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Automatic oxygen titration with O2matic® to patients admitted with COVID-19 and hypoxemic respiratory failure

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ABSTRACT

Introduction: Patients with coronavirus disease (COVID-19) and pneumonitis often have hypoxemic respiratory failure and a need of supplementary oxygen. Guidelines recommend controlled oxygen, for most patients with a recommended interval of SpO_2 between 92 and 96%. We aimed to determine if closed-loop control of oxygen was feasible in patients with COVID-19 and could maintain SpO_2 in the specified interval.

Methods: Patients were prospectively enrolled in an observational study on a medical ward dedicated to patients with COVID-19. Closed-loop controlled oxygen was delivered by O2matic® which can deliver 0–15 liters/min and adjusts flow every second based on 15 seconds averaging of SpO_2 measured by pulse oximetry. Lung function parameters were measured at admission.

Results: Fifteen patients (six women, nine men) participated in the study. Average age was 72 years. Lung function was severely impaired with FEV_1, FVC and PEF reduced to approximately 50%. The average stay on the ward was 3.2 days and O2matic was used on average for 66 hours, providing 987 hours of observation. O2matic maintained SpO_2 in the desired interval for 82.9% of the time. Time with $SpO_2 > 2\%$ below interval was 5.1% and time with $SpO_2 > 2\%$ above interval was 0.6%.

Conclusion: Closed-loop control of oxygen to patients with COVID-19 is feasible and can maintain SpO_2 in the specified interval in the majority of time. Closed-loop automated control could be of particular benefit for patients in isolation with decreased visibility, surveillance and monitoring. Further studies must examine the clinical benefits.

Introduction

A common feature of most patients admitted with coronavirus disease 2019 (COVID-19), pneumonitis and lower respiratory symptoms is hypoxemic respiratory failure and need of supplementary oxygen. Oxygen supplementation is a lifesaving treatment but is also associated with side effects. There is increasing awareness that oxygen, besides minor side effects such as dryness of the mucosa in the airways, also poses risks due to formation of reactive oxygen species (ROS), pulmonary toxicity and coronary and cerebral vasoconstriction [1]. The pulmonary toxicity of oxygen has been known since it was demonstrated in a mouse model by Lorrain Smith in 1899 [2]. Recently, a meta-analysis of 25 randomized controlled trials with 16,037 acutely ill patients admitted to hospital showed an increased mortality associated with liberal oxygen treatment compared to a conservative

oxygen treatment [3]. Most patients in these studies had myocardial or cerebral ischemia, but excess mortality with liberal oxygen has also been demonstrated in other patients. One randomized controlled trial with 480 patients admitted to a medical-surgical ICU found that a conservative strategy with SpO_2 between 94 and 98% reduced mortality when comparing with a liberal strategy with SpO_2 from 97 to 100%, and patients in the conservative group had fewer episodes of shock, liver failure and bacteremia [4].

It is not known if it is critical to control SpO_2 in a narrow interval for patients with COVID-19. In general, guidelines for oxygen treatment of patients with acute illness recommend that SpO_2 is maintained within an interval from 94 to 98%, unless special conditions, such as risk of hypercapnic failure, dictates more conservative oxygen treatment [5]. An ICU trial with acute respiratory

distress syndrome (ARDS) randomized patients to a very conservative oxygen treatment (SpO_2 at 88–92%) versus a liberal oxygen treatment with $SpO_2 > 96\%$ [6]. This trial was stopped early due to safety concerns and low likelihood of meeting the primary endpoint, which was mortality at 28 days. Five cases with mesenteric ischemia occurred in the group with a conservative oxygen strategy. Due to the above studies, the Surviving Sepsis Campaign's guidelines for COVID-19 recommend starting oxygen therapy if $SpO_2 < 92\%$ and recommend that SpO_2 is maintained no higher than 96% [7].

