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Review

Oxygen and carbon dioxide targets after cardiac arrest: an updated systematic review

Mathias J. Holmberg[a,*], *Takanari Ikeyama*[b,c], *Rakesh Garg*[d], *Ian R. Drennan*[e,f,g,h], *Eric J. Lavonas*[i,j], *Janet E. Bray*[k,l], *Theresa M. Olasveengen*[m,n], *Katherine M. Berg*[o,p], *on behalf of the International Liaison Committee on Resuscitation Basic Life Support and Advanced Life Support Task Forces*[1]

Abstract

Aim: To perform an updated systematic review and *meta*-analysis of oxygen and carbon dioxide targets in patients with sustained return of spontaneous circulation after cardiac arrest.

Methods: Searches were conducted in MEDLINE, Embase, and Evidence-Based Medicine Reviews from August 2019 to March 2025 for randomised trials comparing specific oxygen or carbon dioxide targets in post-cardiac arrest patients. Two investigators independently reviewed trials for relevance, extracted data, and assessed risk of bias. Data were pooled using random-effects models. The certainty of evidence was evaluated using GRADE methodology.

Results: Fifteen manuscripts from 12 trials were included. All trials were limited to adult patients, primarily including out-of-hospital cardiac arrests. Five trials evaluated oxygen targets in the prehospital setting, while six evaluated oxygen targets and three evaluated carbon dioxide targets in the intensive care unit setting. Risk of bias was assessed as moderate for most outcomes. Meta-analyses found no differences in survival or favourable functional outcomes when comparing restrictive to liberal oxygen targets in either setting. There was also no difference in outcomes when comparing mild hypercapnia to normocapnia. The certainty of evidence was rated as low to moderate.

Conclusions: Among patients resuscitated from cardiac arrest, neither restrictive oxygen targets nor mild hypercapnia, compared to conventional targets, improved survival or functional outcomes.

Keywords: Cardiac arrest, Carbon dioxide, ventilation, Oxygenation, Systematic review, Meta-analysis

Introduction

Survival after cardiac arrest remains poor despite extensive research efforts in post-resuscitation care.[1,2] Mechanical ventilation is often required after return of spontaneous circulation (ROSC) to regulate arterial oxygen and carbon dioxide levels.[3] However, the optimal targets for oxygenation and ventilation in the post-cardiac arrest period remain uncertain.

Abnormal oxygen and carbon dioxide levels may contribute to poor outcomes through multiple pathophysiological mechanisms.[4,5] Hypoxemia may exacerbate global ischemic injury, while hyperoxemia has been associated with increased oxidative stress and reperfusion injury in the post-cardiac arrest period.[6] Similarly, carbon dioxide is a major regulator of cerebral blood flow, with hypocapnia potentially reducing cerebral perfusion, and hypercapnia increasing intracranial pressure by causing cerebral vasodilation.[7]

Current guidelines suggest targeting normoxemia and normocapnia after ROSC, although the evidence supporting this recommendation is limited.[8,9] Since this topic was last addressed by the International Liaison Committee on Resuscitation (ILCOR) in 2020,

* Corresponding author at: Department of Anesthesia and Intensive Care, Palle Juul-Jensens Boulevard 99, Aarhus University Hospital, 8200 Aarhus N, Denmark.

E-mail address: mathias.holmberg@clin.au.dk (M.J. Holmberg), mathias.holmberg@clin.au.dk (M.J. Holmberg).

[1] The members of the International Liaison Committee on Resuscitation Basic Life Support and Advanced Life Support Task Forces are listed in Acknowledgements at the end of the article.

https://doi.org/10.1016/j.resuscitation.2025.110620

Received 17 March 2025; Received in Revised form 12 April 2025; Accepted 13 April 2025

new evidence from randomised trials has become available, warranting an updated systematic review.[10]

The aim of this study was to perform an updated systematic review and *meta*-analysis of oxygen and carbon dioxide targets after cardiac arrest to inform the international cardiac arrest guidelines.

Methods

Protocol and registration

The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) on November 7, 2022 (CRD42022371007). This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[11] The protocol and PRISMA checklist are provided in the Supplement. The review was conducted on behalf of ILCOR.

Eligibility criteria and outcomes

This systematic review is an update of a previous systematic review addressing the same topic in 2020.[10] The specific study question was framed using the PICO (Population, Intervention, Comparison, and Outcome) format: In unresponsive adults (≥18 years) and children (< 18 years) with sustained ROSC after cardiac arrest in any setting (in-hospital or out-of-hospital) (P), does a ventilation strategy targeting a specific peripheral oxygen saturation (SpO_2), partial pressure of arterial oxygen (PaO_2), or partial pressure of arterial carbon dioxide ($PaCO_2$) (I), compared to no specific target or an alternative target (C), change clinical outcomes (O).

Relevant outcomes were selected for review based on the data reported in the literature, including short-term and long-term survival and functional recovery. Outcomes with similar time frames were combined into single categories. A favourable functional outcome was generally defined as a modified Rankin Scale (mRS) of 0–3, a Cerebral Performance Category (CPC) score of 1–2, or a Glasgow Outcome Scale-Extended (GOS-E) score of 5–8, indicating that the patient does not need assistance with activities of daily living.

We included controlled trials in humans, including randomised and non-randomised trials. Observational studies, ecological studies, case series, case reports, reviews, abstracts, editorials, comments, letters to the editor, and unpublished studies were not included. All languages were included if there was an English abstract or full-text article. The previous systematic review by ILCOR included studies published up to August 22, 2019.[10] The current review updates the evidence from that point onward.

