ORIGINAL ARTICLE
EMERGENCY MEDICINE

Automatic *versus* manual oxygen administration in the emergency department

Erwan L'Her[1,2,3,4], Patricia Dias[5], Maelenn Gouillou[5], Anne Riou[6], Luc Souquiere[6], Nicolas Paleiron[6], Patrick Archambault[7], Pierre-Alexandre Bouchard[8] and François Lellouche[4,8]

Affiliations: [1]Réanimation Médicale et Urgences Adultes, CHRU de Brest, Brest, France. [2]LATIM INSERM UMR 1101, Université de Bretagne Occidentale, Brest, France. [3]Chaire de Recherche en Médecine d'Urgence, Hôtel-Dieu de Lévis, Québec, Canada. [4]Oxynov Inc., Québec, Canada. [5]CIC INSERM 1412, CHRU de Brest, Brest, France. [6]HIA Clermont-Tonnerre, Brest, France. [7]Département de médecine d'urgence, Centre intégré en santé et services sociaux Chaudière-Appalaches, Québec, Canada. [8]Centre de recherche IUCPQ, Québec, Canada.

Correspondence: Erwan L'Her, Réanimation Médicale, LATIM INSERM UMR 1101, CHRU de la Cavale Blanche, Bvd Tanguy-Prigent, 29609 BREST Cedex, France. E-mail: erwan.lher@chu-brest.fr

@ERSpublications
Automated oxygen titration is superior to manual administration in terms of time within oxygenation targets http://ow.ly/pgWC30c2sLv

Cite this article as: L'Her E, Dias P, Gouillou M, *et al*. Automatic *versus* manual oxygen administration in the emergency department. *Eur Respir J* 2017; 50: 1602552 [https://doi.org/10.1183/13993003.02552-2016].

ABSTRACT Oxygen is commonly administered in hospitals, with poor adherence to treatment recommendations.

We conducted a multicentre randomised controlled study in patients admitted to the emergency department requiring O_2 ⩾3 L·min^{-1}. Patients were randomised to automated closed-loop or manual O_2 titration during 3 h. Patients were stratified according to arterial carbon dioxide tension (P_{aCO_2}) (hypoxaemic P_{aCO_2}⩽45 mmHg; or hypercapnic P_{aCO_2}>45–⩽55 mmHg) and study centre. Arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) goals were 92–96% for hypoxaemic, or 88–92% for hypercapnic patients. Primary outcome was % time within S_{pO_2} target. Secondary endpoints were hypoxaemia and hyperoxia prevalence, O_2 weaning, O_2 duration and hospital length of stay.

187 patients were randomised (93 automated, 94 manual) and baseline characteristics were similar between the groups. Time within the S_{pO_2} target was higher under automated titration (81±21% *versus* 51 ±30%, p<0.001). Time with hypoxaemia (3±9% *versus* 5±12%, p=0.04) and hyperoxia under O_2 (4±9% *versus* 22±30%, p<0.001) were lower with automated titration. O_2 could be weaned at the end of the study in 14.1% *versus* 4.3% patients in the automated and manual titration group, respectively (p<0.001). O_2 duration during the hospital stay was significantly reduced (5.6±5.4 *versus* 7.1±6.3 days, p=0.002).

Automated O_2 titration in the emergency department improved oxygenation parameters and adherence to guidelines, with potential clinical benefits.

This article has supplementary material available from erj.ersjournals.com

Earn CME accreditation by answering questions about this article. You will find these at erj.ersjournals.com/journal/cme

Received: Dec 28 2016 | Accepted after revision: April 11 2017

Support statement: The study was funded by the Programme Hospitalier de Recherche Clinique National 2010 from the French Ministry of Health for the French centres and by the Ministry of Finance in Québec for Canadian centres. The study was sponsored by Brest University Hospital, which was responsible for data management and control. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

The study was registered at ANSM ID RCB 2010-A00927-32 and ClinicalTrials.gov identifier NCT02027181.

Introduction

Oxygen therapy is administered daily to a wide number of patients in the emergency care setting, either during pre-hospital transportation or hospital care [1]. Current standards for prescribing oxygen recommend providing adequate flows to correct hypoxaemia and avoid hyperoxia [2, 3]. While deleterious effects of hypoxaemia are well known, the potential harmful effects of hyperoxia are underappreciated. Yet, hyperoxia may increase mortality in severe chronic obstructive pulmonary disease (COPD) patients [4–6] and may cause cardiac and neurological adverse toxicities in certain situations [7–9]. In conditions where access to O_2 is limited (pre-hospital care and/or military operations), it is also crucial to minimise its use as much as possible, and to promote rapid O_2 weaning [10].

Precise control of O_2 flows is difficult to achieve in clinical practice and is time-consuming [11]. Automated O_2 administration allows arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) to be maintained within a predetermined range using variable O_2 flows, as opposed to manual O_2 administration where the flow is kept constant with variable S_{pO_2} values. In preterm infants receiving mechanical ventilation, automated O_2 control results in more time spent within the intended S_{pO_2} target [12–14]. In a healthy adult model, such a system was more efficient at maintaining S_{pO_2} within the target, while ensuring a significant reduction of hypoxaemia and hyperoxia periods compared with constant O_2 flows [15].

