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Protocol Article

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Automated versus manual oxygen administration for patients admitted with acute cardiovascular disease – a study protocol of a randomised controlled trial

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ABSTRACT

INTRODUCTION. Oxygen treatment of hypoxaemia is considered an essential part of the treatment of patients who are acutely admitted with medical conditions affecting cardiovascular and/or pulmonary function. Despite the important role of oxygen administration for these patients, clinical evidence on how to control supplemental oxygen to avoid hypoxaemia and hyperoxia is limited. We aim to investigate whether an automatic closed-loop oxygen administration system (O2matic) may maintain normoxaemia better than usual care.

METHODS. This study will be an investigator-initiated, prospective, randomised clinical trial. The patients are randomised during admission after informed consent is obtained, at a 1:1 ratio with conventional oxygen treatment or O2matic oxygen treatment for 24 hours. The primary outcome is time within the desired peripheral capillary oxygen saturation interval: 92-96%.

CONCLUSION. This study will examine the clinical applicability of a novel automated feedback device termed O2matic and assess whether the device is superior to standard care in keeping the patients in the optimal saturation interval. We hypothesise that the O2matic will increase time within the desired saturation interval.

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Oxygen treatment of hypoxaemia is considered an essential part of the treatment of patients acutely admitted with medical conditions affecting their cardiac function [1]. Most acute cardiovascular patients frequently receive supplemental oxygen during their admission. From a physiological view, the arterial oxygen saturation ought to remain within a regulated interval as a constant delivery of oxygen is needed for organ function and survival, whereas hyperoxia may induce direct damage due to vasoconstriction in conditions such as acute coronary syndrome, heart failure and ischaemic stroke [2-5].

Despite the important role of oxygen administration in acutely admitted patients, in both Denmark and abroad,

clinical evidence on how to control supplemental oxygen to avoid hypoxaemia and hyperoxia is limited [1]. Oxygen administration is often titrated by blood gas analyses or by a non-invasive method such as pulse oximetry (peripheral capillary oxygen saturation, SpO_2). In Eastern Denmark, an Early Warning Score (EWS, ranging from 0 to 20, the lower the better) is used to determine the frequency of control for all vital values, including SpO_2 [6]. For the most stable patients with a low EWS score, the recommended control frequency is two times daily. With increasing EWS, the frequency of vital value control increases. The traditional observation and adjustment method is time consuming for the nursing staff and leaves room for severe hypoxaemia and hyperoxia between measurements as it is based only on snapshots of the patient's condition. Hyperoxia enhances the formation of reactive oxygen species, which may potentially cause harm due to increased inflammation and vasoconstriction [2]. Due to these circumstances, several research groups have worked on methods to automise SpO_2 measurements and the subsequent adjustment of the oxygen supply [7-9].

Since 2011, a Danish research group has worked on an automatic closed-loop oxygen administration system called O2matic. The first prototypes were tested at Copenhagen Academy for Medical Education and Simulation (CAMES), where tests in simulation models of chronic obstructive pulmonary disease (COPD) exacerbations demonstrated that O2matic is feasible and superior to a fixed oxygen supply to keep saturation within the desired interval. O2matic is now developed and manufactured in a version that operates in conformity with the demands stated by the Medical Device Directive and has recently been CE marked. The system was tested in a crossover trial, where automated and continuous oxygen treatment was assessed and compared with manual control in patients admitted with COPD exacerbations. The results demonstrated a significantly better oxygen regulation (85% of the time within the predefined interval versus 47% of the time) [10]. The system has not been tested in a cardiac department serving a different patient group than COPD patients, nor in a randomised clinical trial.

The aim of this study was to investigate whether oxygen control with O2matic is superior to conventional control at keeping the oxygen saturation within the preferred interval and reduce the time with significant hypoxaemia or hyperoxia in acutely hospitalised cardiac patients with an oxygen demand.

