ORIGINAL RESEARCH

Automated oxygen titration and weaning with FreeO$_2$ in patients with acute exacerbation of COPD: a pilot randomized trial

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Introduction: We developed a device (FreeO$_2$) that automatically adjusts the oxygen flow rates based on patients' needs, in order to limit hyperoxia and hypoxemia and to automatically wean them from oxygen.

Objective: The aim of this study was to evaluate the feasibility of using FreeO$_2$ in patients hospitalized in the respiratory ward for an acute exacerbation of COPD.

Methods: We conducted a randomized controlled trial comparing FreeO$_2$ vs manual oxygen titration in the respiratory ward of a university hospital. We measured the perception of appropriateness of oxygen titration and monitoring in both groups by nurses and attending physicians using a Likert scale. We evaluated the time in the target range of oxygen saturation (SpO$_2$) as defined for each patient by the attending physician, the time with severe desaturation (SpO$_2$ <85%), and the time with hyperoxia (SpO$_2$ >5% above the target). We also recorded length of stay, intensive care unit admissions, and readmission rate. Fifty patients were randomized (25 patients in both groups; mean age: 72±8 years; mean forced expiratory volume in 1 second: 1.00±0.49 L; and mean initial O$_2$ flow 2.0±1.0 L/min).

Results: Nurses and attending physicians felt that oxygen titration and monitoring were equally appropriate with both O$_2$ administration systems. The percentage of time within the SpO$_2$ target was significantly higher with FreeO$_2$, and the time with severe desaturation and hyperoxia was significantly reduced with FreeO$_2$. Time from study inclusion to hospital discharge was 5.8±4.4 days with FreeO$_2$ and 8.4±6.0 days with usual oxygen administration (P=0.051).

Conclusion: FreeO$_2$ was deemed as an appropriate oxygen administration system by nurses and physicians of a respiratory unit. This system maintained SpO$_2$ at the target level better than did manual titration and reduced periods of desaturation and hyperoxia. Our results also suggest that FreeO$_2$ has the potential to reduce the hospital length of stay.

Keywords: oxygen inhalation therapy, technological innovations, hypoxia, hyperoxia, closed-loop

Introduction

Patients with COPD who are hospitalized for an acute exacerbation often receive oxygen therapy as a part of their treatment. Despite current recommendations,[1] oxygen therapy is often suboptimally adjusted during acute exacerbation of COPD, with episodes of both hypoxemia and hyperoxia reported.[2] Hyperoxia may be particularly problematic in COPD because of its association with hypercapnia,[3–7] especially in the acute phase of exacerbations,[3,4,8] where it may be associated with adverse clinical outcomes, including respiratory acidosis and even increased mortality.[4,8,9] Continuous adjustment of oxygen flows is time consuming, and clinicians are more concerned with oxygen desaturation

than with hyperoxia, potentially leading to the utilization of higher than required oxygen flows for longer than necessary.

Closed-loop adjustment of oxygen administration based on pulsed oxygen saturation (SpO_2) may optimize oxygen therapy and improve patients' safety.[10] We recently developed a closed-loop device, $FreeO_2$, that automatically adjusts the oxygen flows administered to spontaneously breathing patients to maintain SpO_2 in a predefined target set by physicians and to progressively and automatically wean patients from oxygen.[11] This pilot trial was intended to test the acceptability of $FreeO_2$ by nurses and attending physicians and the potential clinical impact of using such a device in patients hospitalized in the respiratory ward for acute exacerbation of COPD. Our hypotheses were that 1) nurses and physicians would conclude that $FreeO_2$ is an acceptable oxygen administration device, 2) time spent in the target SpO_2 zone would be increased by automatic O_2 flow adjustments in comparison to manual O_2 titration, and 3) weaning time from oxygen would be shortened by the automatic O_2 adjustment device ($FreeO_2$).