We conducted a prospective, multicentre, randomised, controlled trial involving adult patients admitted to the emergency department (ED) for acute hypoxaemic respiratory failure. We hypothesised that automated O_2 administration would improve oxygenation and promote better adherence to clinical guidelines during the early emergency care of adult patients than conventional O_2 therapy [2].

Methods

Study design

From August 2011, to October 2014, we recruited adult patients that had been evaluated in four French and Canadian University Hospital EDs for an acute respiratory failure. The study protocol was approved by human research ethics committees in France and in Canada.

The trial was overseen by a steering committee and an independent safety monitoring board. All centres were monitored to check adherence to the protocol and the accuracy of recorded data. An investigator at each centre was responsible for enrolling patients and ensuring adherence to the protocol. Research assistants were responsible for patients' 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.

The study was registered at ANSM ID RCB 2010-A00927-32 and ClinicalTrials.gov identifier NCT02027181.

Patients

Patients were eligible if they were adult and admitted to the ED within less than 2 h for acute respiratory disorder still requiring $\geqslant 3$ L·min^{-1} of O_2 for maintaining a S_{pO_2} $\geqslant$92%, whatever the original pathology. Patients were ineligible if they presented life-threatening hypoxaemia, any clinical signs of ventilatory assistance requirement or if they required emergent surgery or coronary angiography. Details of the exclusion criteria are provided in the supplementary material.

All patients or their next of kin provided written informed consent.

Randomisation

A computer-generated block-randomisation sequence with random block sizes was used. All patients were stratified according to arterial carbon dioxide tension (P_{aCO_2}) (purely hypoxaemic respiratory failure, P_{aCO_2} $\leqslant$45 mmHg; or mildly hypercapnic respiratory failure P_{aCO_2} >45 and $\leqslant$55 mmHg) and study centre. Patients were randomly assigned in a 1:1 ratio to either automated oxygen administration (FreeO_2) or conventional oxygen administration (manual O_2) using a centralised web-based electronic datafile system (Clinsight, Ennov, Paris, France).

Study intervention

Automated O_2 administration was performed using the FreeO_2 system (Oxynov Inc., Québec, QC, Canada) that was set to maintain S_{pO_2} between 92% and 96% for purely hypoxaemic respiratory failure or between 88% and 92% for hypercapnic respiratory failure. FreeO_2 is equipped with a S_{pO_2} monitor and an electronically controlled valve that automatically adjusts O_2 flows on a per second basis, according to a closed-loop algorithm, in order to reach the predetermined S_{pO_2} goal [15].

Conventional O_2 was administered using manual flowmeters, according to standard procedures. All participating units were encouraged to use the same standardised S_{pO_2} goals as in the automated O_2 administration group. The intervention period was set to 3 h, considering that such duration may enable stabilisation of the patient with medical treatment, and/or to determine any deterioration with a high level of confidence.

In both groups, we used an O_2 mask to administer either low or high O_2 flow. Considering the variety of pathological cases requiring O_2 administration in an ED, medical treatment was determined by the attending physicians on the basis of clinical needs assessment, except for ventilatory assistance requirements, which were standardised to avoid delaying endotracheal intubation. Following this initial treatment period, patients could be hospitalised to receive further treatment if deemed necessary by the attending physician.

Data collection and study outcomes

At the time of enrolment, physiological characteristics, coexisting medical conditions and oxygen flow rates were recorded. In both study groups, S_{pO_2}, respiratory rate (RR) and heart rate (HR) were continuously monitored using dedicated software (FreeOview v2, Oxynov Inc.) and an oximeter (Nonin OEM III, Plymouth, MN, USA) to calculate the time spent within a given S_{pO_2} range.

The primary outcome was the percentage of time spent within the target S_{pO_2} range during the 3-h study period. Secondary outcomes included the percentage of time spent in hypoxaemia as defined by a S_{pO_2} value 2% lower than the minimum S_{pO_2} target (S_{pO_2}<90% for purely hypoxaemic respiratory failure and <86% for mildly hypercapnic respiratory failure), or hyperoxia as defined by a S_{pO_2} value 2% higher than the maximum S_{pO_2} target ($S_{pO_2}\geqslant$98% for purely hypoxaemic respiratory failure and $\geqslant$94% for mildly hypercapnic respiratory failure), duration of oxygen supplementation duration in the entire hospital stay and hospital length-of-stay. Serious adverse events rate at day 28 and during the entire ED and hospital stay. Serious adverse events were predefined and reported to the safety-monitoring board as they occurred. Data were collected until death, or the first discharge from the hospital.

