BMJ Open

Automated control of inspired oxygen fraction in mechanically ventilated patients: A study protocol for a single-centre randomised controlled trial

Christine Eimer [ID] , Helene Selpien, Tatiana Bastian, Lara Hartmann, Armin Sablewski, Matthias Lindner, Tobias Becher, Dirk Schädler

Department for Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Kiel, Schleswig-Holstein, Germany

Correspondence to
Dr Christine Eimer;
christine.eimer@uksh.de

ABSTRACT

Background A novel automated system for the control of the inspired fraction of oxygen, named LeoClac, has been implemented on a mechanical ventilator. The system uses a separate sensor for the measurement of peripheral oxygen saturation which is connected directly to the ventilator. We hypothesise that LeoClac will be superior to manual control in keeping critically ill and mechanically ventilated patients in a SpO_2-target range (93–96%).

Methods This is a randomised controlled, single-centre superiority study with two parallel groups including 40 patients. Mechanically ventilated patients treated on the intensive care unit (ICU) will be screened for eligibility and included in the study after written informed consent. Patients in the intervention group will be treated with LeoClac. In the control group, FiO_2 will be controlled manually by the intensive care team. The primary endpoint of the study is the proportion of time in the target zone for peripheral oxygen saturation within the first 24 hours following randomisation. Secondary endpoints include the analysis of hyperoxia and hypoxia, number of changes in FiO_2, number and reasons for self-aborts and manual overrides of the automated system, proportion of time in target zone for peripheral oxygen saturation in the subgroups of patients with hypoxemic respiratory failure and acute hypercapnic respiratory failure. Furthermore, ventilator-free days and ICU mortality at day 28 will be analysed.

Analysis The precise control of FiO_2 with the aim of avoiding both hyperoxia and hypoxia is a fundamental challenge in the highly technical field of mechanical ventilation. Incorporation of patient heterogeneity, the benefits of reduced manual intervention and the potential to optimise treatment outcomes underscore the importance of this research. By addressing the complexities of precise oxygen control in adults, this study contributes to the advancement of critical care practices and may improve patient outcomes.

Ethics The study protocol was approved by the ethics committee of the Christian-Albrechts-University Kiel, Germany, on 17 May 2023.

Trial registration number DRKS00032113.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study aims to evaluate whether an automated system can effectively optimise oxygen therapy in critically ill, invasively ventilated patients.
⇒ This study plans to investigate the benefits and limitations of automated oxygen control in a very heterogeneous sample of adult intensive care patients.
⇒ The novel system will be used for up to 28 days per patient to evaluate the feasibility of the sensors in daily routine.

INTRODUCTION
Background and rationale

Oxygen therapy plays a crucial role in the therapy of critically ill patients, ensuring adequate oxygen delivery while avoiding hypoxia and hyperoxia. Nevertheless, overdosing oxygen may be harmful, as both excessively high and low arterial partial pressure of oxygen (PaO_2) are associated with increased mortality.[1 2] Stolmeijer *et al* indicated that liberal oxygen therapy leads to hyperoxia and may affect survival.[3] A recent meta-analysis also highlighted the risks of liberal oxygen therapy, showing increased mortality compared with conservative oxygen therapy.[4] The current German guideline recommends titrating peripheral oxygen saturation (SpO_2) between 92% and 96% in mechanically ventilated patients.[5] In adult patients, sensitivity to oxygen is not as pronounced; yet, neither the consequences of hypoxia or hyperoxia nor the associated economic follow-up costs should be underestimated.[6–8]

Currently, manual oxygen (FiO_2) control based on SpO_2 and PaO_2 measurements is the standard in clinical practice. However, based on neonatal studies, compliance to peripheral oxygen targets is poor.[9 10] This finding might also be applicable to adults and carries the risk of unrecognised hypoxia

or hyperoxia. Additionally, healthcare professionals often prioritise avoiding desaturation over avoiding hyperoxia, potentially leading to oxygen oversupply.[11] Therefore, it is crucial to carefully monitor patients' response to therapy and adjust oxygen delivery accordingly.