Methods
Participants
We conducted a randomized trial (Clinical Trial Registration: NCT01393015) comparing manual oxygen titration and automated oxygen adjustment with $FreeO_2$ in patients hospitalized for an acute exacerbation of COPD in whom oxygen therapy was prescribed by the attending physician based on the documentation of resting hypoxemia ($SpO_2 <90\%$). We included patients aged ≥40 years with a past or current smoking history of at least 10 pack-years. Patients had to maintain an SpO_2 of $\geq92\%$ with supplemental oxygen at a maximum flow rate of 8 L/min. We excluded patients admitted for >24 hours, patients infected with multidrug-resistant bacteria, patients on intermittent noninvasive ventilation (including CPAP for obstructive sleep apnea), and patients with cognitive impairment precluding informed consent or collaboration. The study was conducted at the Institut Universitaire de Cardiologie et de Pneumologie de Québec. The study was approved by the Institutional Ethics Committee (# 20694), and a signed consent was obtained from each participant.

FreeO$_2$ system
The $FreeO_2$ system automatically adjusts oxygen flow rates administered via nasal cannula or nonocclusive mask, using a closed-loop algorithm based on physiological data.[11] It also provides continuous monitoring of respiratory parameters in spontaneously breathing patients.[11] The main parameter that is monitored within this closed-loop system is SpO_2 that continuously feeds the algorithm at a rate of 1 value/s.

A proportional integral controller adjusts the oxygen flow delivered by a mass-flow controller from 0 L/min to 20 L/min (flow accuracy ±0.1 L/min), with the aim of maintaining SpO_2 at a predefined target. The system was developed by the authors (FL and ELH) in collaboration with the Department of Electronic and Informatics Engineering, Laval University, Quebec (Figure 1).

Protocol
Randomization was conducted with sealed envelopes after inclusion of the patients in the study. Randomization sequences were externally generated using www.random.org. Patients were allocated to either 1) automated oxygen titration by $FreeO_2$ with continuous monitoring of physiological parameters, including SpO_2 and oxygen flow rates ($FreeO_2$ arm), at bedside and remotely at the nursing station or 2) manual oxygen administration with bedside titration from usual oxygen flowmeter (rotameter) and usual oxygen monitoring with bedside pulsed oximetry (control arm). In the control group, the nurses manually adjusted the oxygen flows guided by local protocols and by SpO_2 target provided by the attending physician before randomization. SpO_2 monitoring was conducted as per the local practice (ie, approximately three times per day). However, there were no specific training to the oxygen management guidelines and no recording of the compliance to these guidelines. In the $FreeO_2$ arm, oxygen was titrated automatically every second to maintain SpO_2 in the target zone set by the attending physician before randomization.

The principal investigators of the study did not manage the patients included in the study and were not involved in the treatment and discharge decisions.

Measurements
At baseline, demographic data, arterial or capillary blood gases, oxygen flow rate, and respiratory rate were recorded. Pulmonary function tests (forced expiratory volume in 1 second and forced vital capacity) were conducted using standardized postbronchodilator spirometry. These pulmonary parameters were recorded during a stable period of COPD within 1 year before or after exacerbation and during hospitalization.

In order to evaluate whether $FreeO_2$ could be used in daily practice and to quantify its acceptance and ease of use by caregivers (primary outcomes), the nurses and physicians' perception of the appropriateness of the oxygen management was monitored by direct interview when available on a daily basis using a 10-point Likert scale (from 0: not appropriate at all to 10: perfectly appropriate). The secondary outcomes were 1) time spent within the SpO_2 target (±2%), 2) time with severe desaturation ($SpO_2 <85\%$), 3) time with hyperoxia

Figure 1 Main features of the FreeO$_2$: oxygen automated titration and weaning with SpO$_2$–O$_2$ flow closed-loop and monitoring.
Notes: The FreeO$_2$ adjusts the oxygen flow rate from 0 L/min to 20 L/min (flow accuracy ±0.1 L/min) every second, based on the patient's needs. A proportional integral controller adjusts the oxygen flow based on the difference between the SpO$_2$ target set by clinicians and the continuously measured SpO$_2$. Several cardiorespiratory parameters are continuously recorded (O$_2$ flow rate, SpO$_2$, respiratory rate, and heart rate), and trends for these parameters are available for clinicians. Both heart rate and respiratory rate are derived from the pulse oximeter plethysmographic wave form. The version used in the study was a previous version of the device with similar technical features.

