J Cardiol 2016;215:238-43.

49- Campbell EJ. The J. Burns Amberson Lecture. The management of acute respiratory failure in chronic bronchitis and emphysema. Am Rev Respir Dis 1967;96:626-39.

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;316:1583-9.

51- Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation 2015;131:2143-50.

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

53- Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet 2018;391:1693-705.

54- Helmerhorst HJ, Schultz MJ, van der Voort PH, et al. Effectiveness and Clinical Outcomes of a Two-Step Implementation of Conservative Oxygenation Targets in Critically Ill Patients: A Before and After Trial. Crit Care Med 2016;44:554-63.

55- The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med 2020;382:989-98.

56- Barrot L, Asfar P, Mauny F, et al., for the $LOCO_2$ Investigators and REVA Research Network. Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. N Engl J Med 2020;382:999-1008.

57- Kelly RF, Hursey TL, Parrillo JE, Schaer GL. Effect of 100% Oxygen Administration on Infarct Size and Left Ventricular Function in a Canine Model of Myocardial Infarction and Reperfusion. Am Heart J. 1995;130:957-65.

58- Stub D, Smith K, Bernard S, et al.; AVOID Investigators. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation 2015;131:2143-50.

59- Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. Circulation 2015;131:2143-50.

60- Siemieniuk RAC, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ 2018;363:k4169.

61- Angus DC. Oxygen Therapy for the Critically Ill. N Engl J Med 2020;382:1054-6.

62- Hofmann R, James SK, Jernberg T, et al.; DETO2X–SWEDEHEART Investigators. Oxygen Therapy in Suspected Acute Myocardial Infarction. N Engl J Med 2017;377:1240-9.

63- 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;56:429-34.

64- 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;56:1901-5.

65- L'Her E, N'Guyen QT, Pateau V, Bodenes L, Lellouche F. Photoplethysmographic Determination of the Respiratory Rate in Acutely Ill Patients: Validation of a New Algorithm and Implementation Into a Biomedical Device. Ann Intensive Care 2019;9:11. doi: 10.1186/s13613-019-0485-z.

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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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. provided the automated oxygen therapy equipment to all the participating centers but had no other involvement in the study.

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.

Table 1: Characteristics of the patients at randomization

	Total	**Manual**	**Automated**
Age - yr.	62.7 ± 13.0	63.1 ± 13.5	62.2 ± 12.6
Male - no. (%)	110 (55.3)	57 (55.3)	53 (55.2)
COPD - no. (%)	17 (8.5)	10 (9.7)	7 (7.3)
Surgery characteristics - no. (%)			
Abdominal	141 (71.2)	74 (71.8)	67 (70.5)
Thoracic	57 (28.8)	29 (28.2)	28 (29.5)
ARISTAT risk class - no. (%)			
Moderate risk (26 to 44)	150 (75.4)	78 (75.7)	72 (75.0)
High risk (≥ 45)	49 (24.6)	25 (24.3)	24 (25.0)
Co-morbidities - no. (%)			
Alcohol abuse	26 (14.9)	11 (12.1)	15 (17.9)
Diabetes	26 (14.8)	13 (14.1)	13 (15.5)
Cardiovascular			
Arterial hypertension	67 (37.9)	32 (34.8)	35 (41.2)
Coronaropathy	17 (9.7)	9 (9.8)	8 (9.5)
Cardiac insufficiency	2 (1.1)	0 (0)	2 (2.4)
Respiratory			
Allergy	18 (10.3)	15 (16.5)	3 (3.6)
Smokers	101 (57.7)	48 (52.7)	53 (63.1)
Asthma	7 (4.0)	5 (5.5)	2 (2.4)
LTOT	1 (0.6)	1 (1.1)	0 (0)
Home ventilation	0 (0)	0 (0)	0 (0)
Renal insufficiency	14 (8.0)	8 (8.7)	6 (7.1)
Physiological parameters			
Pain control	2.8 ± 3.1	3.0 ± 3.1	2.6 ± 3.2
Respiratory rate – breaths/min.	16 ± 5	16 ± 5	16 ± 4
SpO_2 - %	97.6 ± 2.5	98.0 ± 2.5	97.2 ± 2.3
Respiratory comfort	9.1 ± 1.5	9.0 ± 1.5	9.2 ± 1.5
Heart rate – beats/min.	82 ± 16	81 ± 16	83 ± 15
Systolic arterial pressure - mmHg	124 ± 23	123 ± 23	126 ± 22
Mean arterial pressure - mmHg	85 ± 15	84 ± 15	87 ± 15