To address the limitations of manual control, an automated system for FiO_2 control would be desirable. Its aim is to continuously modulate oxygen supply, ensure normoxemia and prevent desaturation. In a study by Lellouche *et al*, automated oxygen flow titration was superior to constant oxygen flow in maintaining SpO_2 levels.[12] Saihi *et al* demonstrated that an automated FiO_2 controller, based on continuous oxygen saturation, was capable of maintaining SpO_2 reliably within a predefined target range.[13] Intellivent-ASV (fully automated closed loop ventilation) has been the sole available ventilation mode including automated FiO_2 control in invasively ventilated adult patients. The algorithm in Intellivent-ASV compares SpO_2 values with the target range and automatically adjusts the FiO_2 to maintain desired saturation levels.[11] However, access to Intellivent-ASV is limited, available only on selected ventilators. A new alternative, the Loewenstein closed-loop automatic oxygen control (LeoClac), offers rapid modulation of FiO_2 based on a separate SpO_2 measurement attached to the ventilator. The user sets a target SpO_2 range to be maintained before starting the FiO_2 control. The user also defines a FiO_2 threshold for receiving an alarm. An alarm is triggered if the FiO_2 alarm threshold is exceeded; however, the automatic regulation continues until deactivation by the user ('manual override'). The SpO_2 measurement is based on a configurable number of pulse waves. FiO_2 reductions occur every 2 minutes, increases are limited to every 45 seconds to avoid 'swinging' of the system.

Recent publications suggest that closed-loop control devices maintain higher saturation levels, spend less time below the target saturation and save oxygen resources.[11 14 15] Moreover, an automated system may contribute to maintaining sufficient oxygenation during exercise and physiotherapy when oxygen consumption rises.[16]

While automated closed-loop systems have been well evaluated in infants to prevent hyperoxia and retinal damage, long-term evaluation in adults is lacking.[11 17 18] However, Bialais *et al* were able to demonstrate that Intellivent-ASV provides safe ventilation with optimised oxygenation and reduced workload on caregivers over a time period of 48 hours.[19] Nevertheless, the aim of this study is to further investigate the benefits and limitations of automated control of inspired FiO_2 in invasively ventilated critically ill adults. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) figure provides an overview of the phases of the trial and data collection timepoints (figure 1). The primary endpoint of this trial is the proportion of time in the target zone for peripheral oxygen saturation within the first 24 hours following randomisation, calculated based on all usable time with a valid SpO_2 signal. This also includes the

analysis of blood gas samples, self-aborts and manual overrides of the automated system and the number of changes in FiO_2. Furthermore, the proportion of time in the peripheral oxygen target zone in patients with acute hypoxaemic respiratory failure and acute hypercapnic respiratory failure will be further analysed.

Explanation for the choice of comparators

The primary objective is to examine the compliance with the target zone for peripheral oxygen saturation (SpO_2) using the LeoClac automated system compared with manual control. Thus, the comparators in this trial are manual and automated FiO_2 control. Manual control refers to the standard practice of manually adjusting the inspired fraction of oxygen (FiO_2) based on clinical judgement. Periodic assessments of the patient's condition and reference to current and recent SpO_2 levels. It represents the current approach used in clinical practice.

The use of manual control as a comparator allows for a direct comparison with the LeoClac automated system. By assessing the efficacy of LeoClac in maintaining SpO_2 within the target zone, it can be determined whether the automated system provides improved control and adherence to the desired oxygen saturation levels compared with standard manual control methods.

By comparing the performance of the LeoClac system to manual control, the trial aims to evaluate whether the automated system can effectively optimise oxygen therapy and improve patient outcomes in critically ill, invasively ventilated patients.

Objectives

The primary objective of this study is to investigate compliance within the predefined SpO_2 target zone of 93% to 96% in critically ill and invasively ventilated patients comparing the novel 'LeoClac' controller to manual control.

Trial design

This trial is a randomised, controlled, single-centre superiority trial with two parallel groups. The study aims to assess the proportion of time spent in the target zone for peripheral oxygen saturation within the first 24 hours following randomisation as the primary endpoint. Randomisation is conducted using random permuted block randomisation with a 1:1 allocation ratio. Blinding is not feasible in this study.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES
Study setting

The study will be performed on all interdisciplinary surgical intensive care units of the Department of Anesthesiology and Intensive Care Medicine, University Medical Centre Schleswig-Holstein, Campus Kiel.