It is well known that it is difficult to maintain a stable level of SpO_2 with manual oxygen titration. When compared to closed-loop automated oxygen titration, it has been demonstrated in randomized controlled trials that manual titration by nursing staff maintains SpO_2 in the right interval in 38–56% of the time compared to closed-loop titration which maintains SpO_2 in the right interval for 77–85% of the time [8–10]. Closed-loop systems are based on continuous measurement of SpO_2, which in a feed-back circuit controls the amount of oxygen delivered to the patient, and they have predominantly been used for neonates, patients with COPD, and patients with hypoxemic respiratory failure in the emergency ward [8–11].

In the management of patients with COVID-19, the task of manually controlling the oxygen supply becomes more cumbersome, due to the isolation regime, which requires a gown, face mask, gloves and goggles for even simple tasks at the patient bed. Thus, the benefits of closed-loop titration could be greater than with non-isolated patients in terms of use of nursing resources. However, it is not known if closed-loop automated oxygen control is feasible for patients with COVID-19. The pathophysiology behind COVID-19 is different from other etiologies to hypoxemic respiratory failure and ARDS. It is probably due to a combination of damage to the airway epithelium, especially type 2 alveolar cells, vascular endothelial damage and thromboinflammation [12]. The result is impaired hypoxemic vasoconstriction in the pulmonary vessels, interstitial edema, and leakage of fluid to the alveoli. These key mechanisms contribute to a worsening of ventilation/perfusion (V/Q) mismatch and even shunting [13]. In case of shunting, it is difficult to maintain normal SpO_2, as well-oxygenated blood from areas with a high V/Q ratio cannot compensate for admixture with poorly oxygenated blood from areas with low V/Q or absent ventilation with high perfusion.

We aimed to determine if it was possible to maintain SpO_2 in the desired interval for patients with mild to moderate hypoxemic failure admitted with COVID-19 pneumonitis, with a closed-loop automated oxygen control device, O2matic®, which has previously been tested on patients with a COPD exacerbation [10]. Furthermore, we wanted to characterize the patients in terms of severity by doing spirometry at admission as supplement to radiology and biochemistry.

Methods

Study design

The study was performed as a prospective observational study at a university hospital in Copenhagen. Patients were recruited from a newly created medical ward, dedicated to patients admitted with COVID-19. Nursing staff and physicians who attended the patients were from all medical and surgical specialities and were not previously familiar with patients with COVID-19 or other severe infectious or pulmonary conditions with hypoxemic respiratory failure. It was decided to use O2matic as standard for oxygen treatment for patients who needed an oxygen supply of 0 to 15 liters of oxygen, which was delivered either by standard nasal cannula or high flow cannula. All nursing staff and physicians received training in use of O2matic. As O2matic was implemented as standard of care, the regional ethics committee did not require informed consent from the patients (20023238).

Patients

Patients were included from 15 April 2020 until the ward was closed down at the end of May due to lack of patients. Patients were included if they were older than 18 years, had a positive COVID-19 PCR analysis in pharyngeal swab or in tracheal secretion, needed oxygen supply to maintain $SpO_2 \geq 92\%$ and were able to comply with continuous measurement of SpO_2 by pulse oximetry. Patients were excluded if they required oxygen supply >10 liters/min at admission. Furthermore, it was a prerequisite for inclusion that an investigator (LMK or CSB) was present to include the patient within the first 48 hours of admission.

The following parameters were registered at inclusion:

- Hemoglobin, white blood cell count with differential, platelets, electrolytes, albumin, liver parameters, LDH, CRP.
- Chest X-ray.
- Bed-side spirometry with forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF).
- Co-morbidities and symptoms at presentation.
- Decisions on the extent of care and ceiling of treatment.

The patients participated in the study as long as they were admitted to the dedicated COVID-19 medical ward. The participation ended if they were weaned from oxygen supplementation and discharged, transferred to ICU for mechanical ventilation, to other ward in order to receive treatment with continuous positive airway pressure (CPAP), or died.