Statistical analysis

Based on preliminary data, we anticipated a percentage of time within the S_{pO_2} range of 70% using the automated system compared with 60% using conventional O_2. We determined that a sample of 190 patients was required to show the superiority of automated oxygenation with a power of 90%. We allowed the switch to conventional oxygen when there were technical problems, but there was no crossover to $FreeO_2$. The primary outcome was short-term treatment efficacy rather than death or morbidity, because of the lack of data on outcome after O_2 administration in the ED, and the absence of clinical data on automated systems. All analyses were performed on an intention-to-treat basis, and patients remained in their assigned group for all outcomes.

The primary outcome was analysed using a generalised linear model with normal distribution, adjusted for the study site (random effect) and the subgroup (hypoxaemic or hypercapnic). Homogeneity between subgroups was tested adding an interaction term in the model. Secondary outcomes were analysed using the same statistical method, except that binary data were evaluated using a binomial distribution with identity link and exchangeable correlation structure to account for study centre. Hospital length of stay (LOS) was analysed using the raw data, and subsequently censored for survivors; log-rank tests were used for the univariate analysis and a Cox proportional hazards model was adjusted for study centre and subgroup. All analyses were performed by an independent study statistician using SAS, version 9.3 (SAS Institute, Cary, NC, USA). p-values equal or less than 0.05 were considered statistically significant.

Results

Study patients

From August 2011, to October 2014, 1247 patients were screened for eligibility. A total of 190 patients were included and a total of 187 patients underwent randomisation (93 to the automated O_2 group ($FreeO_2$)and 94 to the conventional O_2 group (Manual O_2)) (figure 1). Hypoxaemic respiratory failure represented the most frequent clinical presentation (n=137; 73.3%). Sixty-five patients had a diagnosis of COPD at enrolment (34.8%), of whom 17 patients were receiving long-term oxygen therapy. Initial mean oxygen flow rates were as follows: in the $FreeO_2$ group, 6.2±3.1 L·min^{-1}; in the Manual O_2 group, 5.5±3.1 L·min^{-1} (table 1).

Primary outcome

$FreeO_2$ was found superior to Manual O_2 to maintain S_{pO_2} within the assigned range (adjusted between-group difference of 29.4 percentage points; 95% confidence interval, 25.7–33.2), either for the entire group or for any of the subgroups of respiratory failure (hypoxaemic and hypercapnic) (table 2).

