PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Closed-loop oxygen control for hypoxemic patients during hospitalization: a living systematic review and meta-analysis protocol
AUTHORS	Mol, Caroline; Vieira, Aléxia; Garcia, Bianca; Pereira, Emanuel; Caserta, Raquel; Pinto, Ana; Nawa, Ricardo

VERSION 1 – REVIEW

REVIEWER	jean-damien Ricard Université de Paris
REVIEW RETURNED	13-Jun-2022

GENERAL COMMENTS	Thank you for giving me the opportunity to revise the manuscript. I have several comments I would like to be addressed. 1) Authors justify the need for a new metaanalysis by the fact that several RCT have been published since the former metaanalyses were published. I believe it is important authors provide those references in the introduction. 2) Authors do not precise if they will be addressing all kinds of O2 therapy (i.e., both high and low flow oxygen or only low flow)? This is important because I'm aware of at least two recent studies using cloosed-loop with nasal high flow therapy. 3) Authors should be more precise on the O2 target. The width of the target is an issue. It's easier to stay within a wider target. In addition, as secondary outcomes, I would also add some evaluation of what happens outside the target. Indeed, if the it cloose-loop allows for a considerable amount of time within the target range, but otherwise, the SpO2 is far below an acceptable level, then perhaps a device that has lesser time spent within the target range but much less "out of boundaries" SpO2 is preferable in terms of patient safety. 4) Finally, the recent pandemic has highlighted the dramatic shortage of O2 in several countries. One of the benefits of these cloosed-loops would be to help reduce O2 consumption. I think this data should be provided. Even if just to mention that O2 consumption was not evaluated in the X% of studies.

REVIEWER	Christian Poets University Children's Hospital, Tübingen, Neonatology
REVIEW RETURNED	14-Jun-2022

GENERAL COMMENTS	The authors want to do a systematic review of study on automated

	oxygen control in adults. However, the main purpose of FiO2-control is the avoidance of episodes of hyper- und hypoxemia, and I am surprised that neither is addressed in this systematic review. The authors write themselves “either hypoxemia or hyperoxia have potential harmful side effects and complications”. Thus, an analysis of such episodes, e.g. SpO2 <80% for hypoxemia, and >98% for hyperoxemia, should be added to the current protocol. Minor comments: Language requires editing (e.g., abstract, first few lines: Oxygen instead of “The oxygen”, “certainty of evidence is low”, not “are low”. Abbreviations need to be spelled out, e.g. what is “CINALH – via EBSCO” It should be stated who the third reviewer is (in case of discrepencies between reviewer #1 and #2).

VERSION 1 – AUTHOR RESPONSE

REVIEWER #1

Prof. Jean-Damien Ricard, Université de Paris

Comments to the Author: Thank you for giving me the opportunity to revise the manuscript. I have several comments I would like to be addressed.

1) Authors justify the need for a new meta-analysis by the fact that several RCT have been published since the former meta-analyses were published. I believe it is important that authors provide those references in the introduction.

Thank you for carefully revising and suggesting the inclusion of new references in the introduction section. We really appreciate your effort supporting us to improve the intro. So far, we have added to the introduction section a total of 9 (nine) "new" references of randomized clinical trials, as follows:

1. Chelly J, Mazerand S, Jochmans S, *et al.* Automated vs. conventional ventilation in the ICU: a randomized controlled crossover trial comparing blood oxygen saturation during daily nursing procedures (I-NURSING). *Crit Care* 2020;**24**:453.

2. De Bie AJR, Neto AS, van Meenen DM, *et al.* Fully automated postoperative ventilation in cardiac surgery patients: a randomised clinical trial. *Br J Anaesth* 2020;**125**:739–49.

3. Denault M-H, Ruel C, Simon M, *et al.* Evaluation of hyperoxia-induced hypercapnia in obese patients after cardiac surgery: a randomized crossover comparison of conservative and liberal oxygen administration. *Can J Anaesth* 2020;**67**:194–202.