Information sources and search strategy

MEDLINE, Embase, and Evidence-Based Medicine Reviews were searched via the Ovid interface for publications since August 22, 2019, with searches performed in each database on October 27, 2022, July 2, 2023, May 14, 2024, and March 7, 2025. The bibliographies of included articles were reviewed for potential additional articles. The search strategy for each database is provided in the protocol.

To identify ongoing registered trials, the International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov were searched on January 20, 2025. Additional details are provided in the Supplement.

Study selection

Two reviewers independently screened all titles and abstracts retrieved from the systematic search. Disagreements regarding inclusion or exclusion were resolved through discussion. A third reviewer was consulted when necessary. Kappa-values were calculated to assess inter-observer agreement as outlined in the protocol. Two reviewers then independently screened the full-text articles of eligible publications passing the screening stage. Disagreements on eligibility were resolved through discussion.

Data collection

Two reviewers independently extracted data from the included studies using a predefined standardized extraction form. Discrepancies in the extracted data were identified and resolved through discussion. Missing statistical parameters and variance measures were calculated if the data permitted.

Risk of bias in individual studies

Two reviewers independently assessed the risk of bias for each included study using version 2 of the Cochrane risk-of-bias tool for randomised trials.[12] Disagreements were resolved through discussion. Bias was assessed for each outcome within individual trials but reported as the highest risk of bias across all outcomes. Additional considerations regarding bias assessments are provided in the Supplement.

Data synthesis

Studies were assessed for clinical (participants, interventions, and outcomes), methodological (study design and risk of bias), and statistical (forest plots, Chi-squared statistics, and I-squared statistics) heterogeneity.[13] DerSimonian and Laird random effects *meta*-analyses with the Mantel Haenszel method were conducted using RevMan version 5.4 (The Cochrane Collaboration, 2020). Results are reported as risk ratios with 95% confidence intervals.

Meta-analyses were performed separately for trials investigating oxygenation or ventilation targets in the prehospital and intensive care unit setting. Pre-specified subgroup analyses were not feasible based on the available data.

Confidence in cumulative evidence

The certainty of evidence for a given comparison and outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology based on trials identified in the previous and present version of the review.[14] GRADEpro (McMaster University, 2020) was used to draft the GRADE tables.

Results

Overview

The search identified 2593 records of which 39 full-text articles were assessed for eligibility (Kappa = 0.84). Eight new manuscripts met the inclusion criteria, adding to the seven manuscripts from the previous version of this systematic review[10], yielding 15 manuscripts representing 12 unique trials published between 2006 and 2024 (eFig. 1). No neonatal or paediatric trials were identified. No additional trial was identified after reviewing the bibliographies of included studies. The search for registered ongoing trials identified three records (eTable 1).

Oxygen targets in the prehospital setting

Five trials investigated oxygen strategies following ROSC in the prehospital setting (Table 1).[15–19] All trials included adult patients with a

Table 1 – Oxygen targets in the prehospital setting.

Study	Inclusion period	Main eligibility criteria	Sample size	Treatment	Control	Treatment duration
Kuisma, 2006[15]	Not reported	OHCA, witnessed, shockable rhythm	28	FiO_2 0.30	FiO_2 1.00	One hour
Young, 2014[16]	2012–2013	OHCA, cardiac cause, shockable rhythm	17	SpO_2 90–94%	SpO_2 > 95%	72 hours
Bray, 2018[17]	2015–2017	OHCA, cardiac cause, shockable rhythm	61	2–4 L/min oxygen	10 L/min oxygen	Until ED arrival
Thomas, 2019[18]	2014–2015	OHCA, non-traumatic cause	35	SpO_2 90–94%	FiO_2 1.00	One hour
Bernard, 2022[19]	2017–2020	OHCA, cardiac cause	426	SpO_2 90–94%	SpO_2 98–100%	Until ICU admission

Abbreviations: OHCA, out-of-hospital cardiac arrest; FiO2, fraction of inspired oxygen; SpO2, peripheral oxygen saturation; ED, emergency department; ICU, intensive care unit.

cardiac arrest of a presumed cardiac cause. A restrictive approach was defined as a target SpO_2 of 90–94%, and the liberal strategy ranged from a target SpO_2 of 98–100% to a fraction of inspired oxygen (FiO_2) of 100. Sample sizes ranged between 17 and 426 patients. One small feasibility trial, which applied the therapy in the prehospital setting and continued in the intensive care unit, was not included in the *meta*-analyses.[16]

Meta-analyses found no difference between a restrictive and liberal oxygen therapy strategies for survival to hospital discharge (4 trials; RR, 0.98; 95%CI, 0.70 to 1.37) or favourable functional outcome at hospital discharge (2 trials; RR, 0.92; 95%CI, 0.70 to 1.21) (Fig. 1). The largest trial reported similar results at 12 months for both survival (RR, 0.82; 95%CI, 0.64 to 1.06) and favourable functional outcome (RR, 0.85; 95%CI, 0.62 to 1.17) between a restrictive and liberal oxygen strategy.[19].

All trials had some risk of bias, primarily due to lack of blinding (eTable 2). The overall certainty of evidence was rated as moderate (eTable 3).