**Plus-minus values are means ± SD, unless specified otherwise; other values are provided as number, (%). There was no significant differences among the study groups in any of the characteristics listed. Patients who were assigned to receive Automated oxygen administration were connected to the FreeO$_2$ system, set on the automated mode. Patients assigned to*

Manual O_2 administration were also connected to the FreeO_2 system for monitoring purposes, but the system was set to the recording mode solely.

ARISCAT: a score that predicts the risk of pulmonary complications after surgery, including respiratory failure. To be randomized, patients had to have a predicted ARISCAT score ≥ 26 prior to surgery; COPD: chronic obstructive pulmonary disease; Treatment limitation and do-not-intubate order: it was systematically assessed on admission by either the emergency physician or the intensivist, according to patient's health status; LTOT: long-term oxygen therapy; SpO_2: pulse oximetry value. Pain control and Respiratory comfort were assessed using hetero-evaluation by the anesthesiology nurse in the Recovery room, using analogic numerical scale (from 1 to 10; 1 being the worse and 10 the best value).

O_2 flow was the value measured immediately after randomization; the flow was significantly lower in the Automated group while FreeO2 takes only several seconds to adjust to the real patients' needs.

Table 2 : Main outcome parameters

	Post-Operative Short Term *(Recovery room - 3 hours)*				**Post-Operative Long Term** *(Surgical ward – up to 3 days)*			
	Automated	***Standard***	***Adjusted difference*** *[CI 95%]*	***P***	***Automated***	***Standard***	***Adjusted difference*** *[CI 95%]*	***P***
SpO_2 value *- %*	94.7 ± 4.1	96.2 ± 3.1	-1.6 [-2.6 ; -0.5]	**0.004**	95.2 ± 1.3	94.6 ± 2.7	0.6 [0 ; 1.2]	0.09
Time within range *- min*	**156 ± 32**	**71 ± 63**	**85 [69 ; 100]**	**<0.0001**	**2694 ± 1134**	**1969 ± 1031**	**714 [401 ; 1027]**	**<0.0001**
Time within range *- %*	**91.4 ± 13.7**	**40.2 ± 35.1**	**51.0 [42.8 ; 59.2]**	/	**94.0 ± 11.3**	**62.1 ± 23.3**	**31.9 [26.3 ; 37.4]**	/
Hypoxemia *- min*	2.8 ± 4.9	7.8 ± 18.4	-5.0 [-9.2 ; -0.8]	**0.02**	31 ± 57	373 ± 591	-342 [-471 ; -213]	**<0.0001**
Severe Hypoxemia *- min*	0.1 ± 0.3	0.3 ± 1.0	-0.1 [-0.4, 0.1]	0.23	2 ± 3	10 ± 27	-8 [-14 ; -2]	**0.007**
Hyperoxemia *- min*	11.9 ± 22.6	97.3 ± 68.4	-85.2 [-100.9 ; -69.5]	**<0.0001**	148 ± 401	800 ± 716	-643 [-818 ; -469]	**<0.0001**
Severe Hyperoxemia *- min*	0.9 ± 3.2	45.2 ± 57.8	-44.6 [-57.2 ; -31.9]	**<0.0001**	4 ± 7	174 ± 274	-172 [-232 ; -113]	**<0.0001**
SpO_2=100% *- min*	0.3 ± 1.5	19.3 ± 36.5	-19.2 [-27.2 ; -11.1]	**<0.0001**	1 ± 2	46 ±82	-45 [-63; -28]	**<0.0001**