Equipment

The O2matic® oxygen controller (O2matic Ltd., Herlev, Denmark) is a closed-loop system that, based on continuous monitoring of pulse rate and SpO_2 by a standard wired pulse oximeter, adjusts oxygen flow to the patient (Figure 1). The algorithm in O2matic samples the last 15 seconds of input from the pulse oximeter and calculates increments or decrements in oxygen flow every second based on the last 15 seconds' average. Increments and decrements are proportionally increased relative to the difference between actual SpO_2 and target SpO_2. Target SpO_2 is set as an interval, and in this study, it was set according to COVID-19 guidelines, which recommend SpO_2 of 92 to 96% for most patients [7]. Oxygen flow is also set as an interval. Patients with an initial need of oxygen <5 liters/min had oxygen delivered by a standard nasal cannula and a flow range set by O2matic from 0 to 8 liters/min (Figure 2). Patients in need of 5–10 liters of oxygen had oxygen delivered by a high flow nasal cannula and a flow range set by O2matic from 0 to 15 liters/min (Figure 2). Three kinds of sensors were used at nurses' and physicians' discretion: A Nonin® 8000 A multiple use finger sensor, a Nonin® 8000 Q2 multiple use ear sensor and a Nonin® 6000 C single patient finger sensor (Nonin Medical Inc., Plymouth, US). Spirometry was performed with a handheld spirometer, NDD EasyOne (NDD Medizintechnik AG, Zurich, Switzerland).

Statistical analysis

All data were managed and analyzed with IBM SPSS statistical package version 25. Demographic variables were analyzed using non-parametric statistics. Data from O2matic regarding SpO_2, pulse rate and oxygen flow were aggregated with average values for each minute of observation, and fraction of time within

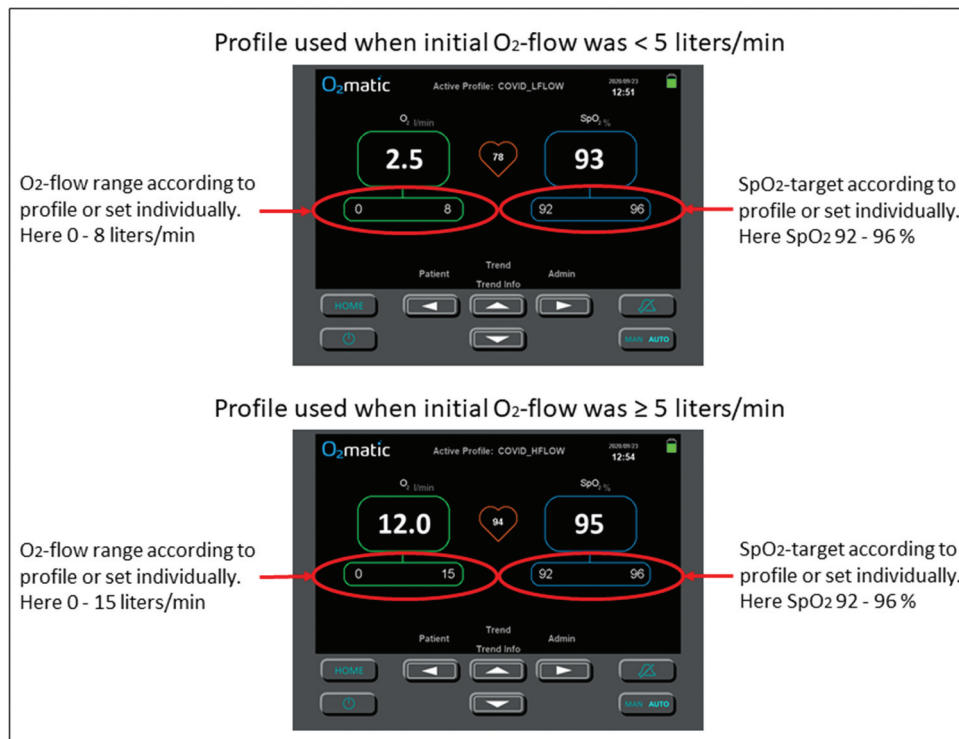**Figure 1.** The O2matic closed-loop oxygen controller.