Oxygen targets in the intensive care unit setting

Nine manuscripts representing six trials investigated oxygen strategies after ROSC and intensive care unit admission (Table 2).[16,20–27] The trials included mainly adult patients with out-of-hospital cardiac arrest, except one trial which also included in-hospital cardiac arrests.[21] Targets ranged from an SpO_2 of 88–97% or a PaO_2 of 8–15 kPa (60–113 mmHg) in the restrictive therapy group, and an SpO_2 > 90% or a PaO_2 of 12–25 kPa (90–188 mmHg) in the liberal therapy group. Sample sizes ranged between 17 and 789 patients. One small feasibility trial, which applied the therapy in the prehospital setting and continued in the intensive care unit, was not included in the *meta*-analyses.[16]

Meta-analyses found no difference between a restrictive and liberal oxygen therapy for survival to hospital discharge or 30 days (4 trials; RR, 1.10; 95%CI, 0.95 to 1.27), survival at 3 to 6 months (4 trials; RR, 1.05; 95%CI, 0.92 to 1.20), favourable functional outcome at 3 to 6 months (3 trials; RR, 1.07; 95%CI, 0.96 to 1.20), or survival at 12 months (2 trials; RR, 1.03; 95%CI, 0.93 to 1.14)) (Fig. 2).

All trials had some risk of bias, primarily due to lack of blinding (eTable 2). The overall certainty of evidence was rated as low (eTable 4).

Carbon dioxide targets in the intensive care unit setting

Three trials investigated carbon dioxide strategies after ROSC and intensive care unit admission (Table 3).[20,28,29] Two trials included adult patients with out-of-hospital cardiac arrest of a presumed cardiac cause, whereas one trial also included in-hospital cardiac

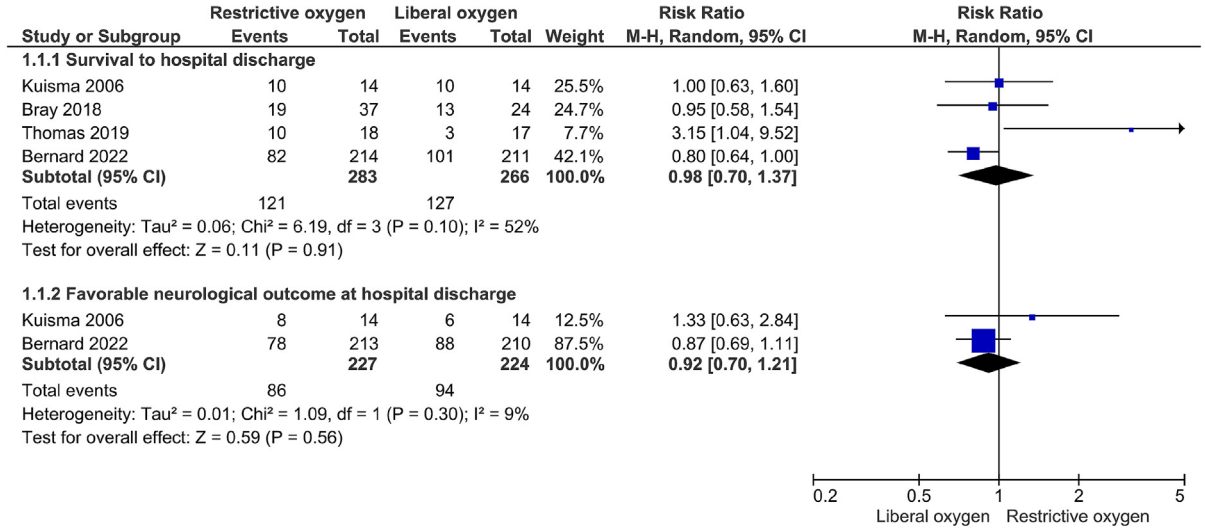

Fig. 1 – Meta-analyses of oxygen targets in the prehospital setting. Random-effects meta-analyses of restrictive compared to liberal oxygen targets after return of spontaneous circulation in the prehospital setting.

Table 2 – Oxygen targets in the intensive care unit setting.

Study	Inclusion period	Main eligibility criteria	Sample size	Treatment	Control	Treatment duration
Young, 2014[16]	2012–2013	OHCA, cardiac cause, shockable rhythm	17	SpO_2 90–94%	SpO_2 > 95%	72 hours
Jakkula, 2018[20]	2016–2017	OHCA, cardiac cause, witnessed, shockable rhythm	120	PaO_2 10–15 kPa	PaO_2 20–25 kPa	36 hours
Young, 2020[21,a]	2015–2018	Subgroup of OHCA/IHCA	166	SpO_2 90–97%	SpO_2 > 90%	Until ICU discharge
Schmidt, 2022[26,b]	2017–2021	OHCA, cardiac cause	789	PaO_2 9–10 kPa	PaO_2 13–15 kPa	Until extubation
Semler, 2022[23]	2018–2021	Subgroup of cardiac arrest	334	SpO_2 88–96%	SpO_2 96–100%	Until ICU discharge
Crescioli, 2023[24,c]	2017–2020	OHCA	335	PaO_2 8 kPa	PaO_2 12 kPa	Up to 90 days

Abbreviations: OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; SpO2, peripheral oxygen saturation; PaO_2, partial pressure of oxygen; ICU, intensive care unit.

[a] Subgroup analysis of the ICU-ROX trial (Mackle, 2020)[25].

[b] Long-term outcomes reported in sub-study (Meyer, 2024)[22].