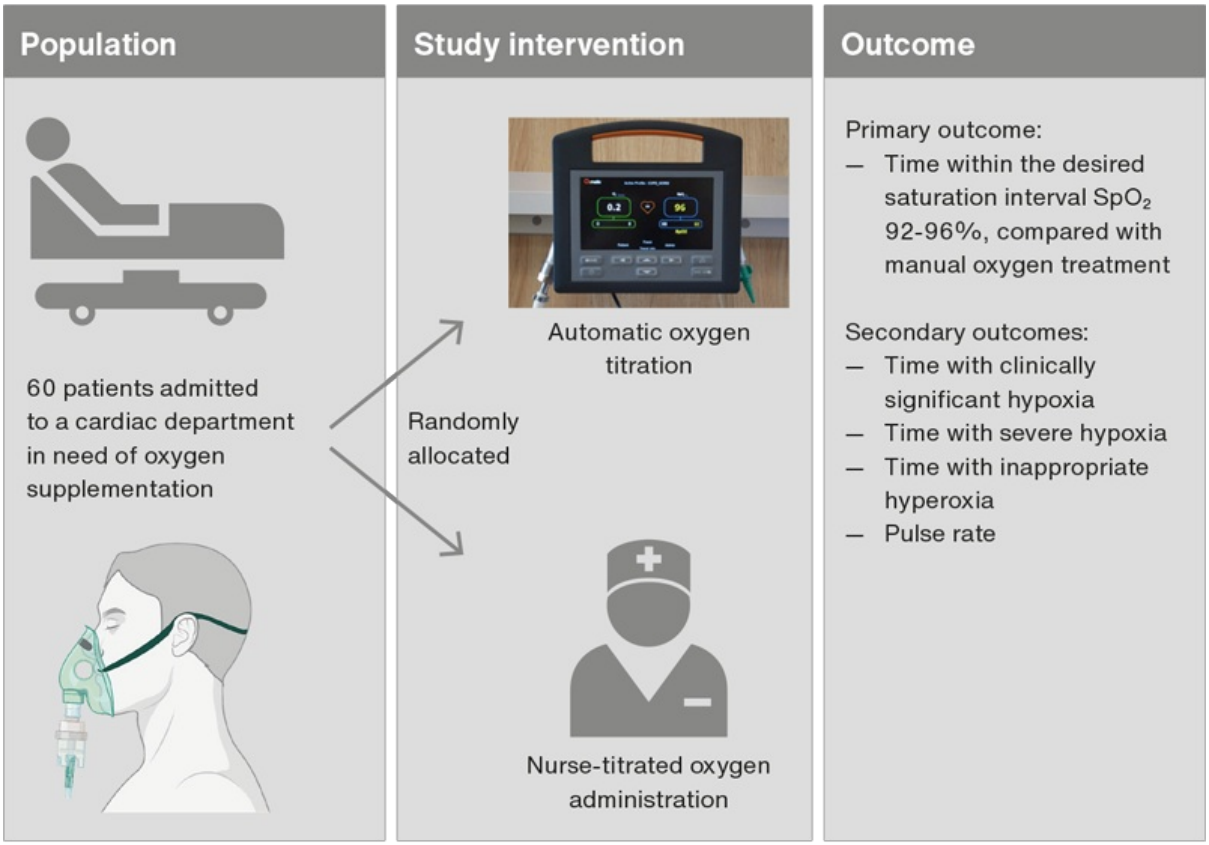
Our hypothesis is that O2matic significantly increases the duration of time during which SpO_2 is within the preferred 92-96% interval.

METHODS

Study design, setting and population

This study will be an investigator-initiated, prospective, randomised clinical trial. It will not be possible to blind the investigators or the clinical staff to the allocation. After the device is set up, the screen is turned off in the control group for as much time as possible during the trial to mimic clinical practice. Patients will be included when acutely admitted with a primary cardiac disease at the Department of Cardiology, Hvidovre Hospital, Copenhagen, Denmark (**Figure 1**). The study population consists of patients admitted to a department of cardiology who are in need of oxygen, see **Table 1** for inclusion and exclusion criteria. Inclusion was initiated on 1 March 2022 and is expected to be completed within one year. The study is registered with ClinicalTrials.gov (Identifier: NCT05452863).

FIGURE 1 Study design.
Illustration made with BioRender.com



SpO_2 = peripheral capillary O_2 saturation.

TABLE 1 Inclusion- and exclusion criteria.

Inclusion criteria
Patients admitted with heart disease: acute coronary syndrome or cardiac incompensation and a saturation < 92%
Age ≥ 30 yrs
Cognitively able to understand the study
Verbal and written informed consent, the declaration of consent and power of attorney need to be signed before the patient may be included in the study
Exclusion criteria
Unstable patients who might be transferred for acute revascularisation
COPD or other conditions with an increased risk of hypercapnia
Fertile women < 55 yrs with a positive pregnancy test at the time of inclusion
Verbal or cognitive barrier for adherence to the study protocol

COPD = chronic obstructive pulmonary disease.