Eligibility criteria

To be considered eligible for the study, patients must meet the following inclusion criteria: (1) Intubated or

	Screening		Study period	Close-out
	Enrolment	Allocation	Post-allocation	
TIMEPOINT:	Day 0	Day 0	Day 0-28	Day 28
ENROLMENT:	X			
Eligibility Screen	X			
Written informed consent	X			
ALLOCATION:		X		
INTERVENTIONS:				
LeoClac Oxygen control			X	
Manual oxygen control			X	
ASSESSMENTS:				
Proportion of time of oxygen saturation in target zone			X	
Duration of time of hyperoxia and hypoxia (pulse oximetry; blood gas samples)			X	
Collection of self- and user-aborts of the automated system			X	
CLOSE OUT: Ventilator-free days				X
ICU Mortality				X

Figure 1 The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) figure provides an overview of the different phases of the trial and outlines the data collection timepoints. ICU, intensive care unit.

tracheotomised patients requiring mechanical ventilation for a duration of at least 9 hours as of 09:00 am, (2) participants must be at least 18 years old and written informed consent must be obtained. Potential patients will be excluded from the study if any of the following exclusion criteria are met: (1) Inability to measure peripheral oxygen saturation, (2) absence of a detectable pulsatile plethysmography curve, (3) clinical indication for hyperoxia (SpO_2 target >96%), (4) expected extubation within the next 24 hours, (5) negative presumed will regarding study participation or (6) known pregnancy.

Patient and public involvement
Patients or the public are not involved in the design, or conduct, or reporting or dissemination plans of our research.

Intervention description
After obtaining written informed consent, patients will be included in the study. Patients randomised to the intervention group will be mechanically ventilated with an automated control of the inspired oxygen fraction. Therefore, the ventilator will automatically adjust the amount of oxygen required based on oxygen saturation, with the goal of always maintaining oxygen saturation between 93% and 96%. Regardless of group assignment, all patients receive an additional oxygen sensor as part of the LeoClac system. If the two oxygen saturation sensors show different values, the measurements from the LeoClac device should be used. In case of uncertainty, an arterial blood gas analysis should be performed for verification. LeoClac will be used from the start of the study period until the end of invasive ventilation (extubation, decannulation, dismission or death) or day 28. Figure 2 shows the participant timeline and provides an overview of screening, intervention and close-out.

Criteria for discontinuing or modifying allocated interventions
If instances of uncontrollable respiratory instability occur during the intervention, the intervention will be
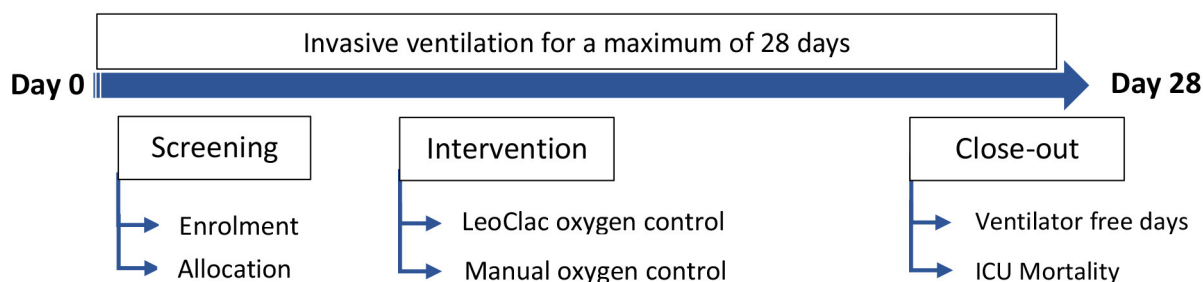
Figure 2 The participant timeline provides an overview of screening, intervention and close-out. ICU, intensive care unit.

discontinued. Treating physicians (who are not part of the study team) can suspend the study at any time. LeoClac can be deactivated at any time and for any reason. The reason will be documented in the case report form. Furthermore, participants/representatives may withdraw from the study without citing a reason at any time. There is no provision for modifying the assigned intervention.

Strategies to improve adherence to interventions
Adherence to the study protocol is ensured by staff training courses and information leaflets, which are attached to the patient's ventilator.