[c] Subgroup analysis of the HOT-ICU trial (Schjørring, 2021)[27].

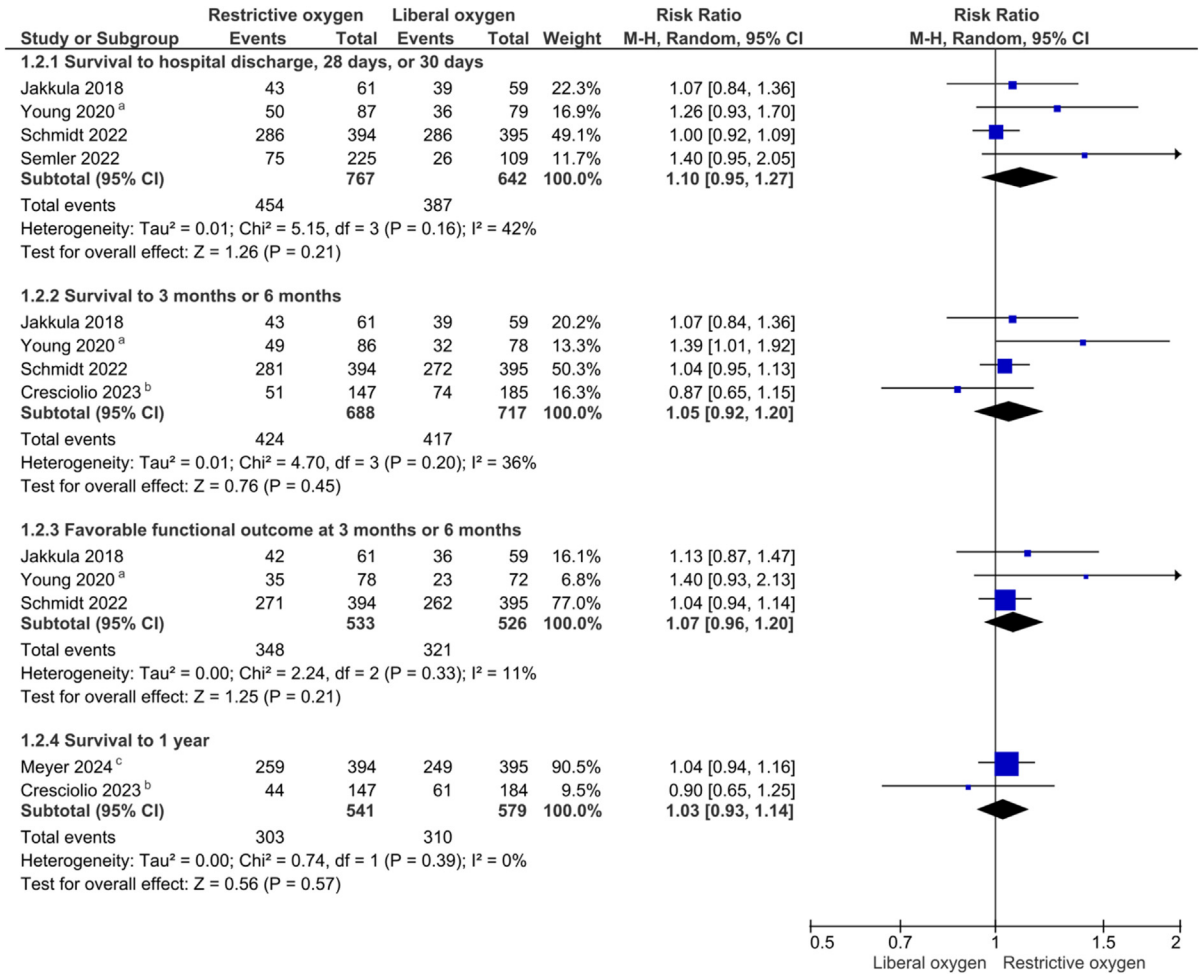

Fig. 2 – Meta-analyses of oxygen targets in the intensive care unit setting. Random-effects meta-analyses of restrictive compared to liberal oxygen targets after return of spontaneous circulation in the intensive care unit setting. [a] Subgroup analysis of the ICU-ROX trial (Mackle, 2020)[25]. [b] Subgroup analysis of the HOT-ICU trial (Schjørring, 2021)[27]. [c] Sub-study reporting long-term outcomes of the BOX trial (Schmidt, 2022)[26].

Table 3 – Carbon dioxide targets in the intensive care unit setting.

Study	Inclusion period	Main eligibility criteria	Sample size	Treatment	Control	Treatment duration
Eastwood, 2016[29]	Not reported	OHCA/IHCA, non-traumatic cause	83	$PaCO_2$ 50–55 mmHg	$PaCO_2$ 35–45 mmHg	24 hours
Jakkula, 2018[20]	2016–2017	OHCA, cardiac cause, witnessed, shockable rhythm	120	$PaCO_2$ 5.8–6.0 kPa	$PaCO_2$ 4.5–4.7 kPa	36 hours
Eastwood, 2023[28]	2018–2021	OHCA, cardiac cause	1700	$PaCO_2$ 50–55 mmHg	$PaCO_2$ 35–45 mmHg	24 hours

Abbreviations: OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; $PaCO_2$, partial pressure of carbon dioxide.