Study procedure

The patients are included and randomised during admission, in a 1:1 ratio with conventional oxygen treatment or O2matic oxygen treatment for 24 hours. All patients will be treated with the O2matic device, but automated oxygen titration will be deactivated in the control group thus enabling manual oxygen titration through the machine similar to usual care. Patients will be equipped with a continuous saturation meter coupled to the O2matic, controlling the oxygen supplement. The O2matic machine is set to a standard titration of oxygen of 0-10 l per minute, a pre-defined saturation interval (92-96%) and a target saturation of 93%. Nasal catheters without moisturising the oxygen will be used as the standard. For patients expected to have an oxygen demand exceeding 6 l, an interval of 0-15 l of oxygen per minute with moisturising and supplied with 5 l atmospheric air per minute may be applied. The mix is applied by a face mask with side holes. Deviations according to oxygen intervals, saturation intervals or the air device used (nasal catheter, face mask, moisturising) is justified and documented in case report form.

Patients in the control group will also be coupled to the O2matic, set to registration mode, which will continuously monitor the oxygen saturation. The oxygen supply will be controlled manually on the O2matic. Additionally, alarms for saturation, pulse and oxygen flow are turned off, whereas technical alarms remain active. The oxygen treatment in the control group operates by manual saturation measurements with a standard pulse oximeter, for example via the EWS standard, followed by manual adjustments on the O2matic device. The intervals for measurements and adjustments are set according to EWS guidelines [6] and clinical judgment by doctors and nursing staff.

With patients in the active group, manual override is possible provided that the patient's condition makes automatic adjustments inappropriate, e.g., if an acute need arises for a higher oxygen supply than the set interval. Randomisation is done using the randomisation module in REDCap. All data are registered in the scientific database REDCap. REDCap is double-protected by a two-factor authentication. It is hosted on the servers of the Capital Region of Copenhagen, thus back-ups are secured similar to other clinical data.

All patients in both the active and the control group are manually monitored by the nursing staff with saturation, pulse and other vital values according to the EWS guidelines [6]. The guideline describes the frequency of measurements and an action algorithm for changes in the monitoring frequency and optionally the medical assessment and plan in relation to the measured EWS score.

Monitoring

See **Table 2** for data recorded at the time of inclusion. This study aims to test the feasibility of the O2matic device in relation to maintaining the preferred SpO_2 interval. Clinical endpoints will not be the focus of this study.

TABLE 2 Data recorded at the time of inclusion.

Date of birth, age and gender
Height, weight and BMI
Blood pressure, pulse, ECG, echocardiography
Systematic screening for comorbidities
Smoking history, including package years and current smoking status
Thoracic X-ray with recording of the presence of possible pneumonia or stasis
The use of O_2 at home, and if so, the duration of this
Arterial blood gas analysis: pH, pCO_2, pO_2, standard base excess, supplemental O_2
Basal biochemistry: haemoglobin, leukocytes, CRP, pro-brain natriuretic peptide
Enzymes will be measured 3 × as according to usual practice in patients admitted with acute coronary syndrome

CRP = C-reactive protein; pCO_2 = CO_2 pressure; pO_2 = O_2 pressure.

The intervention stops when one of the criteria presented in **Table 3** is met.

TABLE 3 Criteria for ending the intervention.

24 h of treatment is concluded
The patient is discharged or is granted a temporary leave of absence
The patient is moved to the intensive care unit or another department not participating in this study
The patient has had a treatment period of < 2 h due to lacking compliance, lack of need for O_2 treatment or other circumstances
The patient dies
The patient no longer wishes to participate in the study
If any serious adverse events occur with presumed relation to the study

Outcome measures

The primary outcome of this study is time within the desired saturation interval (SpO_2 92-96%), compared with manual oxygen treatment.

Secondary outcomes

- Time with clinically significant hypoxaemia (saturation 85-90%)

- Time with severe hypoxaemia (saturation < 85%)

- Time with inappropriate hyperoxia (saturation > 96%)

- Pulse rate.

Subgroups

We will compare patients with systolic heart failure (left ventricular ejection fraction < 45%) with patients with preserved ejection fraction, and patients with supraventricular arrythmias with patients without arrythmias.

Ethics

The trial does not imply any known risks and no patient health risk has been revealed in the eight articles previously published on similar equipment [7-9, 11-15]. Inconvenience might occur in the trial due to restricted mobility as the patient will be connected to the O2matic for a long period of time via the SpO_2 finger clamp. This inconvenience is considered small compared with the therapeutic advantage of optimised and more secure oxygen treatment. No participants in the trial will risk poorer treatment because of the trial as they will receive standard treatment or better. Before randomisation and inclusion, the participants will give oral and written consent for participation and allow access to their medical records. Participants can at any point withdraw from the study. Participants are covered by the patient insurance of Hvidovre Hospital. The study is approved by the Scientific Ethical Committee, H-19033702, and the data protection authorities in Denmark P-2019-369.