4. Eremenko AA, Komnov RD, Titov PA, *et al.* Comparing the Intellivent-ASV® Mode with Conventional Ventilation Modes during Weaning after Uncomplicated Cardiac Surgery. Messenger of ANESTHESIOLOGY AND RESUSCITATION. 2021;**18**:36–45. doi:10.21292/2078-5658-2021-18-3-36-45

5. Hansen EF, Hove JD, Bech CS, *et al.* Automated oxygen control with O2matic during admission with exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis* 2018;**13**:3997–4003.

6. Harper JC, Kearns NA, Maijers I, *et al.* Closed-Loop Oxygen Control Using a Novel Nasal High-Flow Device: A Randomized Crossover Trial. *Respir Care* 2021;**66**:416–24.

7. L’Her E, Jaber S, Verzilli D, *et al.* Automated closed-loop standard manual oxygen

administration after major abdominal or thoracic surgery: an international multicentre randomised controlled study. *Eur Respir J* 2021;**57**. doi:10.1183/13993003.00182-2020

8. Roca O, Caritg O, Santafé M, *et al.* Closed-loop oxygen control improves oxygen therapy in acute hypoxemic respiratory failure patients under high flow nasal oxygen: a randomized cross-over study (the HILOOP study). *Crit Care* 2022;**26**:108.

9. Arnal J-M, Garnero A, Novotni D, *et al.* Closed loop ventilation mode in Intensive Care Unit: a randomized controlled clinical trial comparing the numbers of manual ventilator setting changes. *Minerva Anestesiol* 2018;**84**:58–67.

2) Authors do not precise if they will be addressing all kinds of O2 therapy (i.e., both high and low flow oxygen or only low flow)? This is important because I'm aware of at least two recent studies using closed-loop with nasal high flow therapy.

As suggested, the type of intervention was better described in the “Inclusion criteria” in the methods section (page 7), as follow: *“... 2)type of interventions: any devices that allow an automatic oxygen delivery, including invasive and non-invasive devices; low and high flow oxygen devices.”*

3) Authors should be more precise on the O2 target. The width of the target is an issue. It's easier to stay within a wider target. In addition, as secondary outcomes, I would also add some evaluation of what happens outside the target. Indeed, if the it close-loop allows for a considerable amount of time within the target range, but otherwise, the SpO2 is far below an acceptable level, then perhaps a device that has lesser time spent within the target range but much less "out of boundaries" SpO2 is preferable in terms of patient safety.

Thanks for your comment, we really appreciate your observation. We agree that the width of the oxygen target is a relevant issue which can influence the ability of the closed-loop devices in maintaining the SpO2 within the predefined target. However, this variability is expected between the different studies and populations. To not limit the studies inclusion we prefer not to define a precise oxygen target in the study protocol. This data will be included in the final publication of this systematic review.

Regarding the percentage of time spent outside oxygen target, indeed it is a very relevant outcome, however, it was not included in the initial protocol approved under PROSPERO registration number [CRD42022306033]. Aware that automated oxygen control devices are proposed to avoid episodes of hyper- and hypoxemia, we would like to check the possibility to not include these outcomes in the present manuscript once we already planned to report it in the final publication of this systematic review.

We also would like to inform you that the current stage of this systematic review is the writing of the final version of the manuscript where we will include the outcomes mentioned. Find below preliminary data of the final analysis of the percentage of time outside the oxygen target for both hypoxia and hyperoxia, as follows:

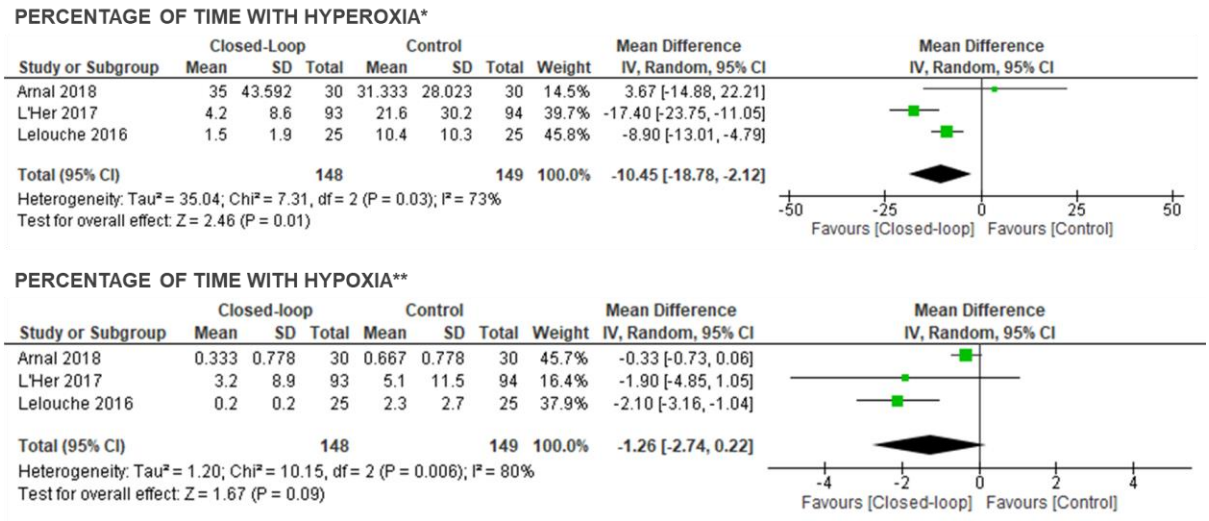


Figure legend: *Hyperoxia definitions: Arnal 2018 - SpO2 > 96%; L'Her 2017 - SpO2 ⩾98% for purely hypoxaemic respiratory failure and ⩾94% for mildly hypercapnic respiratory failure; Lelouche 2016 - SpO2 5% above the target defined by the physicians. ** Hypoxia definitions: Arnal 2018v - SpO2 < 88%; L'Her 2017 - SpO2 <90% for purely hypoxaemic respiratory failure and <86% for mildly hypercapnic respiratory failure; Lelouche 2016 - SpO2 < 85%.

4) Finally, the recent pandemic has highlighted the dramatic shortage of O2 in several countries. One of the benefits of these closed-loops would be to help reduce O2 consumption. I think this data should be provided. Even if just to mention that O2 consumption was not evaluated in the X% of studies.

Thanks for your relevant suggestion. Oxygen consumption can be considered a very important outcome, especially after COVID-19 pandemic and the dramatic shortage of O2 faced by several countries, including our own (Brazil). As previously mentioned, we are pleased to inform you that this systematic review is currently in the final stage of the manuscript writing. We ensure that qualitative analysis of O2 consumption will be reported and included as an outcome in the final publication of this systematic review, once quantitative analysis was not able to be performed because only one study has investigated this outcome.

REVIEWER #2

Dr. Christian Poets, University Children's Hospital, Tübingen

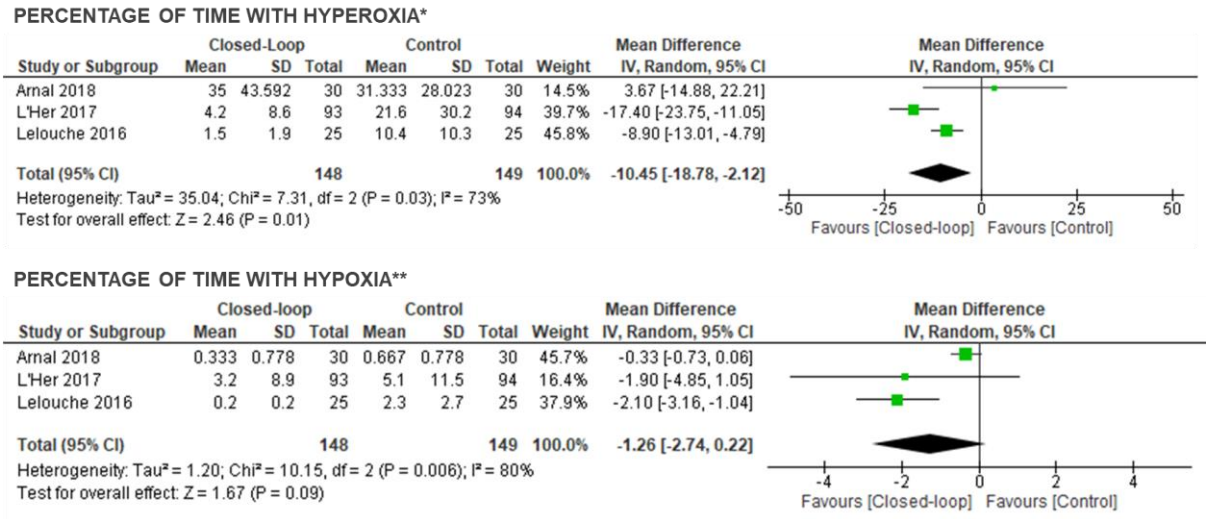
Comments to the Author:

The authors want to do a systematic review of study on automated oxygen control in adults. However, the main purpose of FiO2-control is the avoidance of episodes of hyper- und hypoxemia, and I am surprised that neither is addressed in this systematic review. The authors write themselves "either hypoxemia or hyperoxia have potential harmful side effects and complications". Thus, an analysis of such episodes, e.g. SpO2 <80% for hypoxemia, and >98% for hyperoxemia, should be added to the current protocol.

Thanks for your comment, we appreciate your observation. This topic was raised by reviewer #1 - comment #3. Indeed, the percentage of time spent outside the oxygen target is very relevant,

however it was not included in the initial protocol approved under PROSPERO registration number [CRD42022306033]. Aware that automated oxygen control devices are proposed to avoid episodes of hyper- and hypoxemia, we would like to check the possibility to not include these outcomes in the present manuscript once we already planned to report it in the final publication of this systematic review. We also would like to inform you that the current stage of this systematic review is the writing of the final version of the manuscript where we will include the outcomes mentioned. Find below preliminary data of the final analysis of the percentage of time outside the oxygen target for both hypoxia and hyperoxia.

Figure legend: *Hyperoxia definitions: Arnal 2018 - SpO2 > 96%; L'Her 2017 - SpO2 ⩾98% for purely hypoxaemic respiratory failure and ⩾94% for mildly hypercapnic respiratory failure; Lelouche 2016 - SpO2 5% above the target defined by the physicians. ** Hypoxia definitions: Arnal 2018v - SpO2 < 88%; L'Her 2017 - SpO2 <90% for purely hypoxaemic respiratory failure and <86% for mildly hypercapnic respiratory failure; Lelouche 2016 - SpO2 < 85%.



Minor comments:

1) **Language requires editing (e.g., abstract, first few lines: Oxygen instead of "The oxygen", "certainty of evidence is low", not "are low".**

Thanks for your comment. A careful review of English grammar and spelling were performed throughout the manuscript and errors identified were corrected.

2) **Abbreviations need to be spelled out, e.g. what is "CINALH – via EBSCO"**

Thanks for your observation. We carefully revised the entire manuscript adding all definitions of abbreviations utilized throughout the manuscript.

3) **It should be stated who the third reviewer is (in case of discrepancies between reviewer #1 and #2).**

Thank you for your comment. The authors agree that it is not clear who is the third reviewer cited in the manuscript protocol. Committed to transparency, we decided to add the reviewer's initials to clarify who is each reviewer author, as follows:

- *"Two review authors (CGM and AGV) will independently…"* (page 8).
- *"If a consensus will not be reached, a third reviewer (ACP) will be consulted…"* (page 8).
- *"Two reviewers (CGM and AGV) will independently extract…"* (page 8).
- *"We involved a third reviewer (ACP) if a consensus could not be reached."* (page 10)

VERSION 2 – REVIEW

REVIEWER	jean-damien Ricard Université de Paris
REVIEW RETURNED	29-Aug-2022

GENERAL COMMENTS	reviewing this paper is very frustrating. when authors state they won't make the required changes because the paper related to the protocole is already written and on the verge of being submitted, then I do not see any point in reviewing the study. Indee, twice, authors mention that the paper is in its final stage and that changes won't/can't be made : "as previously mentioned, we are pleased to inform you that this systematic review is currently in the final stage of the manuscript writing. "