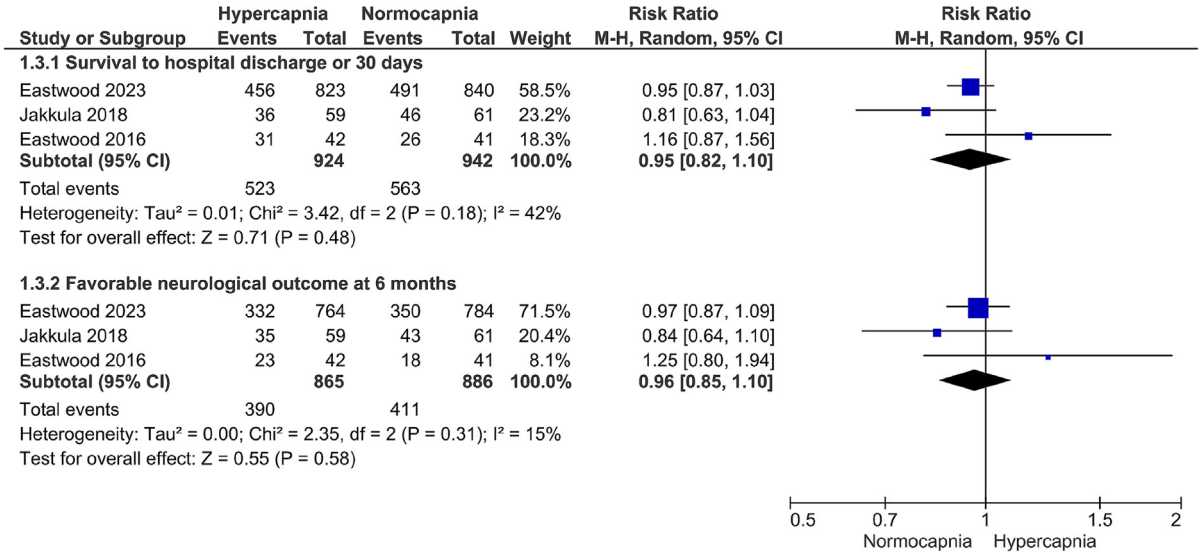

Fig. 3 – Meta-analyses of carbon dioxide targets in the intensive care unit setting. Random-effects meta-analyses of hypercapnia compared to normocapnia targets after return of spontaneous circulation in the intensive care unit setting.

arrests. Targets included a $PaCO_2$ of 6.7–7.3 kPa (50–55 mmHg) or 5.8–6.0 kPa (44–45 mmHg) in the mild hypercapnia group and a $PaCO_2$ of 4.7–6.0 kPa (35–45 mmHg) or 4.5–4.7 kPa (34–35 mmHg) in the normocapnia group. Sample sizes ranged from 83 to 1700 patients. No trials evaluated carbon dioxide strategies in the prehospital setting.

Meta-analyses of these three trials found no difference between mild hypercapnia and normocapnia for survival to hospital discharge or 30 days (RR, 0.95; 95%CI, 0.82 to 1.10) or favourable functional outcome at 6 months (RR, 0.96; 95%CI, 0.85 to 1.10) (Fig. 3). The largest trial reported similar results for 6-month survival (RR, 0.95; 95%CI, 0.88 to 1.05).[28]

All trials had some risk of bias, primarily due to lack of blinding (eTable 2). The overall certainty of evidence was rated as moderate (eTable 5).

Discussion

This systematic review, including 15 manuscripts from 12 randomised trials, provides an update on oxygen and ventilation targets following ROSC in cardiac arrest patients. Meta-analyses did not detect any differences in patient outcomes when comparing restrictive to liberal oxygen targets or mild hypercapnia to normocapnia in the prehospital or intensive care unit settings. The overall certainty of evidence was rated as low to moderate, depending on the outcome, largely due to imprecision in the effect estimates.

Experimental and observational evidence suggest a complex relationship between oxygenation levels and post-cardiac arrest outcomes.[4,5] While hypoxemia directly limits oxygen delivery to vulnerable tissues, hyperoxemia can trigger the formation of reactive oxygen species, leading to oxidative stress, and potential vasoconstriction through altered nitric oxide signaling.[6] Animal models of cardiac arrest have shown that hyperoxemia during the reperfusion phase may exacerbate neuronal injury through these mechanisms.[30,31] Observational data in humans similarly support a U-shaped relationship between PaO_2 levels and outcomes, with both severe hypoxemia and hyperoxemia being associated with increased mortality,[32–37] but this relationship has not been seen in clinical trials.

Translating these findings into clinical targets remains challenging. In the prehospital setting, the Reduction of Oxygen After Cardiac Arrest (EXACT) trial, which is the largest trial conducted in this setting, found a potential signal towards harm of targeting an SpO_2 of 90–94% compared to 98–100% (OR, 0.68; 95%CI, 0.46 to 1.00; P

= 0.05).[19] Although the trial was stopped early due to external factors, these results raise concerns that aiming for a lower SpO_2 range could inadvertently cause harmful episodes of hypoxemia. Other pilot studies in the prehospital setting have hinted at similar risks but had insufficient power to detect any outcome differences or had difficulties ensuring accurate oxygen titration.[15–18] Despite the inconclusive evidence, there is a general agreement that targeting narrow restrictive oxygen targets in the prehospital setting carries a risk of inadvertent hypoxemic injury.[38]

The intensive care unit setting has greater capacity for controlled oxygen titration, yet trials comparing restrictive to liberal oxygen targets have shown neutral results. The largest trial in this setting, the Blood Pressure and Oxygenation Targets in Post Resuscitation Care (BOX) trial, found no difference in survival or favourable functional outcomes when comparing PaO_2 targets of 68–75 mmHg to 98–105 mmHg in patients admitted after out-of-hospital cardiac arrest.[22,26] One possible explanation for these results is that relatively moderate PaO_2 ranges were maintained in both arms, potentially limiting detection of effects that might occur with the more extreme differences in oxygen levels that are generally reported in the observational literature.