Sample size

The sample size is calculated with an expected 20% improvement in the primary outcome to be clinically

relevant. The standard deviation for this parameter was 25% in a Danish study [10]. A power of 80% and a significance level of 0.05 requires 25 participants in each group. On this basis, we have chosen to include 30 patients in each arm to allow for dropouts.

Statistical analysis plan

Descriptive information and patient characteristics will be presented with potential differences between the two groups being described by an appropriate significance test. Categorical data will be compared using the χ^2 test or Fisher's exact test. Continuous variables will be tested for normality and analysed with unpaired t-test when normally distributed and by the Wilcoxon-Mann-Whitney test in case of a non-normal distribution.

Between-group differences in SpO_2, oxygen-administration and pulse rate measured for 24 hours will be assessed by repeated-measurements mixed models with an unstructured covariance structure. Group and time point will be fixed effects. The interaction term of group with time will be included. Output from the model will be used to illustrate the SpO_2 and oxygen administration during the intervention phase. p values are denoted p-group. Skewed data will be log-transformed before analysis. All simultaneously obtained values of pulse, SpO_2 and oxygen administration collected during the intervention phase will be pooled and regression lines will be fitted to describe the correlations. Statistical analyses are made using the SAS statistical software, version 9.4 (SAS Institute, Cary, NC). Figures will be made in Graph Pad Prism version 8.0 (GraphPad Software, San Diego, CA). All tests are two-tailed, and statistical significance is defined as $p < 0.05$.

Trial registration: ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT05452863). Registered 11 July 2022.

DISCUSSION

This study will examine the clinical applicability of a novel automated feedback device termed O2matic and assess whether the device is superior to standard monitoring in keeping optimal saturation levels. The O2matic device was previously tested in a crossover trial but not in a parallel group trial, giving our study more power than previous trials. Little evidence exists for the use of optimal clinical monitoring of SpO_2. In a recent trial, the combination of clinical assessment and EWS reduced the number of routine measurements without increasing mortality [16].

Little has been published on the use of automated oxygen titration to improve SpO_2 levels, minimise the number of routine measurements and thus decrease nurse workload. A Canadian research group has developed a closed-loop system ($FreeO_2$), which works in a similar way as O2matic. In a study with 25 patients admitted with a COPD exacerbation, treated with automated oxygen treatment by $FreeO_2$ and 25 patients with conventional manual adjustments, $FreeO_2$ was significantly superior in keeping the oxygen saturation within the desired interval (81% versus 51%) [12]. The study did not have statistical power to evaluate parameters of health economics, but a non-significant reduction was recorded in both the duration of oxygen treatment of 1.8 days in the $FreeO_2$ group and duration of hospitalisation of 2.6 days in the $FreeO_2$ group ($p = 0.051$). Subsequently, a study randomised 187 patients with hypoxaemia to oxygen treatment with either $FreeO_2$ or manual control and adjustment in a three-hour period in an emergency department [14]. The patients were in the desired saturation interval for a higher share of the time than the group with manual adjustments (81% versus 52%). The oxygen supply was also phased out significantly faster in the $FreeO_2$ group.

Current standard care is time consuming for nurses. A prognosis made for the Danish Nursing Council predicted a peak lack of 6,423 nurses in 2025 in Denmark [17]. The O2matic may save precious nursing time so that nurses may focus on other tasks. This may possibly have a health economic impact in addition to saving oxygen as the

treatment is stopped when the desired saturation level is reached.

Patients are often treated with oxygen even in the absence of arterial hypoxaemia because the patient or clinicians believe that this will improve organ oxygenation [18]. In current guidelines, a consensus exists on treatment of severe hypoxaemia, but the indication for oxygen treatment in the absence of severe hypoxaemia remains unclear [1]. Avoiding hyperoxaemia may possibly be crucial for patients with cardiac disease as it is believed to cause systemic vasoconstriction, involving the myocardium and thus reducing cardiac output [19]. Undesirable effects of hyperoxia have been demonstrated in several physiologic studies [20]. Due to these possible adverse effects of oxygen treatment, automation may possibly improve the patient's clinical outcome by avoiding hyperoxaemia.

CONCLUSION

In this clinical trial, we will compare oxygen administration with O2matic with standard care in patients who require oxygen and are hospitalised due to an acute cardiovascular condition. We hypothesise that this will increase the time that the patient achieves the desired saturation interval in addition to reducing hypoxaemic and hyperoxaemic events.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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