Figure 2. O2matic profiles according to initial oxygen need.

Abbreviations: SpO$_2$: Oxygen saturation measured by pulse oximetry.

SpO$_2$ interval and fraction of time less than 2% and more than 2% outside SpO$_2$ interval was calculated.

Results

Sixteen patients were included. One patient was excluded due to not having COVID-19. Fifteen patients provided data from use of O2matic. Demographics are presented in Table 1. Only abnormal biochemical values are presented. The most common comorbidities were hypertension (67%) and diabetes (47%). The most common symptoms were dyspnea (87%), cough (60%) and fever (60%). Twelve patients were able to perform spirometry within the first 5 days of admission. Lung function was in general severely impaired, around 50% of predicted. Lung function data are presented in Table 2.

The 15 patients had automatic oxygen titration on average for 66 hours, providing a total of 987 hours of observation with O2matic. There was a missing signal in 8% of the time, either due to true missing signal despite sensor in place, or due to sensor intendedly removed during meals, personal hygiene, etc. Average flow of oxygen was 3.7 liters/min. Average pulse rate was 76 bpm (±14 bpm). Fourteen patients had the SpO$_2$ target set to 92 to 96%, and one patient had the SpO$_2$ target set to 88–92%, due to presence of COPD. Distribution of SpO$_2$-values within target, not more than 2% outside target and more than 2% outside target is shown in Figure 3. The average proportion of time spent within intended SpO$_2$ target was 82.9%. The proportion of time spent within intended SpO$_2$ target ± 2% was 94.3%, which means that patients with an SpO$_2$ target of 92–96% were within an SpO$_2$ interval of 90–98% in 94.3% of the time. The SpO$_2$ was more than 2% below target in 5.1% of the time and more than 2% above target in 0.6% of the time. Time with SpO$_2$ < 85% was on average 1.4%. The average duration of participation in the study was 3.2 days. Six patients were weaned from oxygen supplementation and discharged from the ward. Nine patients were transferred to more intensive care, of whom three later died.

Discussion

Our small observational study showed that supplementary oxygen titration in patients with COVID-19 pneumonitis and hypoxemic respiratory failure was feasible and resulted in satisfactory oxygenation for the majority of the time required.

Closed-loop oxygen control has been used in several settings but has until now not been used to patients with COVID-19. It is not evident that the principles can be extrapolated from one condition to another. In

Table 1. Demographics, comorbidities and symptoms.

N = 15	Median (25–75% range)
Gender (Females/males) (%)	40/60
Age (years)	72 (60–84)
BMI (kg/m^2)	29.1 (23.0–34.7)
Smoking status (actual/ex/never) (%)	7/53/40
SpO$_2$ at inclusion (%)	94 (93–95)
Oxygen-flow at inclusion (liters/min)	3.5 (2.0–6.5)
Lymphocytes (x10^9/liter)	0.85 (0.68–1.30)
C-reactive protein (CRP) (mg/liter)	110 (55–140)
LDH (units/liter)	336 (232–469)
Acute abnormalities on chest X-ray (%)	93
Comorbidities	
• Atrial fibrillation	20%
• Heart failure	13%
• Hypertension	67%
• Diabetes	47%
• History of cancer	27%
• Obstructive lung disease (asthma or COPD)	20%
Symptoms at presentation	
• Dyspnea	87%
• Cough	60%
• Phlegm	13%
• Sore throat	13%
• Fever	60%
• Headache	13%
• Muscle pain	7%
• Gastrointestinal symptoms	33%
Limitation in treatment (DNI/DNR)	47%

DNI: Do not intubate, DNR: Do not resuscitate

Table 2. Lung function data.