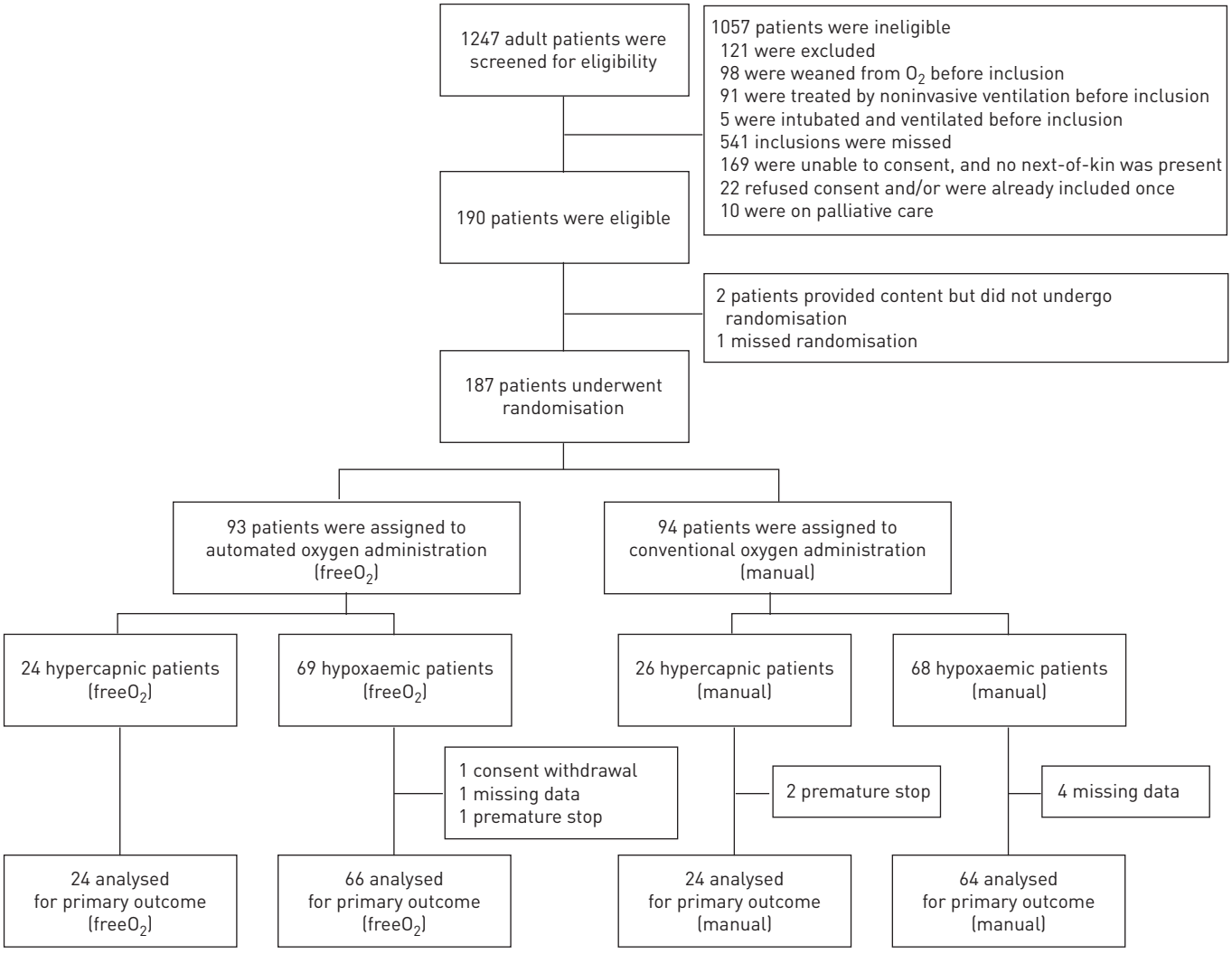

FIGURE 1 Enrolment and outcome.

Secondary outcomes during the 3 h of emergency care

More time was spent with hypoxaemia in the Manual O_2 group than in the FreeO_2 (adjusted difference 2 percentage points; 95% confidence interval 0–4). At 3 h, 24.1% of the patients were experiencing hyperoxia despite the use of oxygen in the Manual O_2 group (18.2% and 26.2% for hypercapnic and hypoxaemic respiratory failure patients, respectively) compared with 7.9% in the FreeO_2 group (6.7% and 8.2% for hypercapnic and hypoxaemic respiratory failure patients, respectively; $p<0.001$). The time was spent with hyperoxia was higher in the Manual O_2 group than in the FreeO_2 (adjusted difference 17 percentage points; 95% confidence interval 15–19), this effect being prominent in the hypercapnic subgroup (adjusted difference 35 percentage points; 95% confidence interval 26–44). No significant worsening of hypercapnia was detected within groups. Oxygen administration longer than 3 h was lower (adjusted difference 15.2 min; 95% confidence interval 18.1–12.4) and weaning was more frequent (adjusted difference 10 percentage points; 95% confidence interval, 8–11) under FreeO_2; this effect on oxygen duration was more pronounced in the hypercapnic subgroup (absolute time difference 29.6 min.; 95% confidence interval, 38.5–20.8). Mean oxygen flow during the 3 h was lower under FreeO_2 in the hypercapnic subgroup (absolute flow difference 0.85 $L{\cdot}min^{-1}$; 95% confidence interval, 1.27–0.44) (table 2), while flow changes were more homogeneously distributed in the hypoxaemic subgroup (supplementary figure S1).

Secondary outcomes during the entire hospital stay and adverse events

Oxygen administration duration during the entire hospital stay was lower in the FreeO_2 group (absolute duration difference 1.4 days; 95% confidence interval, 2.3–0.5) (table 3). While a difference was observed for the raw overall length of stay, it was not significant when considering censored data for death. No

TABLE 1 Characteristics of the patients at baseline, according to the study group and stratification

Characteristics	Total (N=187)		Hypoxaemic respiratory failure (N=137)		Hypercapnic respiratory failure (N=50)	
	$FreeO_2$ (N=93)	Manual O_2 (N=94)	$FreeO_2$ (N=69)	Manual O_2 (N=68)	$FreeO_2$ (N=24)	Manual O_2 (N=26)
Age years	74.6±13.2	77.7±12.2	73.5±13.3	76.2±12.8	77.8±12.4	81.6±9.7
Male	56 (60.9)	48 (51.1)	45 (66.2)	38 (55.9)	11 (45.8)	10 (38.5)
COPD	29 (31.5)	36 (38.3)	19 (27.9)	22 (32.4)	10 (41.7)	14 (53.8)
Immunodeficiency[#]	25 (26.9)	22 (23.4)	20 (29.0)	16 (23.5)	5 (20.8)	6 (23.1)
Do-not-intubate order[¶]	7 (7.6)	4 (4.3)	6 (8.8)	4 (6.0)	1 (4.2)	0 (0.0)
LTOT	9 (9.8)	8 (8.5)	4 (5.9)	4 (5.9)	5 (20.8)	4 (15.4)
Home mechanical ventilation	4 (4.3)	1 (1.1)	3 (4.4)	0 (0)	1 (4.2)	1 (3.8)
O_2 flow[+] L·min^{-1}.	6.2±3.1	5.5±3.1	6.4±3.3	5.4±3.0	5.5±2.2	5.9±3.5
Respiratory rate breaths·min^{-1}	25±6	24±5	25±6	24±5	24±5	25±4
S_{pO_2} %	94.5±3.4	94.6±3.5	94.5±3.6	94.4±3.5	94.5±3.2	95.2±3.6
Heart rate beats·min^{-1}	91±22	93±22	93±21	94±21	86±23	90±25
Systolic arterial pressure mmHg	128±21	127±21	127±22	126±21	130±19	128±19
Mean arterial pressure mmHg	89±17	90±14	87±17	91±16	94±17	89±10
pH[§]	7.40±0.05	7.40±0.06	7.41±0.04	7.42±0.05	7.36±0.05	7.36±0.07
P_{CO_2} mmHg[§]	41.5±10.3	40.4±8.5	37.2±5.9	36.2±5.1	53.9±10.2	51.5±4.9
P_{O_2} mmHg[f]	84.6±5.6	90.6±6.6	83.3±6.0	90.3±8.4	87.6±12.7	87.3±9.8