The ideal carbon dioxide management strategy remains similarly unresolved despite physiological rationales for mild hypercapnia.[4,5] While hypercapnia could benefit post-cardiac arrest patients through cerebral vasodilation, increased cerebral blood flow, and potential anti-inflammatory effects that may reduce secondary injury, excessive levels could worsen cerebral oedema and increase intracranial pressure.[7] In contrast, hypocapnia may cause vasoconstriction that could exacerbate cerebral ischemia.[34] However, randomised trials have not detected any clear benefits of mild hypercapnia when compared to normocapnia. The largest trial in this area, the Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME) trial, found no differences in mortality or favourable functional outcomes at six months when comparing a $PaCO_2$ target of 50–55 mmHg to 35–45 mmHg.[28] The inconclusive results may reflect an incomplete understanding of the relationship between carbon dioxide levels and cerebrovascular control after cardiac arrest or potential interactions with other physiological parameters. Moreover, these findings suggest that permissive mild hypercapnia is acceptable in post-arrest patients for whom a normal $PaCO_2$ is difficult to achieve without risking lung injury.

From a practical standpoint, several key principles can be derived from the available evidence. Early avoidance of severe hypoxemia appears critical for preventing further ischemic injury, particularly in the prehospital setting where monitoring capabilities are limited, and the risk of targeting lower oxygen levels may outweigh any potential benefits.[38] Within intensive care units, while strictly restrictive oxygen targets have not shown clear benefits, avoiding extreme hyperoxemia seems reasonable given the theoretical rationale and previous observational evidence of harms at these levels.[39]

Our systematic review has several limitations. First, despite comprehensive searches across multiple databases with high inter-rater agreement, we cannot exclude missing relevant trials. Second, while observational studies might have provided additional insights, particularly about patients with more extreme PaO_2 or $PaCO_2$ values, we excluded these studies given the substantial number of published clinical trials and the high risk of bias in the previously identified observational studies. Third, bias assessments are inherently subjective, and other reviewers might have made different decisions about trial inclusion in *meta*-analyses. Fourth, the available trial data did not enable subgroup analyses that might have identified important effect modifiers. Future individual patient data *meta*-analyses could potentially address this limitation. Fifth, most trials did not report details of withdrawal of life-sustaining therapy, meaning some patients could potentially have been withdrawn prematurely and thus masking a true treatment effect.[40] Although the two trials that did report withdrawal of life sustaining data found no differences between groups,[19,28] this lack of information in most trials adds some uncertainty to our findings. Lastly, by design, this systematic review did not evaluate oxygenation or ventilation strategies during cardiac arrest.

Conclusion

This systematic review and *meta*-analysis revealed no significant differences in survival or favourable functional outcomes when comparing restrictive to liberal oxygen targets or mild hypercapnia to normocapnia in adults with sustained ROSC after cardiac arrest. The overall certainty of evidence was rated as low to moderate.

CRediT authorship contribution statement

Mathias J. Holmberg: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Takanari Ikeyama:** Writing – review & editing, Methodology, Conceptualization. **Rakesh Garg:** Writing – review & editing, Methodology, Conceptualization. **Ian R. Drennan:** Writing – review & editing, Methodology, Conceptualization. **Eric J. Lavonas:** Writing – review & editing, Methodology, Conceptualization. **Janet E. Bray:** Writing – review & editing, Methodology, Conceptualization. **Theresa M. Olasveengen:** Writing – review & editing, Methodology, Conceptualization. **Katherine M. Berg:** Writing – review & editing, Visualization, Methodology, Formal analysis, Conceptualization.

Funding

There was no specific funding for this study.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JEB was the lead investigator of the EXACT pilot trial and a co-author of the EXACT trial and was therefore not involved in the bias assessments of those studies.[17,19] JEB, IRD, and TMO are Editorial Board Members of Resuscitation. JEB is an Associate Editor of Resuscitation Plus. JEB (#104751) is funded by a Heart Foundation of Australia Fellowship. None of the remaining authors have any conflicts of interest to report.

Acknowledgements

The following ILCOR Task Force members are acknowledged as collaborators on this review.

Basic Life Support Task Force Members: Michael Smyth, Anthony Lagina, Baljit Singh, Julie Considine, Sung Phil Chung, Vihara Dassanayake, Katie Dainty, Guillaume Debaty, Maya Dewan, Bridget Dicker, Fredrik Folke, George Lukas, Carolina Malta Hansen, Nicholas J. Johnson, Rebecca Cash, Siobhán Masterson, Ziad Nehme, Tatsuya Norii, Violeta Raffay, Aloka Samantaray, Anastasia Spartinou, Giuseppe Ristagno, Christopher M. Smith, Christian Vaillancourt, Frederico Semeraro, Gavin D Perkins.