(SpO$_2$ >5% above the target), 4) total duration of oxygen therapy, and 5) hospital length of stay.

Patients in both groups had continuous monitoring of SpO$_2$, respiratory rate, heart rate, and end-tidal CO$_2$ with the FreeO$_2$ system set in the "FreeO$_2$ mode" (automated closed-loop adjustment of oxygen and continuous recording) or in the "recording mode" (continuous recording of physiological data without administration of oxygen by the device for those in the control group). Capillary blood gases were collected every day during the first week or up to discharge.

Statistical analyses

We could not calculate a priori a sample size based on the primary outcome as we did not have any data to estimate how the system would be accepted by the caregivers. Nevertheless, we chose to include 50 patients to obtain sufficient exposure and experience with FreeO$_2$. Data were expressed using mean with standard deviation or median with interquartile ranges for continuous variables or proportions for categorical data, respectively. Categorical variables were compared between groups using the chi-square or Fisher's exact tests, and

continuous variables were compared using one-way analyses of variance. Wilcoxon rank sum tests (nonparametric tests) were performed for data that did not fulfill the normality or variance assumptions after transformation. When different conclusions between analyses from one-way analysis of variance and nonparametric tests occurred, the latest approach was retained. The results were considered significant with *P*-values ≤0.05. All analyses were conducted using the statistical package SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

We randomized 25 patients with COPD in each group (total of 50 patients) from August 2011 to February 2015. The flow chart of patient participation in the study is shown in Figure 2. Patients' baseline characteristics are shown in Table 1. Overall, baseline characteristics were similar between the two study groups. The mean age was 72±9 years, and the mean forced expiratory volume in 1 second was 1.00±0.49 L, representing 37%±22% predicted. Twenty-three patients (46%) were women.
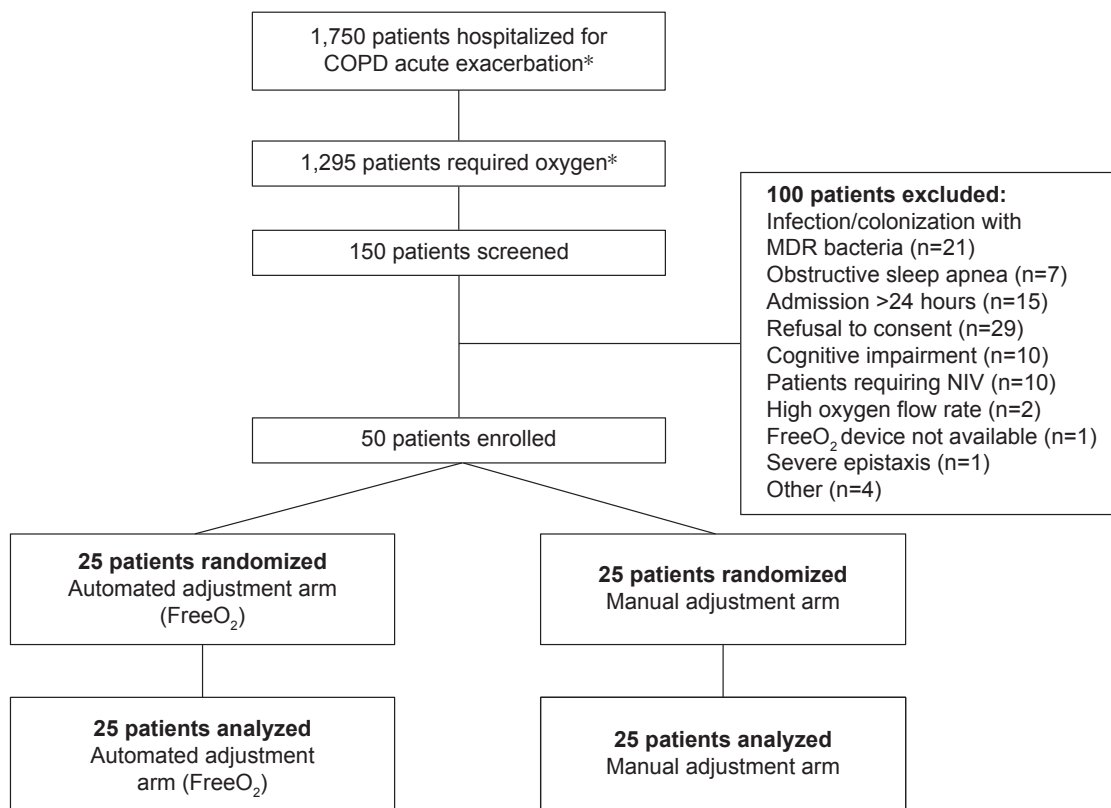
Figure 2 Flow chart of the study.
Note: *Based on administrative records of the institution.
Abbreviations: MDR, multidrug resistant; NIV, noninvasive ventilation.