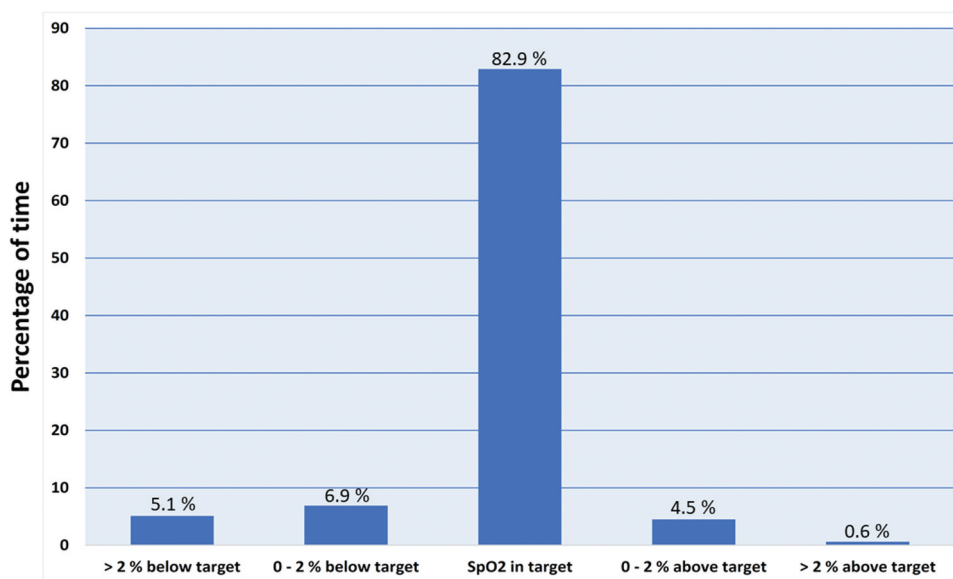| N = 12	Median (25–75% range)
FEV$_1$ (liters)	1.31 (0.96–1.64)
FEV$_1$ (% predicted)	51 (43–59)
FVC (liters)	1.56 (1.33–2.44)
FVC (% predicted)	51 (42–68)
PEF (liters/min)	177 (112–322)
PEF (% predicted)	50 (24–75)

Figure 3. Distribution of SpO$_2$ values in target and outside target.

Abbreviations: SpO$_2$: Oxygen saturation measured by pulse oximetry.

COPD, where the main body of evidence is for adult use of closed-loop control, the need for oxygen supplementation is often limited to a few liters of oxygen per minute, and the changes in oxygen need during an admission are often also minor and are due to worsening of V/Q mismatch resulting from regional impaired ventilation [8,10]. In COVID-19 another pathophysiology is causing a more severe V/Q mismatch and shunting due to a perfusion disorder with impaired hypoxic vasoconstriction and a vascular leakage into the interstitium and the alveoli impeding oxygen diffusion. Collapsed alveoli results in areas without ventilation, and if perfusion remains, the consequence is shunting, where oxygen supplementation has little effect [14]. Thus, it is interesting that in patients handled on moderate oxygen supplementation, closed-loop control is able to maintain oxygenation within a 4% SpO_2-interval, from 92 to 96%, in 82.9% of the time, which is at the same level that has been demonstrated in COPD [8,10]. Furthermore, an acceptable oxygen saturation within an 8% SpO_2-interval, from 90 to 98%, was achieved in 94.3% of the time. We know from closed-loop studies that manual oxygen control only is able to achieve the target in approximately 50% of the time [8–10]. In COVID-19 the gain in terms of use of nursing staff resources is larger, as the isolation regime makes it difficult and time-consuming to do simple tasks such as manually adjusting the oxygen flow.

Some reservations regarding the study results must be made. The sample size was small and might not be representative for all patients admitted with COVID-19. However, compared to a larger cohort of all 175 patients admitted with COVID-19 to the same hospital during the same period, the patients in this study had comparable demographics in terms of age, smoking history and body mass index [15]. Biochemistry at baseline was also similar. Compared to the larger cohort, our patients had more frequent dyspnea on admission, were more in need of oxygen supplementation, and more frequently had diabetes or hypertension. Our study was without a control group, and the benefit demonstrated is based on the assumption that manual oxygen control would not have done better than we have seen in other studies, resulting in around 50% of the time with optimal control of SpO_2, compared to the 82.9% demonstrated in the actual study. Furthermore, the patients in this study were only moderately hypoxemic. When the need for oxygen supplementation exceeded 15 liters/min the patients were transferred to a unit where they could receive higher oxygen flow in combination with CPAP, where the latter demonstrated a very positive effect on oxygenation. It is important to emphasize that oxygen

supplementation is only part of the ventilation strategy in COVID-19, and in more severe cases recruitment of alveoli and improvement in pulmonary compliance by instruments such as CPAP or mechanical ventilation is necessary [16].