Advanced Life Support Task Force Members: Markus Skrifvars, Ari Moskowitz, Asger Granfeldt, Brian Grunau, Carolyn Zelop, Helen Pocock, Karen Hirsch, Keith Couper, Nikolaos Nikolaou, Anders Aneman, Shannon Fernando, Shinichiro Ohshimo, Sonai D'Arrigo, Tommas Scquizzato, Yew Woon Chia, Carrie Leong, Conor Crowley, Neville Vlok, Bernd Bottiger, Brian O'Neil, Charles Deakin, Jasmeet Soar, Michael Parr, Michelle Welsford, Peter Kudenchuk, Robert Neumar, Tonia Nicholson, Jerry Nolan.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2025.110620.

Author details

on behalf of theInternational Liaison Committee on Resuscitation Basic Life Support and Advanced Life Support Task Forces[1]

[a]Department of Anesthesiology and Intensive Care, Aarhus University Hospital, Aarhus, Denmark [b]Center for Pediatric Emergency and Critical Care Medicine, Aichi Children's Health and Medical Center, Aichi, Japan [c]Department of Comprehensive Pediatric Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan [d]Department of Onco-Anesthesia and Palliative Medicine, All India Institute of Medical Sciences, New Delhi, India [e]Division of Emergency Medicine, Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada [f]Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada [g]Department of Emergency Services and Sunnybrook Research Institute, Sunnybrook Health Science Centre, Toronto, Ontario, Canada[h]Ornge Air Ambulance And Critical Care Transport, Toronto, ON, Canada [i]Department of Emergency Medicine and Rocky Mountain Poison and Drug Safety, Denver Health, Denver, CO, USA [j]Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA [k]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia [l]Prehospital, Resuscitation and Emergency Care Research Unit, Curtin University, Perth, Australia [m]Institute of Clinical Medicine, University of Oslo, Norway[n]Department of Anesthesia and Intensive Care Medicine, Oslo University Hospital, Norway[o]Center for Resuscitation Science, Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA[p]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

REFERENCES

1. Martin SS, Aday AW, Almarzooq ZI, et al. 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. *Circulation* 2024;149(8):e347–913. https://doi.org/10.1161/CIR.0000000000001209.
2. Gräsner JT, Wnent J, Herlitz J, et al. Survival after out-of-hospital cardiac arrest in Europe - Results of the EuReCa TWO study. *Resuscitation* 2020;148:218–26. https://doi.org/10.1016/j.resuscitation.2019.12.042.
3. Hirsch KG, Abella BS, Amorim E, et al. Critical Care Management of Patients After Cardiac Arrest: A Scientific Statement from the American Heart Association and Neurocritical Care Society. *Neurocrit Care* 2024;40(1):1–37. https://doi.org/10.1007/s12028-023-01871-6.
4. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care 2017;21(1):90. https://doi.org/10.1186/s13054-017-1670-9.
5. Perkins GD, Callaway CW, Haywood K, et al. Brain injury after cardiac arrest. *Lancet* 2021;398(10307):1269–78. https://doi.org/10.1016/S0140-6736(21)00953-3.
6. Thomas A, van Diepen S, Beekman R, et al. Oxygen supplementation and hyperoxia in critically Ill cardiac patients: from pathophysiology to clinical practice. JACC Adv 2022;1(3). https://doi.org/10.1016/j.jacadv.2022.100065.
7. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. *Crit Care* 2010;14(2):220. https://doi.org/10.1186/cc8926.
8. Panchal AR, Bartos JA, Cabañas JG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2020;142(16_suppl_2):S366–446. https://doi.org/10.1161/CIR.0000000000000916.
9. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. *Intensive Care Med* 2021;47(4):369–421. https://doi.org/10.1007/s00134-021-06368-4.
10. Holmberg MJ, Nicholson T, Nolan JP, et al. Oxygenation and ventilation targets after cardiac arrest: A systematic review and meta-analysis. *Resuscitation* 2020;152:107–15. https://doi.org/10.1016/j.resuscitation.2020.04.031.
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n71. https://doi.org/10.1136/bmj.n71.
12. Higgins J, Sterne J, Savović J, et al. *A revised tool for assessing risk of bias in randomized trials*. 2016, Issue 10 (Suppl 1). *Cochrane Methods*.
13. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. Available from: www.handbook.cochrane.org.
14. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924–6. https://doi.org/10.1136/bmj.39489.470347.AD.
15. Kuisma M, Boyd J, Voipio V, Alaspää A, Roine RO, Rosenberg P. Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study. *Resuscitation* 2006;69(2):199–206. https://doi.org/10.1016/j.resuscitation.2005.08.010.
16. Young P, Bailey M, Bellomo R, et al. HyperOxic Therapy OR NormOxic Therapy after out-of-hospital cardiac arrest (HOT OR NOT): a randomised controlled feasibility trial. *Resuscitation* 2014;85(12):1686–91. https://doi.org/10.1016/j.resuscitation.2014.09.011.
17. Bray JE, Hein C, Smith K, et al. Oxygen titration after resuscitation from out-of-hospital cardiac arrest: A multi-centre, randomised controlled pilot study (the EXACT pilot trial). *Resuscitation* 2018;128:211–5. https://doi.org/10.1016/j.resuscitation.2018.04.019.