Table I Patient characteristics

Characteristics	FreeO$_2$ patients (n=25)	Control patients (n=25)
Age (years)	71±8	73±8
Men, n (%)	15 (60)	12 (48)
ED admission to inclusion (days)	0.6±0.7	0.6±1.1
Spirometry during stable state[a]		
FEV$_1$ (L)	1.1±0.3	1.1±0.4
FEV$_1$ (% predicted)	40±11	51±20
FEV$_1$/FVC (%)	41±0.11	47±20
Spirometry during hospital stay[b]		
FEV$_1$ (L)	1.0±0.5	1.0±0.5
FEV$_1$ (% predicted)	36±19	38±24
FEV$_1$/FVC (%)	45±12	49±13
Physiologic data at study inclusion		
O$_2$ flow (L/min)	2.0±1.0	2.0±1.0
pH	7.40±0.05	7.39±0.05
PaCO$_2$ (mmHg)	46±12	46±11
HCO$_3^-$ (mmol/L)	28±5	27±5
SpO$_2$ (%)	93±2	93±2
Body temperature (°C)	36.6±0.6	36.7±0.6
Respiratory rate (breaths/min)	22±3	21±2

Notes: Data expressed as mean ± SD, unless otherwise specified. [a]Forced spirometry performed within 1 year before or after hospitalization, during a stable state (value available for 62% of the patients). [b]Forced spirometry performed during the hospital stay (available for all patients).
Abbreviations: ED, emergency department; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.

Primary outcomes

There were 924 evaluations of the oxygen adjustment and monitoring by nurses and 96 evaluations by physicians. Nurses and physicians considered FreeO$_2$ adjustments and monitoring to be at least as appropriate and as acceptable as manual oxygen management. Only monitoring was deemed slightly better with FreeO$_2$ by the physicians, but the difference was not statistically significant (Table 2). We did not directly evaluate patient's tolerance of the system, but 80% of the patients completed the study in both groups. The main reason to prematurely stop the study was related to the difficulty in continuously wearing a pulse oximeter and the reduced mobility (70% of the reasons to stop); this occurred similarly in both groups.

Secondary outcomes
Oxygenation and blood gases

SpO$_2$ targets chosen by physicians were similar in both groups, averaging 90.0% and 90.1% for FreeO$_2$ and manual O$_2$ adjustment, respectively. The mean SpO$_2$ during the study was 90.9±1.2 in the FreeO$_2$ group and 91.9±1.2 in the manual adjustment group (P=0.009). The proportion of time within SpO$_2$ target was 81.2%±19.9% with FreeO$_2$ vs 51.3%±19.7%

Table 2 Evaluation of the nurses' and physicians' perception of the appropriateness of the oxygen therapy management