The clinical importance of maintaining SpO_2 within an interval such as 92 to 96% as recommended by the Surviving Sepsis Campaign is uncertain [7]. Pulmonary toxicity of oxygen is probably not present at a fraction of inspired oxygen (FiO_2) less than 60%, which means that in terms of pulmonary toxicity 15 liters/min by nasal cannula can be administered safely [17]. However, a high PaO_2 can still be associated with myocardial vasoconstriction, which could be a problem in patients with COVID-19, where cardiovascular function also seems to be affected [18]. At the lower end of the SpO_2 interval, we have some documentation in similar conditions that hypoxemia is dangerous. The $LOCO_2$ trial comparing very conservative oxygen treatment with liberal oxygen treatment in patients with ARDS, was stopped early, due to safety concerns, as more cases of mesenteric ischemia were seen with conservative oxygen strategy, indicating that longer periods with SpO_2 below 90–92% could be associated with increased morbidity [6].

We did not in this study examine patient compliance and discomfort related to the need for continuous measurement of SpO_2. The average time with use of O2matic was 66 hours, which is close to the average stay at the ward, which was 3.2 days. The use of different pulse oximetry sensors made it possible to individualize this part of the treatment. The finger sensor for single patient use was convenient for patients as well as the nursing staff. The fraction of time with missing signal, which was 8%, is on the same level as in another closed-loop study of several days duration [8], but longer than in a study of only a few hours duration [10]. The reasons for loss of signal were in part that patients were allowed to remove the sensor while eating, visiting the bathroom, etc. In these periods, the oxygen flow was automatically fixed at the same level as when the signal was lost. Loss of signal during sleep, due to displacement of the sensor was probably also part of the reason for more frequent loss of signal compared to a daytime study (10). By visual inspection of graphs depicting SpO_2 and oxygen flow versus time for individual patients, we found no indication that loss of signal was preceded by a clinically worsening of the condition with a decrease in SpO_2 or increase in oxygen flow. Thus, we are confident that loss of signal was not a critical issue, and was handled properly by keeping oxygen flow fixed until signal was restored.

Lung function data showed a marked reduction in FEV_1, FVC and PEF, all reduced to approximately 50% of predicted, reflecting a substantial loss of lung volume. It

was not possible to measure diffusing capacity due to patients having dyspnea and tachypnea, which prevented the breath-holding maneuver. Neither do we have data on lung function before admission with COVID-19, but only three patients had known obstructive lung disease, which makes it unlikely that a severe reduction in dynamic volumes was present before admission. Some patients experienced difficulties in performing spirometry due to acute breathlessness and coughing, and acceptability criteria could not be met for all patients. However, we find it unlikely that low quality of the spirometry accounts for a substantial part of the reduction in FEV_1, FVC and PEF. Another study has shown minor reduction in dynamic values at discharge from admission with COVID-19 [19]. Our study was done during the first days after admission, and 93% of the patients had acute radiological abnormalities with infiltrates and interstitial changes which could account for the severely impacted lung function.

In conclusion, we find that it is possible to administer oxygen safely and effectively to patients admitted with COVID-19 with a closed-loop system, O2matic, based on continuous measurement of SpO_2. The automatic adjustment of oxygen flow is advantageous, especially in patients isolated due to contagious disease, such as COVID-19. Further and larger studies must examine the clinical impact of optimized control of SpO_2, in terms of possible reduction in adverse outcomes and faster weaning from oxygen supplementation and discharge from hospital.

Disclosure statement

Funding

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