Data are presented as mean±SD or n (%). COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; P_{CO_2}: carbon dioxide tension; P_{O_2}: oxygen tension. There were no significant differences among the study groups in any of the characteristics listed. $FreeO_2$ indicates patients assigned to the automated oxygen administration group, and Manual O_2 patients assigned to the standard oxygen administration control group. Hypoxaemic respiratory failure indicates the stratification group of patients with $P_{CO_2} \leqslant 45$ mmHg who were assigned to a S_{pO_2} range of 92–96%. Hypercapnic respiratory failure indicates the stratification group of patients with P_{CO_2} >45 mmHg who were assigned to a S_{pO_2} range of 88–92%. Patients who were assigned to receive automated oxygen were connected to the $FreeO_2$ system set on the automated mode. Patients assigned to Manual O_2 were also connected to the $FreeO_2$ system for monitoring purposes, but the system was set to the recording mode solely. [#]: active cancer or haemopathy, chemotherapy, severe neutropenia, long-term steroid therapy; [¶]: treatment limitation and do-not-intubate order was systematically assessed on admission by either the emergency physician or the intensivist, according to patient's health status; [+]: the value measured immediately after enrolment and before randomisation; [§]: blood gas results were obtained from either capillary or arterial blood samples; [f]: P_{O_2} values are only provided for arterial blood gases.

difference for the invasive and noninvasive mechanical ventilation requirements or any other serious adverse events was observed between groups during the entire hospital stay (Supplementary table S1).

Discussion

The use of automated O_2 administration was found superior to manual O_2 administration to improve the time spent within oxygenation targets in adult patients attending the ED for the evaluation and treatment of an acute respiratory failure episode, with a between-group absolute difference of 29.4 percentage points. Patients experienced less time with hypoxaemia and hyperoxia in the $FreeO_2$ group, this effect being prominent in the hypercapnic subgroup. When receiving automated oxygen, partial or complete oxygen weaning was more frequent during the 3 h of care than manual O_2 administration, and patients were less exposed to oxygen during the overall hospital stay, with a between-group difference of 1.5 days.

The main objective of oxygen therapy should be to maintain stable oxygenation within a target chosen by clinicians. In a retrospective before–after study conducted in an ED, the S_{pO_2} target for COPD patients was achieved in 16% of patients before a quality improvement campaign, and in 32% of them following the campaign [16]. In pre-hospital studies, 56–88% of the patients did not receive the assigned treatment in the titrated oxygen arm [13, 17]. In the present study, time spent within the oxygenation target was achieved more than 80% of the time while using automated titration compared with 50% in the manual group.

Despite extensive literature about the adverse events of inadequate use of oxygen, this therapy is still poorly prescribed and junior doctors poorly understand the effects and dangers of oxygen [18–20]. Changing clinical practice in response to research data (knowledge translation or implementation) is difficult in many areas of medicine, resulting in excess morbidity and mortality and significant additional financial costs [14]. This additional cost is difficult to quantify, but is related to the incidence of non-compliance to treatment guidelines [2, 3] and is proportional to disease prevalence. Even though

TABLE 2 Outcomes and oxygen administration characteristics during the 3 h of emergency care