18. Thomas M, Voss S, Benger J, Kirby K, Nolan JP. BMC Emerg Med 2019;19(1):16. https://doi.org/10.1186/s12873-018-0214-1.
19. Bernard SA, Bray JE, Smith K, et al. Effect of Lower vs Higher Oxygen Saturation Targets on Survival to Hospital Discharge Among Patients Resuscitated After Out-of-Hospital Cardiac Arrest: The EXACT Randomized Clinical Trial. *JAMA* 2022;328(18):1818–26. https://doi.org/10.1001/jama.2022.17701.
20. Jakkula P, Reinikainen M, Hästbacka J, et al. Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial. *Intensive Care Med* Dec 2018;44(12):2112–21. https://doi.org/10.1007/s00134-018-5453-9.
21. Young P, Mackle D, Bellomo R, et al. Conservative oxygen therapy for mechanically ventilated adults with suspected hypoxic ischaemic encephalopathy. *Intensive Care Med* 2020;46(12):2411–22. https://doi.org/10.1007/s00134-020-06196-y.
22. Meyer MAS, Hassager C, Mølstrøm S, et al. Combined effects of targeted blood pressure, oxygenation, and duration of device-based fever prevention after out-of-hospital cardiac arrest on 1-year survival: post hoc analysis of a randomized controlled trial. Crit Care 2024;28(1):20. https://doi.org/10.1186/s13054-023-04794-y.
23. Semler MW, Casey JD, Lloyd BD, et al. Oxygen-saturation targets for critically ill adults receiving mechanical ventilation. *N Engl J Med*. 2022;387(19):1759–69. https://doi.org/10.1056/NEJMoa2208415.
24. Crescioli E, Lass Klitgaard T, Perner A, Lilleholt Schjørring O, Steen RB. Lower versus higher oxygenation targets in hypoxaemic ICU patients after cardiac arrest. *Resuscitation* 2023;188:109838. https://doi.org/10.1016/j.resuscitation.2023.109838.
25. Mackle D, Bellomo R, Bailey M, et al. Conservative oxygen therapy during mechanical ventilation in the ICU. *N Engl J Med* 2020;382 (11):989–98. https://doi.org/10.1056/NEJMoa1903297.
26. Schmidt H, Kjaergaard J, Hassager C, et al. Oxygen targets in comatose survivors of cardiac arrest. *N Engl J Med* 2022;387 (16):1467–76. https://doi.org/10.1056/NEJMoa2208686.
27. Schjørring OL, Klitgaard TL, Perner A, et al. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med* 2021;384(14):1301–11. https://doi.org/10.1056/NEJMoa2032510.
28. Eastwood G, Nichol AD, Hodgson C, et al. Mild hypercapnia or normocapnia after out-of-hospital cardiac arrest. *N Engl J Med* 2023;389(1):45–57. https://doi.org/10.1056/NEJMoa2214552.
29. Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: A phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation* 2016;104:83–90. https://doi.org/10.1016/j.resuscitation.2016.03.023.
30. Pilcher J, Weatherall M, Shirtcliffe P, Bellomo R, Young P, Beasley R. The effect of hyperoxia following cardiac arrest - A systematic review and meta-analysis of animal trials. *Resuscitation* 2012;83 (4):417–22. https://doi.org/10.1016/j.resuscitation.2011.12.021.
31. Okuma Y, Becker LB, Hayashida K, et al. Effects of post-resuscitation normoxic therapy on oxygen-sensitive oxidative stress in a rat model of cardiac arrest. J Am Heart Assoc 2021;10(7) e018773. https://doi.org/10.1161/JAHA.120.018773.
32. Awad A, Nordberg P, Jonsson M, et al. Hyperoxemia after reperfusion in cardiac arrest patients: a potential dose-response association with 30-day survival. Crit Care 2023;27(1):86. https://doi.org/10.1186/s13054-023-04379-9.
33. Sanfilippo F, Uryga A, Santonocito C, et al. Effects of very early hyperoxemia on neurologic outcome after out-of-hospital cardiac arrest: A secondary analysis of the TTM-2 trial. Resuscitation 2024110460. https://doi.org/10.1016/j.resuscitation.2024.110460.
34. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, Abu-Hanna A, de Keizer NF, de Jonge E. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. Crit Care 2015;19:348. https://doi.org/10.1186/s13054-015-1067-6.
35. Mckenzie N, Finn J, Dobb G, et al. Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study. *Resuscitation* 2021;158:130–8. https://doi.org/10.1016/j.resuscitation.2020.11.021.
36. Wang HE, Prince DK, Drennan IR, et al. Post-resuscitation arterial oxygen and carbon dioxide and outcomes after out-of-hospital cardiac arrest. *Resuscitation* 2017;120:113–8. https://doi.org/10.1016/j.resuscitation.2017.08.244.
37. Robba C, Badenes R, Battaglini D, et al. Oxygen targets and 6-month outcome after out of hospital cardiac arrest: a pre-planned sub-analysis of the targeted hypothermia versus targeted normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial. Crit Care 2022;26(1):323. https://doi.org/10.1186/s13054-022-04186-8.
38. Elmer J, Guyette FX. Early oxygen supplementation after resuscitation from cardiac arrest. *JAMA* 2022;328(18):1811–3. https://doi.org/10.1001/jama.2022.18620.
39. Klemisch R, Nichol G. Post resuscitation oxygen supplementation: Throw it away?. Resuscitation 2025;207:110485. https://doi.org/10.1016/j.resuscitation.2024.110485.
40. Elmer J, Coppler PJ, Ratay C, et al. Recovery potential in patients after cardiac arrest who die after limitations or withdrawal of life support. JAMA Netw Open 2025;8(3)e251714. https://doi.org/10.1001/jamanetworkopen.2025.1714.