Relevant concomitant care permitted or prohibited during the trial
All procedures and interventions in this study adhere to established internal standard procedures required for optimal patient treatment.

Outcomes
The primary endpoint of this trial is the proportion of time in the target zone for peripheral oxygen saturation within the first 24 h hours following randomisation.

Secondary endpoints apply to the entire study period and include the following:
► Proportion of time with automated control of inspired fraction of oxygen activated.
► Proportion of time with hypoxia according to pulse oximetry ($SpO_2 < 90\%$).
► Proportion of time with hyperoxia according to pulse oximetry ($SpO_2 > 98\%$).
► Number of blood gas samples with hypoxia (n/day; $PaO_2 < 60 \, mm \, Hg$).
► Number of blood gas samples with hyperoxia (n/day; $PaO_2 > 110 \, mm \, Hg$).
► Number of changes of inspired fraction of oxygen (n/day).
► Number of and reasons for self-aborts of the automated system (n/day).
► Number of and reasons for manual overrides of the automated system (n/day).
► Proportion of time in target zone for peripheral oxygen saturation in the subgroup of patients with acute hypoxaemic respiratory failure.
► Proportion of time in the target zone for peripheral oxygen saturation in the subgroup of patients with acute hypercapnic respiratory failure.

► Ventilator-free days alive at day 28.
► Intensive care unit (ICU) mortality within 28 days.

Participant timeline
Figure 2 shows the participant timeline.

Sample size
Based on data with other automated systems and on our clinical experience with manual oxygen control, we expect a time within SpO_2 target range of 80% (SD 20) with LeoClac and of 60% (SD 20) with manual control. For a two-sided Mann-Whitney U test, power calculation with 1-Beta=0.8 and alpha 0.05 yields a required sample size of 2×20 patients to be sufficient.

Recruitment
Eligible patients will be screened for study participation every morning (Monday–Friday). Screening will be conducted by senior physicians. Recruitment will be continuously conducted by physicians of the research team until the target randomised sample size of 40 participants is achieved. Based on current clinical case numbers, this will take approximately 6 months.

Assignment of interventions: allocation
Sequence generation
Randomisation is performed by random permuted block randomisation with a 1:1 allocation ratio, minimum block size: 4; maximum block size: 8; increment: 2. The randomisation is performed electronically using www.studyrandomizer.com.

Concealment mechanism
The randomisation is performed electronically using www.studyrandomizer.com.

Implementation
The allocation sequence is generated electronically.

Who will be blinded
Blinding of the study team is not feasible due to the study concept. Patients and their representatives will be blinded to the intervention.

Data collection and management
Plans for assessment and collection of outcomes
Demographic and clinical data are recorded on electronic-based case report forms (eCRFs) by data collectors. Ventilator

measurement data and oxygen saturation values are exported electronically from the ventilator and the monitoring unit. To determine the primary and further secondary outcomes, ventilator data and monitoring data will be analysed by the data analysing team as described in the statistical methods for primary and secondary outcomes section.

Plans to promote participant retention and complete follow-up

No follow-up for clinically relevant outcome measurement needed.

Data management

All participant information will be stored on password-protected databases to which only research team members have access. Collected data are pseudonymised by a coded ID (identification) number. All records that contain names or other personal identifiers, such as informed consent forms, will be stored separately from study records. Demographic and clinical data will be stored on eCRFs. Log files containing ventilator data are exported from ventilators and saved on a password-secured network drive.

Statistical methods for primary and secondary outcomes

Descriptive statistical analyses (mean±SD, median and 95% CI, where appropriate) will be used. As we expect the proportion of time in the target zone for peripheral oxygen saturation within the first 24 hours following randomisation to be non-normally distributed, the primary endpoint will be compared between study groups with a Mann-Whitney U test. Categorical endpoints will be investigated using Fisher's exact test. Other between-group comparisons of numerical endpoints will be conducted using a two-sided t-test or Mann-Whitney U test, as appropriate. Testing for normal distribution will be performed with the Shapiro-Wilk test.

Methods for additional analyses (eg, subgroup analyses)

Not applicable, no further analyses planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Datasets will be excluded if the study intervention was not performed, or if the primary endpoint cannot be evaluated.