	FreeO$_2$	Manual O$_2$	Adjusted difference (95% CI)	p-value
Primary outcome				
Time within S_{pO_2} range %				
Total	81.3±20.7	51.8±30.0	29.4 (25.7; 33.2)	<0.001
Hypoxaemic respiratory failure	82.8±18.5	56.8±29.3	26.0 (20.5; 31.5)	<0.001
Hypercapnic respiratory failure	77.0±25.7	38.3±28.4	38.7 (19.9; 57.4)	<0.001
Secondary outcomes				
Time with hypoxaemia %				
Total	3.2±8.9	5.1±11.5	2.0 (0.1; 3.9)	0.04
Hypoxaemic respiratory failure	4.0±10.2	6.5±13.1	2.6 (0.0; 5.1)	0.05
Hypercapnic respiratory failure	0.8±1.3	1.4±2.3	0.6 (0.5; 0.6)	<0.001
Time with hyperoxia %				
Total	4.2±8.6	21.6±30.2	17.3 (15.5; 19.1)	<0.001
Hypoxaemic respiratory failure	3.8±9.0	14.6±24.5	10.8 (8.6; 13.0)	<0.001
Hypercapnic respiratory failure	5.3±7.5	40.3±35.9	34.8 (25.5; 44.0)	<0.001
Mean O$_2$ flow L·min^{-1}				
Total	4.6±4.8	4.2±1.9	0.4 (0.3; 1.1)	0.243
Hypoxaemic respiratory failure	5.2±5.1	4.3±1.9	0.9 (−0.2; 1.9)	0.112
Hypercapnic respiratory failure	2.9±3.0	3.8±1.7	−0.9 (−1.3; −0.4)	<0.001
O$_2$ modifications n				
Total	6715±2312	1.2±1.3	6721 (6453; 6989)	<0.001
Hypoxaemic respiratory failure	7020±2113	1.0±1.3	7020 (6278; 7761)	<0.001
Hypercapnic respiratory failure	5877±2660	1.7±1.4	5885 (5014; −6757)	<0.001
O$_2$ flow variations >50%				
Total	30 (39)	17 (19.5)	20 (17; 23)	<0.001
Hypoxaemic respiratory failure	22 (36.1)	12 (18.5)	18 (14; 22)	<0.001
Hypercapnic respiratory failure	8 (50)	2 (22.7)	27 (23; 32)	<0.001
O$_2$ weaning				
Total	13 (14.1)	4 (4.3)	10 (8; 11)	<0.001
Hypoxaemic respiratory failure	8 (11.8)	2 (2.9)	8 (6; 10)	<0.001
Hypercapnic respiratory failure	5 (20.8)	2 (7.7)	14 (7; 21)	<0.001

Data are presented as mean±SD or n (%), unless specified otherwise. p-values equal to or below 0.05 were considered as statistically significant. FreeO$_2$ indicates patients assigned to the automated oxygen administration group, and Manual O$_2$ patients assigned to the standard oxygen administration control group. Hypoxaemic respiratory failure indicates the stratification group of patients with carbon dioxide tension (P_{CO_2}) ⩽45 mmHg that were assigned to an arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) range of 92–96%. Hypercapnic respiratory failure indicates the stratification group of patients with P_{CO_2} >45 mmHg that were assigned to a S_{pO_2} range of 90–94%. Hypoxaemia was defined by a S_{pO_2} value 2% lower than the minimum S_{pO_2} target (S_{pO_2} <90% for purely hypoxaemic respiratory failure and <86% for mildly hypercapnic respiratory failure), Hyperoxia was defined by a S_{pO_2} value 2% higher than the maximum S_{pO_2} target (S_{pO_2} ⩾98% for purely hypoxaemic respiratory failure and ⩾94% for mildly hypercapnic respiratory failure). Mean O$_2$ flow was calculated at the end of the 3-h period. O$_2$ modifications and flow variations were evaluated at the end of the 3-h period, either considering FreeO$_2$ software in the Automated group (~1 change per s) and the monitoring files for patients assigned to the Manual O$_2$ group. O$_2$ weaning was considered as a complete stop of flow after at least a 5-min. period.

several studies have shown that compliance to oxygen therapy recommendation may be partially improved through complex multidisciplinary programmes [21], these programmes require frequent training sessions and may only be partially efficient [22]. Automated titration of oxygen may therefore improve compliance to the recommendations.

There is a good level of evidence that hypoxaemia is harmful in various populations, such as adult patients with myocardial ischaemia [23], trauma [24] or in neonates [25]. Such facts are well accepted by the medical community [26, 27], and data also suggest that short periods of hypoxaemia may promote significant negative haemodynamic effects [28]. In an animal model, right ventricular dilation was observed with only 2 h of daily hypoxaemia [29]. In the present study, as also observed in several studies evaluating similar devices, hypoxaemia was less frequent with automated oxygen titration [15, 30, 31].

The physiological risks associated with hyperoxia are also well described, especially in COPD patients, its effect being particularly marked during the acute phase of exacerbations [5]. The first recommendation to adjust oxygen flow rates to reduce the risks of hyperoxia was published in the early 1960s [32], but several recent guidelines have reiterated this recommendation [2, 3, 33]. The recent demonstration of increased mortality because of over-oxygenation during pre-hospital transport in a large randomised controlled trial has revived the debate about the potential harm of excessive oxygen therapy in COPD patients [6]. Other

TABLE 3 Secondary outcomes during the entire hospital stay

Secondary outcomes	$FreeO_2$	Manual O_2	Adjusted difference (95% CI)	p-value
Overall oxygen administration days				
Total	5.6±5.4	7.1±6.3	1.4 (2.3; 0.5)	0.002
Hypoxaemic respiratory failure	5.0±5.0	6.6±6.5	1.6 (2.7; 0.6)	0.003
Hypercapnic respiratory failure	7.4±6.2	8.2±5.8	0.8 (2.0; 0.4)	0.173
ICU LOS days				
Total	4.2±3.2	4.7±3.5	0.6 (2.9; 1.7)	0.630
Hypoxaemic respiratory failure	4.9±3.3	4.7±3.9	0.2 (1.8–2.2)	0.831
Hypercapnic respiratory failure	2.5±2.4	4.7±3.0	2.2 (5.2–0.8)	0.147
Hospital LOS days				
Total	9.2±6.9	11.1±7.0	2.0 (3.1–0.85)	0.001
Total: censored data	9.0 (7.0–10.0)	10 (8.0–11.0)	1.1 (1.5–0.8)	0.452
Hypoxaemic respiratory failure	9.0 (6.0–10.0)	9 (8.0–10.0)	1.0 (1.4–0.7)	0.995
Hypercapnic respiratory failure	9.0 (7.0–11.0)	13 (8.0–16.0)	1.6 (2.9–0.9)	0.122