The main study objectives' results are depicted in bold characters. Hypoxemia was defined as a SpO_2 below 92% for non-COPD and below 88% for COPD patients; severe hypoxemia was defined as a SpO_2 below 85% for all patients. Hyperoxemia was defined as a SpO_2 for patients under O_2 higher than 96% for non-COPD and higher than 92% for COPD patients; severe hyperoxemia was defined as a SpO_2 for patients under O_2 higher than 98% for all. O_2 weaning was defined as a mean O_2 flow equal or below 0.3 L/min during the last 10 min. of the short term post-operative phase or during the last 1 hour of the long-term post-operative phase. A P value equal or below 0.05 was considered statistically significant.

The O_2 flow that is depicted within the Table is the mean value during the recording windows. Time within range is significantly increased for patients assigned to the Automated group, either during the short-term and long-term post-operative periods ($p<0.0001$). This result is explained by a huge difference in terms of O_2 flow adjustments in response to the patients' needs, thus inducing a reduction of time with hypoxemia and hyperoxemia. Severe hypoxemia is decreased during the 3-days recording in patients assigned to the Automated group, while O_2 weaning is higher in the Standard group but time without O_2 higher in the Automated group. Such results may suggest that continuous monitoring and O_2 adjustment to the patients' needs of such patients might be warranted for up to 3-days following high-risk surgery.

Table 3: Secondary Outcomes

	Automated	***Standard***	***Adjusted difference / OR** [CI 95%]*	***P***
Recovery Room				
Treatment duration *– min*	183 ± 14	180 ± 13	-2 [-6 ; 2]	0.26
O_2 flow *– L/min*	0.9 ± 1.4	2.8 ± 1.4	-1.9 [-2.3 ; -1.5]	**<0.0001**
O_2 flow variations *– n*	10290 ± 1352	2 ± 1	/	**<0.0001**
Time without O_2 *– min*	87.6 ± 59.5	17.4 ± 41.9	70.3 [55.2 ; 85.3]	**<0.0001**
O_2 weaning - *n patients (%)*	50 (61.7)	14 (16.3)	8.9 [4.2 ; 18.8]	**<0.0001**
Surgical Ward				
Treatment duration *– min*	3146 ± 1225	3506 ± 982	-357 [-682 ; -33]	**0.03**
O_2 flow *– L/min*	1.0 ± 1.3	1.2 ± 1.0	-0.2 [-0.6 ; 0.1]	0.15
O_2 flow variations *– n*	174030 ± 69484	6 ± 3	/	**<0.0001**
Time without O_2 *– min*	1371 ± 1104	1261 ± 1170	109 [-232 ; 450]	0.53
O_2 weaning - *n patients (%)*	35 (42.2)	50 (58.1)	0.5 [0.3 ; 1.0]	**0.04**
Day-28				
Mortality - *n patients (%)*	3 (3.2)	1 (1.0)	3.3 [0.3 ; 32.0]	0.31
Respiratory assistance - *n patients (%)*	10 (10.4)	11 (10.7)	1.0 [0.4 ; 2.4]	0.94
Hospital length-of-stay - *days*	12.5 ± 12.4	13.3 ± 11.3	-0.6 [-3.9 ; 2.6]	0.7

Differences in between groups are expressed as either Adjusted difference or Odd ratio [CI 95%]. A P value equal or below 0.05 was considered statistically significant. O_2 flow variations are the absolute number of changes in the O_2 flow during the follow-up period. O_2 weaning was defined as a mean O_2 flow equal or below 0.3 L/min during the last 10 min. of the short term post-operative phase (Recovery room) or during the last 1 hour of the long-term post-operative phase. Treatment duration was similar in both groups in the Recovery Room, but higher in the Standard group within the Surgical Ward. The O_2 flow that is depicted within the Table is the mean value during the recording windows; no differences were observed in between groups. O_2 weaning is higher in the Standard group but time without O_2 higher in the Automated group.