Methods: monitoring
Composition of the data monitoring committee, its role and reporting structure

As no interim analyses are planned or will be performed, a data monitoring committee has not been organised for this study.

Interim analyses

Not applicable, there will be no interim analyses.

Adverse event reporting and harms

Adverse events and other unintended effects of the trial will be collected, assessed and immediately reported to the principal investigator.

Frequency and plans for auditing trial conduct

Not applicable, an auditing trail conduct is not required.

ETHICS AND DISSEMINATION
Ethics approval and consent to participate

The local review board of the Medical Faculty of the Christian-Albrecht University approved the study, reference number D 449/22. The patient information has been included in the online supplemental file S1. Written informed consent to participate will be obtained from all patients.

Plans for communicating important protocol amendments to relevant parties (eg, trial participants, ethical committees)

Any changes in protocol will be submitted to the local ethics committee for approval, all changes will be communicated to the study team via email and during the regular study group meetings. The trial record on the German Clinical Trials Register (DRKS) will be updated accordingly.

Who will take informed consent?

In this randomised controlled trial investigating a novel system for automated FO_2 control in critically ill, mechanically ventilated patients, the process of obtaining informed consent will be multistep based due to the patients' critical condition. Since most patients will be unable to provide written consent themselves, the patient's presumed will regarding study participation will be determined in consultation with their relatives or representatives. Written informed consent will then be obtained from the patient's legal representatives prior to their participation in the study.

Patients will be assessed for potential study inclusion daily (Monday–Friday). As soon as a patient regains consciousness, their written informed consent will be sought. It is important to note that in accordance with the principles outlined in the Declaration of Helsinki and national regulations, consent can be withdrawn at any time, without the need to specify reasons, and without compromising the patient's future medical care.

Additional consent provisions for collection and use of participant data and biological specimens

No additional data will be collected.

Confidentiality

Data are handled confidentially, and the storage of patient-related medical data is pseudonymised. No features are transferred that allow direct identification of specific participants. The subject identification code list to personal data is accessible only to the principal investigator. All further records containing names or other personal identifiers, such as informed consent forms, are kept separate from the study data identified by code number. Data collection, coding, security and storage will comply with the provisions of the German Federal Data Protection Act (BDSG) and the EU General Data

Protection Regulation (EU-GDPR). Accordingly, records and documents related to the clinical trial will be kept for at least 15 years.

Provisions for post-trial care
After completion of the study, patients will continue to receive care in our ICU until they reach a level of recovery that allows for transfer to a general ward or a rehabilitation clinic. Patients are encouraged to contact our clinic at any time if they have any concerns.

Dissemination plans
Once the study has been completed, the results will be published in a peer-reviewed scientific journal and presented on national and international conferences for anaesthesiology and intensive care medicine.

Plans to give access to the full protocol, participant level data and statistical code
Datasets containing anonymised patient data will be made accessible on reasonable request to the corresponding author, in compliance with European data protection regulations (EU-GDPR).

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use
No biological specimens will be collected.

DISCUSSION
This study aims to evaluate the efficacy of an automated closed-loop oxygen control system to examine compliance with the SpO_2 target zone in critically ill and invasively ventilated adult patients. The precise control of oxygen demand with the aim of avoiding both hyperoxia and hypoxia is a central challenge in the highly technical field of mechanical ventilation. From the paediatric and neonatal point of view, automatic oxygen control has already been able to demonstrate significant success in numerous studies.[17 20–22] With the novel LeoClac function, the oxygen demand is continuously monitored and checked several times per minute. Increases in oxygen demand are therefore immediately detected, for instance, when the patient is more active or mobilised. This real-time adaptability may significantly reduce the likelihood of sudden fluctuations in oxygen saturations.

It is imperative to acknowledge the patient heterogeneity observed in critically ill patients. Understanding how different patients respond to automated oxygen control is vital for tailoring treatment strategies to individual needs. The reduction of manual intervention could become a significant advantage of automated oxygen control. The current standard often requires manual adjustment and monitoring of oxygen supply, placing a significant burden on medical staff, especially in patients with high oxygen demand. The automation of this process holds promise, especially in high-workload situations or when multiple patients are being cared for simultaneously, where the system can increase efficiency and reduce the burden on medical staff. In addition, the precise and controlled delivery of oxygen holds the potential to optimise treatment outcomes.