Data are presented as mean±SD; for hospital length-of-stay (LOS), values are provided as median (95% CI) when taking into account censored data. p-values equal to or below 0.05 were considered as statistically significant. $FreeO_2$ indicates patients assigned to the automated oxygen administration group, and Manual O_2 patients assigned to the standard oxygen administration control group. Hypoxaemic indicates the stratification group of patients with carbon dioxide tension (P_{CO_2}) ⩽45 mmHg that were assigned to an arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) range of 92–96%. Hypercapnic indicates the stratification group of patients with P_{CO_2} >45 mmHg that were assigned to a S_{pO_2} range of 90–94%. ICU LOS indicates the overall length-of-stay within the intensive care unit in the different groups. Hospital LOS indicates the overall length-of-stay within the hospital, until discharge or death in the different groups; subgroup analysis was performed on censored data for death.

adverse effects of hyperoxia such as increased coronary [7, 8] and carotid artery resistance have been demonstrated [9], all being associated with a potential clinical impact [34, 35].

Automated oxygen titration has already been promoted for infant and neonates [12–14], but only three systems have been evaluated in spontaneously breathing adults [15, 30, 31]. In one study, the authors evaluated a closed-loop system (O_2 flow regulator, Dima, Italy), adjusting low-flow oxygen during exercise in COPD patients receiving long-term oxygen therapy [30], and showed better oxygenation and reduced workload with automated oxygen titration. In another study with a similar device ($AccuO_2$, Optisat medical, Minneapolis, MN), the authors demonstrated better maintenance within the target and a reduction in oxygen consumption [31]. The third device ($FreeO_2$, Oxynov, Québec, Canada) was originally validated in a pilot study on healthy volunteers under experimental hypoxaemia [15]. In the present study, we found better oxygenation with more time within the S_{pO_2} target, less hypoxaemia and less hyperoxia. In addition, we also demonstrated automated oxygen weaning, leading to reduced time under oxygen and safety of the procedure (supplementary table S1). The use of automated oxygen administration was well accepted by clinicians, without differences in terms of premature interruption of treatment.

Our trial, which is the largest study to date evaluating an automated oxygen titration device, has several strengths that suggest that it may be generalised to patients with similar conditions. These strengths include the multicentre design and sealed randomisation to the assigned strategy, a well-defined study protocol over a short period of observation, predefined efficacy criteria, complete follow-up of patients by dedicated research assistants and an intention-to-treat analysis. Several potential limitations can however be highlighted. Since O_2 was continued using a standard flowmeter when needed after the 3-h study period, the potential benefits of automated O_2 flow adjustments over time may have been missed. The choice of a 3-h time period to study the effect of automated O_2 administration is also debatable, since a longer period may be appropriate to elicit significant outcome improvement. However, such duration may be more appropriate when considering the acute care setting of the study and the fact that no such trial has yet been performed using such devices. Second, sample size assumptions were a little different from expected (smaller proportion of hypercapnic patients), but the study was still adequately powered. Third, while the intervention was conducted during the first 3 h of treatment, there are no data to extend these benefits for automated oxygen administration use outside the ED. Fourth, the fact that only one $FreeO_2$ device was available in each centre was responsible for a low randomisation rate, which may limit the external validity of our results. While only 57% of eligible patients were enrolled, these results may not be representative of the total eligible group. Fifth, the unblinded characteristic of the study may have biased clinicians' care.

In conclusion, the use of automated O_2 administration was superior to manual O_2 administration for patients attending the ED with acute hypoxaemic respiratory failure. The potential benefits of automated

O_2 titration may exist for either the patients (better control of oxygenation, better monitoring, reduced hospital length-of-stay) or the healthcare system (reduced number of O_2 manual adjustments, better adherence with treatment recommendations, reduced oxygen use). Additional data are warranted to demonstrate the safety and cost effectiveness of these systems in different clinical settings.

Acknowledgements

We thank the patients, their families, and the ED staff members of our four centres in Canada and France who cared for them, and all research assistants for their help in recruitment and data collection. We would also like to thank François Maltais at the Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Canada for his extensive reviewing of the manuscript, and Julien Coadic from Brest University Hospital (CIC INSERM 1412) for data storage and management.