Figure Legends

Figure 1: Flow chart of the $FreeO_2$ PostOp study

Inclusion was performed during the anaesthesia consultation, and randomisation was performed not later than one hour following extubation in the recovery room. For non-COPD patients, the target was a, SpO_2 range of 92-96%; for COPD patients, the target range was SpO_2 88-92%. Patients were assigned either to standard manual oxygen administration (*Standard*), or automated closed-loop oxygen administration (*Automated*); in both groups, continuous SpO_2 recording was performed for up to 3 days according to the $FreeO_2$ system. Clinical data were recorded each hour during the first three hours of care and twice daily for up to 3 days.

SpO_2: pulse oximetry (%).

Figure 2: Kaplan-Meier estimate of hypoxaemia occurrence in both groups

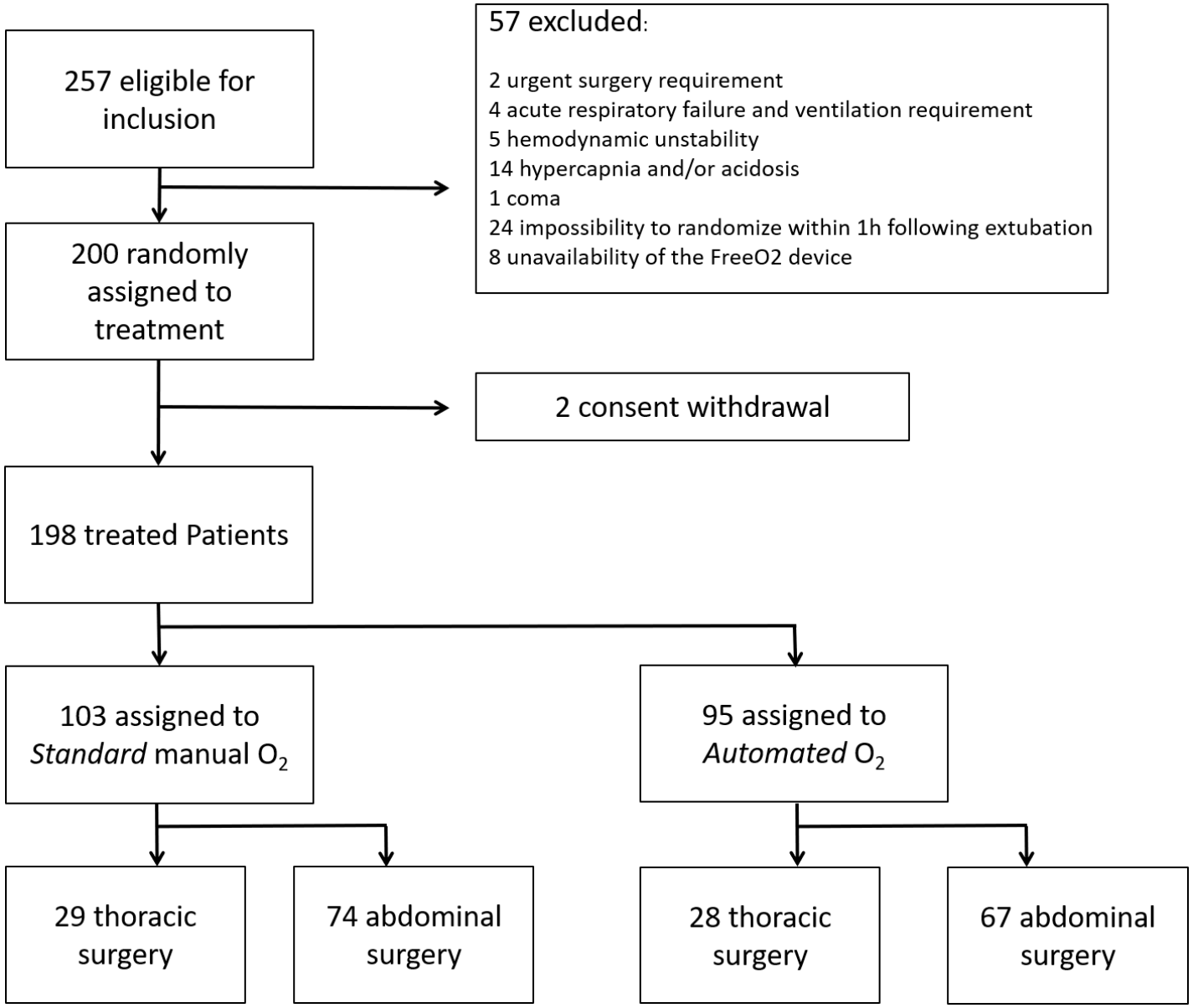
Events are defined as the first occurrence of either a clinically significant hypoxaemia or severe hypoxaemia event