	FreeO$_2$ (n=25)	Control (n=25)	P-value
Nurses			
Oxygen titration	8.9±1.5	8.8±1.8	0.46
Oxygen monitoring	8.9±1.4	8.7±2.0	0.19
Physicians			
Oxygen titration	8.2±2.2	7.8±2.1	0.48
Oxygen monitoring	8.2±2.2	6.7±3.2	0.07

Notes: Data expressed as mean ± standard deviation, unless otherwise specified. Based on a 10-point Likert scale (from 0, not appropriate at all, to 10, perfectly appropriate).

with manual O$_2$ adjustments ($P<0.001$). The percentage of time with severe desaturation (SpO$_2$ <85%) and with hyperoxia (SpO$_2$ >5% above the target) was significantly lower with FreeO$_2$ in comparison with manual oxygen adjustment (Figure 3 and Table 3). There was no significant difference in blood gases measured on day 3 and day 7 between the two groups.

Clinical outcomes

Duration of oxygen administration was reduced by 1.8 days with FreeO$_2$, but this difference did not reach statistical significance (Table 4). Time from randomization to hospital discharge was reduced by 2.6 days with FreeO$_2$ ($P=0.051$). There was no difference between the two groups in the requirement for noninvasive ventilation during hospitalization, need of transfer to the intensive care unit, or death. The readmission rates at 30, 60, and 180 days were also similar in the two groups.

Safety

There was no safety issue as we did not record any oxygen delivery interruption with FreeO$_2$. Few technical issues occurred with end-tidal CO$_2$ monitoring, but none concerned

Table 3 Oxygenation and capillary blood gases

	FreeO$_2$	Control	P-value
SpO$_2$ target defined by the physicians (%)[a]	90.0±1.2	90.1±1.0	0.89
Mean SpO$_2$ (%)	90.9±1.2	91.9±1.2	0.009
% of time in the SpO$_2$ target ±2%	81.2±15.9	51.3±19.7	<0.001
% of time with hyperoxia[b]	1.5±1.9	10.4±10.3	<0.001
% of time with hypoxemia[c]	0.2±0.2	2.3±2.7	0.001
Mean O$_2$ flow (L/min)[d]	0.7±0.7	1.2±1.0	0.06
% of time with SpO$_2$ signal available	90.4±7.6	82.4±12.7	0.01
Day 3[e]			
pH	7.42±0.03	7.41±0.05	0.33
PaCO$_2$	45±7	46±10	0.62
HCO$_3^-$	29±4	29±5	0.94
O$_2$ flow (L/min)	1.0±1.1	1.6±1.4	0.21
Day 7[f]			
pH	7.43±0.02	7.42±0.06	0.46
PaCO$_2$	40±4	47±13	0.09
HCO$_3^-$	27±2	30±6	0.13
O$_2$ flow (L/min)	0.6±0.4	1.2±1.0	0.47

Notes: Data expressed as mean ± standard deviation, unless otherwise specified. [a]At study entry. [b]Hyperoxia was defined by SpO$_2$ >5% above the target. [c]Hypoxemia was defined by SpO$_2$ <85%. [d]During the time of recording. [e]Data available (n=25 in both groups). [f]Data available (n=12 in the FreeO$_2$ arm and n=15 in the control group).

the oxygen delivery valve, and this was not associated with safety issues.