Incorporation of patient heterogeneity, the benefits of reduced manual intervention and the potential to optimise treatment outcomes underscore the paramount importance of this research. By addressing the complexities of precise oxygen control in adults, this study contributes to the advancement of critical care practices and may improve patient outcomes.

Trial status
The study protocol was approved by the ethics committee of the Christian-Albrechts-University Kiel, Germany, on 1 February 2023. Recruitment has begun in December 2023 and is expected to end in June 2025.

ORCID iD
Christine Eimer http://orcid.org/0000-0001-8108-8742

REFERENCES

1 de Jonge E, Peelen L, Keijzers PJ, *et al*. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008;12:R156.

2 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.

3 Stolmeijer R, Bouma HR, Zijlstra JG, *et al*. A systematic review of the effects of hyperoxia in acutely ill patients: should we aim for less? *Biomed Res Int* 2018;2018:7841295.

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

5 Gottlieb J, Capetian P, Hamsen U, *et al*. S3-leitlinie sauerstoff in der akuttherapie beim erwachsenen. *Pneumologie* 2022;76:159–216.

6 Singer M, Young PJ, Laffey JG, *et al*. Dangers of hyperoxia. *Crit Care* 2021;25:440.

7 Ottolenghi S, Sabbatini G, Brizzolari A, *et al*. Hyperoxia and oxidative stress in anesthesia and critical care medicine. *Minerva Anestesiol* 2020;86:64–75.

8 Hochberg CH, Semler MW, Brower RG. Oxygen toxicity in critically Ill adults. *Am J Respir Crit Care Med* 2021;204:632–41.

9 Lim K, Wheeler KI, Gale TJ, *et al*. Oxygen saturation targeting in preterm infants receiving continuous positive airway pressure. *J Pediatr* 2014;164:730–6.

10 Hagadorn JI, Furey AM, Nghiem T-H, *et al*. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics* 2006;118:1574–82.

11 van Kaam AH, Hummler HD, Wilinska M, *et al*. Automated versus manual oxygen control with different saturation targets and modes of respiratory support in preterm infants. *J Pediatr* 2015;167:545–50.

12 Lellouche F, L'her E. Automated oxygen flow titration to maintain constant oxygenation. *Respir Care* 2012;57:1254–62.

13 Saihi K, Richard J-CM, Gonin X, *et al*. Feasibility and reliability of an automated controller of inspired oxygen concentration during mechanical ventilation. *Crit Care* 2014;18:R35.

14 Abdo M, Hanbal A, Asla MM, *et al*. Automated versus manual oxygen control in preterm infants receiving respiratory support: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2022;35:6069–76.

15 Mitra S, Singh B, El-Naggar W, *et al*. Automated versus manual control of inspired oxygen to target oxygen saturation in preterm infants: a systematic review and meta-analysis. *J Perinatol* 2018;38:351–60.

16 Sanchez-Morillo D, Olaby O, Fernandez-Granero MA, *et al*. Physiological closed-loop control in intelligent oxygen therapy: A review. *Comput Methods Programs Biomed* 2017;146:101–8.

17 Sturrock S, Williams E, Dassios T, *et al*. Closed loop automated oxygen control in neonates-A review. *Acta Paediatr* 2020;109:914–22.

18 Hummler H, Fuchs H, Schmid M. Automated adjustments of inspired fraction of oxygen to avoid hypoxemia and hyperoxemia in neonates - a systematic review on clinical studies. *Klin Padiatr* 2014;226:204–10.

19 Bialais E, Wittebole X, Vignaux L, *et al*. Closed-loop ventilation mode (IntelliVent®-ASV) in intensive care unit: a randomized trial. *Minerva Anestesiol* 2016;82:657–68.

20 Kumar J, Meena J. Automated oxygen saturation targeting strategy in neonates. *J Pediatr* 2021;235:S0022-3476(21)00406-6.

21 Nair V, Loganathan P, Lal MK, *et al*. Automated oxygen delivery in neonatal intensive care. *Front Pediatr* 2022;10:915312.

22 Saugstad OD. Automated oxygen control for routine use in the NICU-Are we there? *Acta Paediatr* 2023;112:1142–4.