The events are defined as the first occurrence of either a clinically significant hypoxaemia (A: $SpO_2 < 92\%$ for non-COPD patients, $SpO_2 < 88\%$ for COPD patients) or a severe hypoxaemia (B: $SpO_2 \leq 85\%$ for all patients), for more than a consecutive 30-second period. The evaluation was performed over a three-day period. Censored patients are those for whom oxygen was removed during monitoring, because of either weaning and/or clinical improvement. Analysis was performed over SpO_2 recordings of all patients, providing one value each second.

Both probability conditions were significantly reduced in the *Automated* as compared to the *Standard* group ($P = 0.015$ for hypoxaemia, and $P = 0.0003$ for severe hypoxaemia).

+ Censoring refers to patients with oxygen removed before the end of the maximal three days of follow-up. Numbers in blue depict the remaining patients without event occurrence in the Automated group; numbers in red depict the remaining patients in the Standard group.

Figure 1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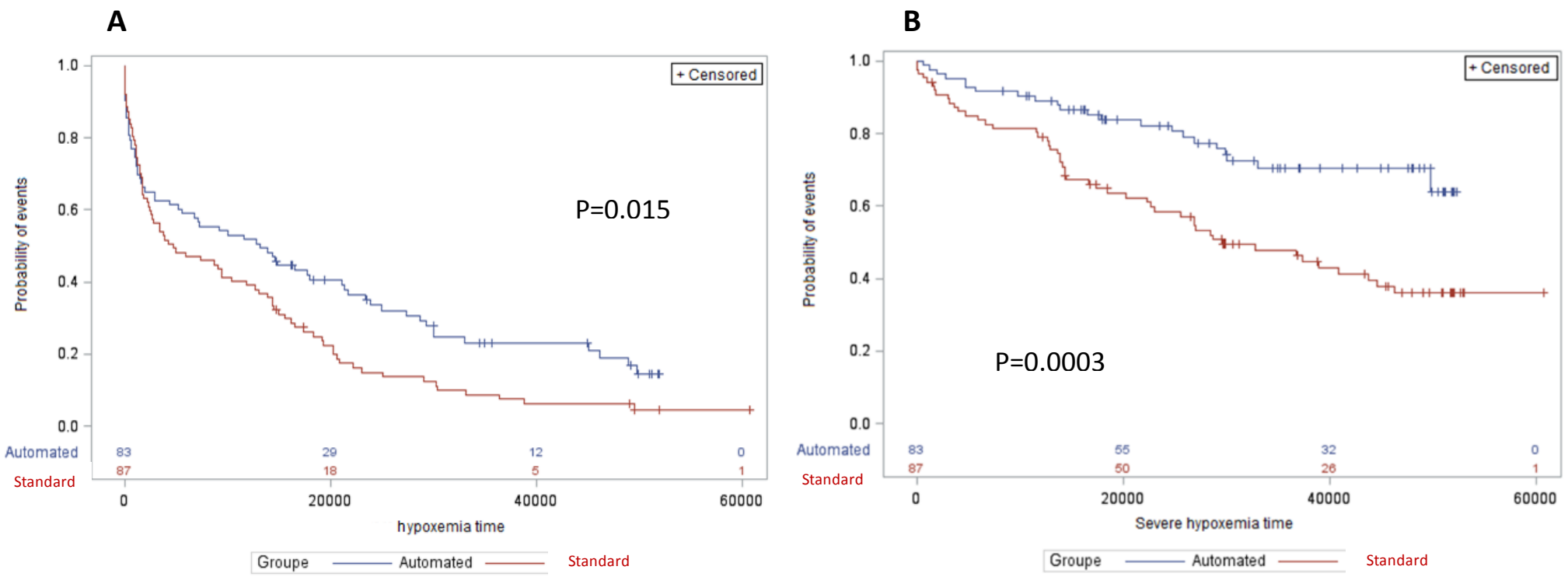
57 excluded:
2 urgent surgery requirement
4 acute respiratory failure and ventilation requirement
5 hemodynamic unstability
14 hypercapnia and/or acidosis
1 coma
24 impossibility to randomize within 1h following extubation
8 unavailability of the FreeO2 device
200 randomly assigned to treatment
2 consent withdrawal
198 treated Patients
103 assigned to *Standard* manual O_2
95 assigned to *Automated* O_2
29 thoracic surgery
74 abdominal surgery
28 thoracic surgery
67 abdominal surgery