Discussion

Our pilot trial demonstrates the feasibility of providing oxygen therapy with FreeO$_2$ to patients hospitalized for an acute exacerbation of COPD, even during prolonged administration of oxygen (up to 8 consecutive days). The device was well accepted by nurses and physicians. FreeO$_2$ maintained SpO$_2$ within the prespecified target better than manual oxygen administration. It also reduced the periods of hyperoxia and desaturation. In addition, our results suggest that FreeO$_2$ may have the potential to reduce hospital length of stay,
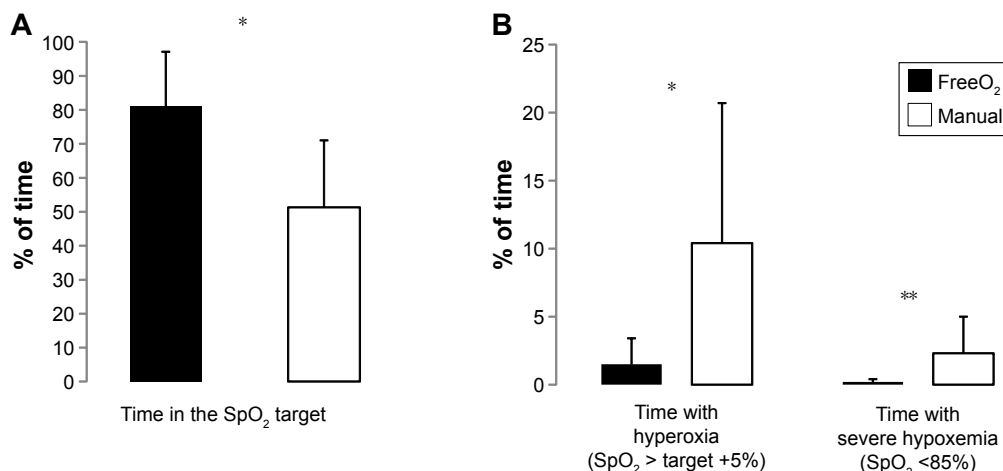

Figure 3 Percentage of time in the SpO$_2$ target (**A**), with hyperoxia and with severe hypoxemia (**B**) with FreeO$_2$ (black bars) and with manual adjustment (white bars).
Notes: *$P<0.001$. **$P=0.01$.

Table 4 Clinical outcome

Outcome	FreeO$_2$ patients (n=25)	Control patients (n=25)	P-value
Duration of O$_2$ administration (days)	4.0±2.1	5.8±9.9	0.14
Length of hospital stay			
Randomization to hospital discharge (days)	5.8±4.4	8.4±6.0	0.051
Admission to hospital discharge (days)	6.7±4.3	9.5±6.0	0.053
Complications			
NIV (n)	0	1	0.48
ICU transfer (n)	0	1	0.48
Death (n)	1	1	1
Readmission rate			
30 days (n)	6	6	1
60 days (n)	6	9	0.54
180 days (n)	10	13	0.57

Note: Data expressed as mean ± standard deviation, unless otherwise specified.
Abbreviations: ICU, intensive care unit; NIV, noninvasive ventilation.

although this pilot observation requires formal testing in a proper clinical trial.

Our study is the first to investigate the potential effects of a continuous and an automated oxygen titration and weaning system on physiological and clinical outcomes in patients hospitalized for an acute exacerbation of COPD. Several studies evaluated similar systems in patients with COPD in other settings, such as home care[12] or during rehabilitation,[13,14] and in other populations, including neonates[15,16] and in patients with acute respiratory failure in the emergency department.[17] Automated therapy has always proved effective in safely providing oxygen in these settings and populations, and our results are consistent with this notion.

The introduction of new devices in clinical practice may not be well accepted, and barriers to technology acceptance should not be overlooked.[18] The primary study outcome was selected accordingly. FreeO$_2$ was deemed at least as adequate for oxygen administration and monitoring as usual oxygen administration. Also, most patients tolerated the instrument, as 80% completed the study in both groups. Few patients did not complete the study due to reduced mobility related to the continuous oximetry recording. Implementation of an oximeter with wireless communication features may further improve the acceptance of O$_2$ automated systems in the future.

We were successful in continuously recording respiratory parameters with identical oximeters in both groups with second-by-second data available 90.4% and 82.4% of the time in the FreeO$_2$ and control groups, respectively. As expected and in line with other evaluations of automated oxygen titration,[10,14,17] oxygenation parameters were improved in the FreeO$_2$ group, with more time spent in the targeted range of SpO$_2$ and less time with oxygen desaturation or hyperoxia. This may be clinically relevant when considering that hyperoxia may induce hypercapnia[3–7] with potentially severe consequences.[4,8,9] Hyperoxia is also of concern in patients with COPD who frequently have coronary artery disease,[19] as it may increase coronary artery resistance.[20,21] On the other hand, periods of oxygen desaturations may be responsible for arythmias and myocardial ischemia,[22,23] and they should also be avoided.