Author contributions: E. L'Her and F. Lellouche designed the prototype, conceived, coordinated the study in France and Canada respectively, analysed and interpreted the data and wrote the article. P. Dias, A. Riou, L. Souquiere, N. Paleiron, P. Archambault and P-A. Bouchard included the patients, supervised monitoring of the data and corrected the manuscript. M. Gouillou was responsible for data analysis. E. L'Her had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1 Hale KE, Gavin C, O'Driscoll BR. Audit of oxygen use in emergency ambulances and in a hospital emergency department. *Emerg Med J* 2008; 25: 773–776.
2 O'Driscoll BR, Howard LS, Davison AG, *et al.* BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; 63: vi1–vi68.
3 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: December 23, 2016.
4 Abdo WF, Heunks LMA. Oxygen-induced hypercapnia in COPD: myths and facts. *Crit Care* 2012; 16: 323.
5 Aubier M, Murciano D, Milic-Emili J, *et al.* Effects of the administration of O_2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis* 1980; 122: 747–754.
6 Austin MA, Wills KE, Blizzard L, *et al.* Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ* 2010; 341: c5462.
7 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.
8 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.
9 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.
10 Johannigman JA, Muskat P, Barnes S, *et al.* Autonomous control of oxygenation. *J Trauma* 2008; 64: S295–S301.
11 Mok W, Wang W, Cooper S, *et al.* Attitudes towards vital signs monitoring in the detection of clinical deterioration: scale development and survey of ward nurses. *Int J Qual Health Care* 2015; 27: 207–213.
12 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: 1120–1124.
13 Claure N, Bancalari E, D'Ugard C, *et al.* Multicenter crossover study of automated control of inspired oxygen in ventilated preterm infants. *Pediatrics* 2011; 127: e76–e83.
14 Hallenberger A, Poets CF, Horn W, *et al.* Closed-loop automatic oxygen control (CLAC) in preterm infants: a randomized controlled trial. *Pediatrics* 2014; 133: e379–e385.
15 Lellouche F, L'Her E. Automated oxygen flow titration to maintain constant oxygenation. *Respir Care* 2012; 57: 1254–1262.
16 Chow JW, Khullar K, Katechia K, *et al.* Controlled oxygen therapy at emergency department presentation increases the likelihood of achieving target oxygen saturations in patients with exacerbations of chronic obstructive pulmonary disease. *Emerg Med Australas* 2016; 28: 44–47.
17 Ringbaek TJ, Terkelsen J, Lange P. Outcomes of acute exacerbations in COPD in relation to pre-hospital oxygen therapy. *Eur Clin Respi J* 2015; 2: 27283.
18 O'Driscoll BR, Howard LS, Bucknall C, *et al.* British Thoracic Society emergency oxygen audits. *Thorax* 2011; 66: 734–735.
19 Boyle M, Wong J. Prescribing oxygen therapy. An audit of oxygen prescribing practices on medical wards at North Shore Hospital, Auckland, New Zealand. *N Z Med J* 2006; 119: U2080.
20 Nippers I, Sutton A. Oxygen therapy: professional compliance with national guidelines. *Br J Nurs* 2014; 23: 382–386.
21 Gatter M, Dixon G, Wall J, *et al.* Changing an ingrained culture: Improving the safety of oxygen therapy at University Hospitals Bristol NHS Foundation Trust. *BMJ Qual Improv Rep* 2015; 4: u203238.w1474o.
22 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: 554–563.
23 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.
24 Prough DS. Blast-induced brain injury and posttraumatic hypotension and hypoxemia. *J Neurotrauma* 2009; 26: 877–887.
25 Poets CF, Roberts RS, Schmidt B, *et al.* association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. *JAMA* 2015; 314: 595–603.
26 Kallstrom TJ, American Association for Respiratory Care (AARC). AARC Clinical Practice Guideline: oxygen therapy for adults in the acute care facility-2002 revision & update. *Respir Care* 2002; 47: 717–720.

27 Bateman NT, Leach RM. ABC of oxygen. Acute oxygen therapy. *BMJ* 1998; 317: 798–801.
28 Selinger SR, Kennedy TP, Buescher P, *et al.* Effects of removing oxygen from patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1987; 136: 85–91.
29 Nattie EE, Doble EA. Threshold of intermittent hypoxia-induced right ventricular hypertrophy in the rat. *Respir Physiol* 1984; 56: 253–259.
30 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.
31 Rice KL, Schmidt MF, Buan JS, *et al.* AccuO_2 oximetry-driven oxygen-conserving device versus fixed-dose oxygen devices in stable COPD patients. *Respir Care* 2011; 56: 1901–1905.
32 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.
33 Murphy R, Mackway-Jones K, Sammy I, *et al.* Emergency oxygen therapy for the breathless patient. Guidelines prepared by North West Oxygen Group. *Emerg Med J* 2001; 18: 421–423.
34 Stub D, Smith K, Bernard S, *et al.* Air *versus* oxygen in ST-segment-elevation myocardial infarction. *Circulation* 2015; 131: 2143–2150.
35 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.