Figure 2


A
+ Censored
P=0.015
Probability of events
1.0
0.8
0.6
0.4
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0.0
Automated
Standard
83
87
29
18
12
5
0
1
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20000
40000
60000
hypoxemia time
Groupe
Automated
Standard
B
+ Censored
P=0.0003
Probability of events
Automated
Standard
83
87
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20000
40000
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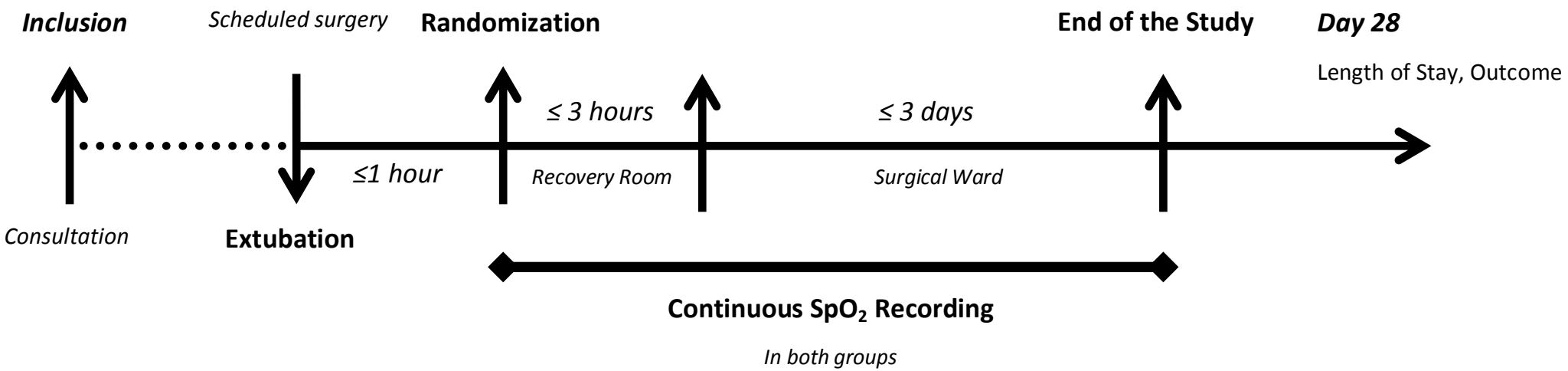
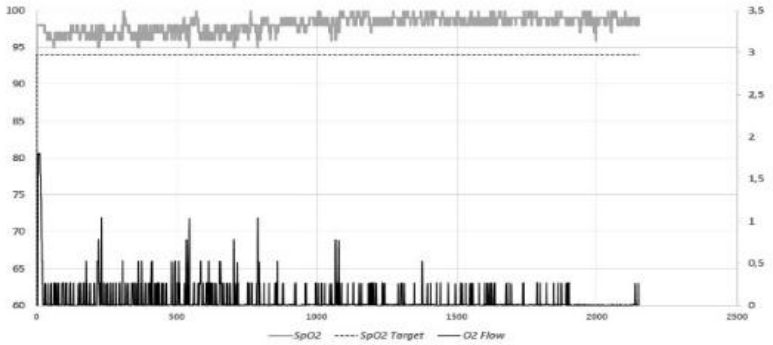
Severe hypoxemia time
Groupe
Automated
Standard