In the control group, patients were in the SpO$_2$ target 50% of the time, which may not be compared with other data, as these are the first data with continuous recording of SpO$_2$ in this situation to our knowledge. In the recent review of Cousin et al,[24] the mean rate of accurate prescription of oxygen therapy in eleven studies was 17.4% before and 51.2% after implementation of specific interventions.

One strength of our study is that we could evaluate an automated oxygen therapy during prolonged duration (ie, up to 8 days), compared with previous studies where automated O$_2$ titration was provided for a duration of <1 hour[11,13,14] and up to 3 hours.[17] An important result of our trial is the trend toward a reduction in duration of oxygen therapy and hospital length of stay with automated oxygen titration, although we cannot ascertain whether this effect was related to closer O$_2$ monitoring and surveillance as a part of the FreeO$_2$ protocol or whether this was due to the FreeO$_2$ device itself. Although the trial was not primarily designed to demonstrate an impact on these outcomes, this finding is in agreement with the hypothesis that unnecessarily high flows and prolonged oxygen therapy are common[25] and that automated weaning may be useful to abbreviate oxygen therapy in hospitalized patients with COPD. Length of stay must be interpreted in comparison to local statistics obtained off-protocol. In 2010, the mean length of stay for acute exacerbation of COPD in our institution was 9.8±8.1 days (unpublished data), which is in-line with the length of stay in the control group of the present study. Reducing the length of hospital stay by 31% as found in this study would be expected to have major logistic and financial impacts on our health care setting. This study was underpowered to conclude on the hospital length of stay, and larger studies will be required to confirm this potential benefit of automated oxygen titration.

Our study has potential limitations that should be considered for proper interpretation. First, this was a pilot study with a small sample size. A more complete evaluation of

relevant clinical outcomes, such as length of stay and cost effectiveness, will likely require more patients. Second, the recruitment rate was low as we recruited only 50 patients in 3 years. The main reason was the limited resources during prolonged periods that did not allow continuous screening of potential study participants. There were >500 COPD hospitalized every year during the study period, and several of these would have been eligible to the trial. Third, the study was not blinded. Nurses had to be aware of the patients' allocation as they were in charge of the manual titration in the control group, and remote monitoring of cardiorespiratory parameters at the nursing station was available only in the FreeO$_2$ arm. To limit the impact of this potential source of bias, study investigators were not involved in any treatment or discharge decisions.

Conclusion

This study demonstrates the feasibility of using automated oxygen titration and weaning as well as remote monitoring with the FreeO$_2$ system in patients hospitalized for acute exacerbation of COPD. The system was well accepted by both nurses and physicians. Automated oxygen titration provided benefits in terms of safety (ie, reduction in the time with severe desaturation and hyperoxia) and may have contributed to a trend toward the reduced hospital length of stay, a potentially important finding, if these benefits are confirmed in subsequent studies specifically designed to demonstrate these effects.

Acknowledgments

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The Fond de Recherche en Santé du Québec contributes to FL's salary for research activities (clinical research scholar) and to the research assistant's salary (clinical research grant). FL and ELH are the coinventors of the FreeO$_2$ system and made the first prototypes with the engineering department of Laval University. FL and ELH are the cofounders of a Laval University spin-off research and development company (OxyNov) to develop automated systems for respiratory support. FM holds a GlaxoSmithKline/Canadian Institutes of Health Research chair on COPD at Laval University. FM and YL participate in Innovair, a company that owns shares in OxyNov, the owner of the FreeO$_2$ device. PAB and MR have no financial interests that may be relevant to the submitted work. The authors report no other conflicts of interest in this work.

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