Supplementary Appendix, Figure S1



Supplementary Appendix: Figure S2



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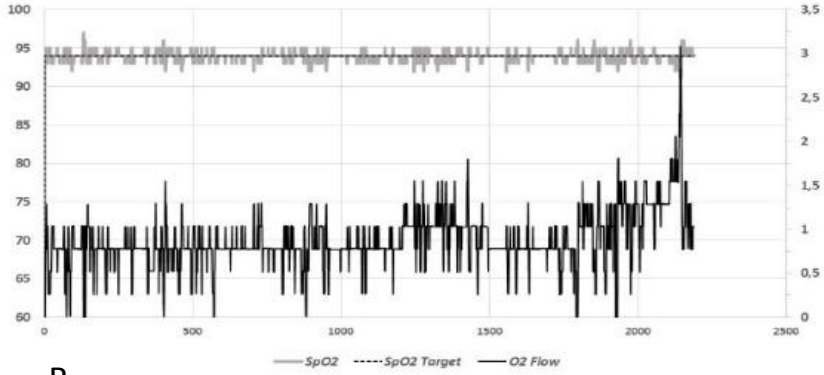

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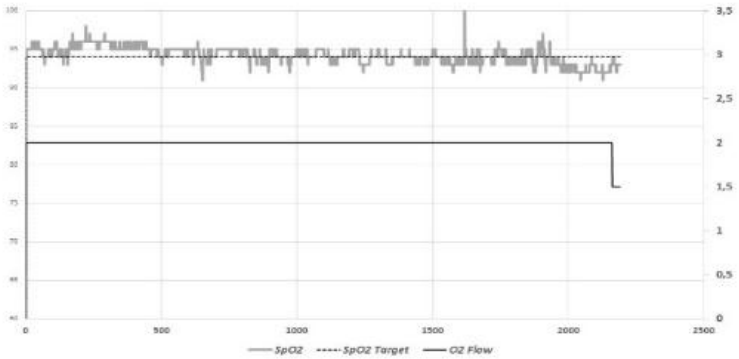

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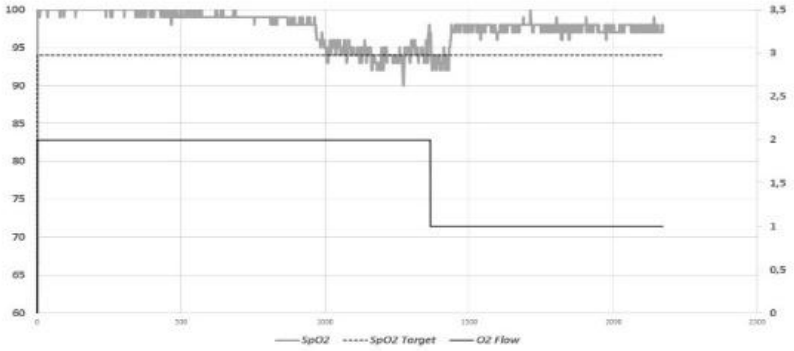
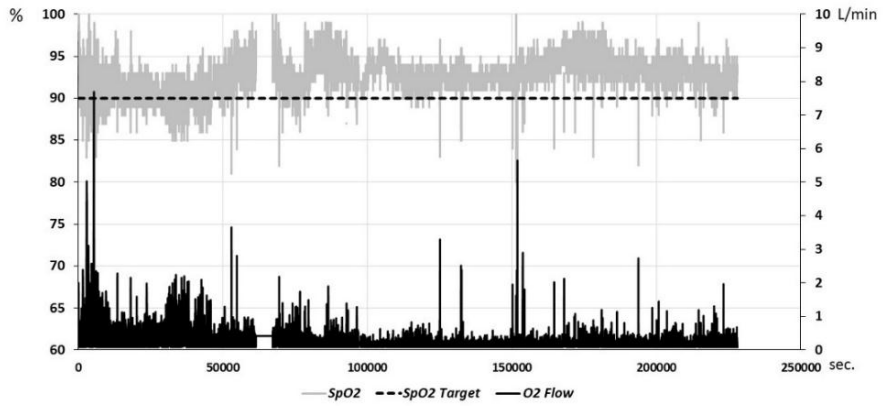
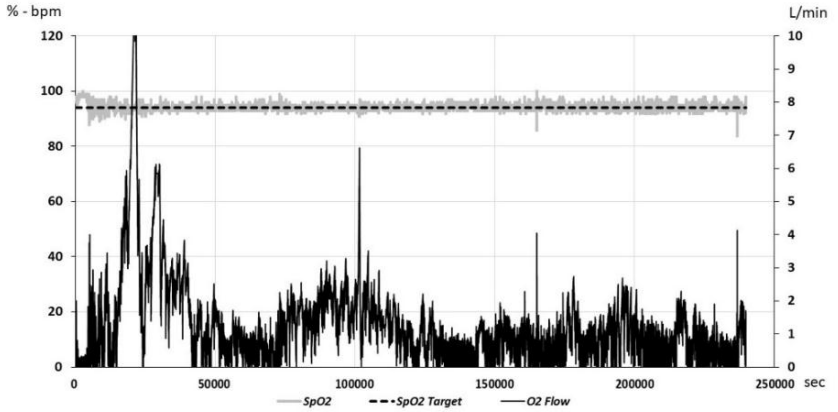


D

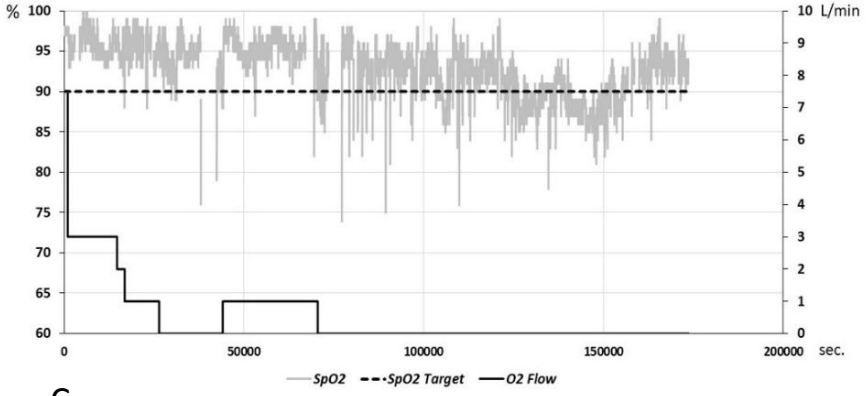
Supplementary Appendix: Figure S3



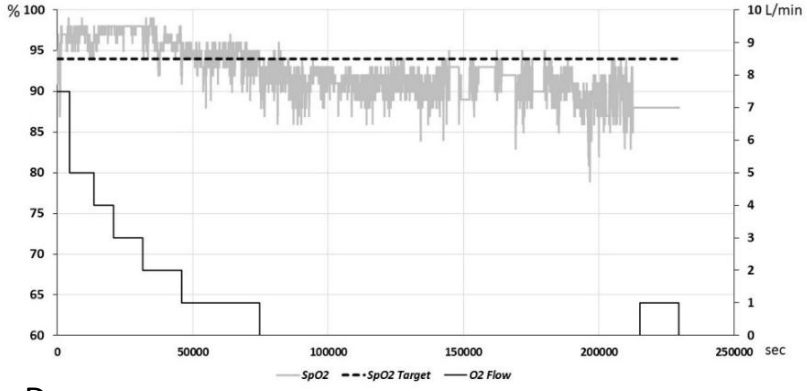
A



B



C



D