Editorial

Oxygenation in post-resuscitation care—how much is too much?

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From pathophysiology to bedside

Despite continuous advances in patient care, both neurologic and psychologic disability after cardiac arrest (CA) still remain dismal with hypoxic brain injury as the main determinant [primary cause of death in 68% of in-hospital CA and 23% of out-of-hospital CA (OHCA)] (1). Pathophysiological explanations of this "post-CA syndrome", such as the "two-hit-model" suggest the release of reactive oxygen species during resuscitative attempts resulting in an imbalance of endogenous antioxidants and free radicals (1). This, in the following, leads to oxidative stress in cellular structures, and contributes to deleterious cell dysfunction and apoptosis induction (1,2). Reactive vasoconstriction of cerebral vessels triggered by hyperoxia further aggravates both, ischemia and reperfusion injuries (3).

Aside of brain injury, hyperoxia proved to contribute to the development of ventilator-associated lung injury, pulmonary edema and systemic inflammatory response, subsequently impacting on the prognosis of this high-risk patient population (4). Facing the potential adverse effects of over-oxygenation during post-resuscitation management on the one, and the need for intermittent hyperoxia (e.g., ventilation with FiO_2 1.0) in critical care on the other hand, the question of "how much" oxygen is "too much" oxygen needs to be answered.

The controversy

While there is no reliable data on optimal arterial blood oxygen saturation (SaO_2) during cardiopulmonary resuscitation (CPR), immediate post-CA care covers a strict treatment approach aiming for normal arterial partial pressure of carbon dioxide ($paCO_2$) and an SaO_2 of 94–98% (5-7). Whereas hypoxemia and hypercapnia both increase the likelihood of recurrent CA (CA) and even may contribute to secondary brain injury, a balance between avoiding hypoxemia and titrating oxygen to an SaO_2 between 94–98% is a dedicated treatment goal in current guidelines (8). However, an abundant load of questionable and controversial evidence gained from mostly retrospective data poses treatment recommendations on a considerably low level of evidence (2).

In this regard, recent investigations indicated that the administration of 100% oxygen proved to be associated with poor neurological outcome in CA animal models. However, due to limitations in study design and poor generalizability to human post-resuscitation care, the clinical applicability of those findings remains uncertain (9). A recent meta-analysis observed a strong and direct association of hyperoxia during post-resuscitation care and in-hospital mortality (10). Interestingly, Ihle and co-workers found that hyperoxia within the first 24 hours after reaching a return of spontaneous circulation (ROSC) lost its predictive potential in patients admitted to an intensive care unit (ICU) following out-of-hospital ventricular fibrillation. Those results subsequently launched the debate of the applicability as a prognosticator in the general CA population (11). In this regard, hyperoxia has also been found to have negative effects on outcomes in various subgroups of ICU patients such as individuals suffering from traumatic brain injury or ischemic stroke (12,13).

Of alarming importance, a hyperoxia after ROSC might be a more common incidence than expected, with a prevalence of up to 40% during the first 48 hours after CA (14). To add to the uncertainty, it remains unclear whether: (I) hyperoxia during the first minutes after ROSC might be acceptable; (II) short period of hyperoxia has the same impact on poor outcome as long-term exposure and (III) which time point of blood gas sampling provides the highest discriminatory power and strongest prognostic value on patient outcome (15,16).

New prospective data

Most evidence regarding hyperoxic injury during post-ROSC care originate from heterogeneous observational studies with inconsistent results, potentially biased by relying on non-standardized blood gas analyses (3).

Based on this gap of knowledge, Roberts and coworkers performed a multi-center prospective cohort study of 280 patients in order to clarify the impact of early post-ROSC hyperoxia on neurological outcome at hospital discharge. Of note, the authors defined neurological outcome by the modified Rankin Scale (mRS) (7). This approach may hold considerable advantages over the standardly measured Cerebral Performance Category (CPC) which was recently challenged whether it should depict the gold-standard measurement of neurological performance after CA (17). This—in comparison to other studies—might allow veritable and in-depth conclusions on neurological function after CA.

The authors followed a protocol with predefined blood gas analyses at baseline and six hours post ROSC and defining hyperoxia as >300 mmHg PaO_2. They were able to demonstrate that hyperoxia was independently associated with poor neurological function, showing a 3% increase of risk for poor outcome per hour of hyperoxia. Only a poor correlation between PaO_2 and SaO_2 (r =0.23) as well as PaO_2 and FiO_2 (r =0.27) was found. Additionally, SaO_2 could not reliably rule out exposure to hyperoxia. This might indicate a potential pitfall in current patient care, as the patient's oxygenation is most commonly monitored by pulse oximetry and only inconsistently reassured via blood gas analyses.

Moreover, FiO_2 [odds ratio (OR) 1.08; 95% CI, 1.05–1.11] and positive end-expiratory pressure (PEEP) (OR 0.83; 95% CI, 0.70–0.97) were independent predictors of hyperoxia at both baseline and 6 hours post ROSC. Considering those results, an elevated PEEP might represent a marker for patients being more difficult to oxygenate and being less likely to develop hyperoxia. Of note, brain injury was a major cause of death in their analysis, fostering the assumption that early hyperoxia-induced neurologic injury mirrors the main determinant of mortality in this high-risk patient population.

Conclusion and future perspectives

Roberts and colleagues were able to support the recommendations of current guidelines to avoid prolonged exposure to hyperoxia, and most importantly demonstrate that hyperoxic brain injury is clearly dependent of the duration of hyperoxic exposure (7). Furthermore, SaO_2 and PaO_2 are possibly not accurate enough to estimate tissue oxygen delivery, particularly in situations of decreased cerebral blood flow. Therefore, regional cerebral tissue oxygenation saturation (rSO_2) monitoring conducted by near-infrared-spectroscopy (NIRS) could provide real-time data on the situation of brain oxygenation during CPR and the post-ROSC-period (18). Since NIRS is an emerging technology yet to be fully established, it recently showed promising potential in predicting outcomes after CA (5). Therefore, this diagnostic tool might add discriminatory power in being part of a multimodal approach in post-ROSC prognostication (19,20). For instance, the exact period of time in which hyperoxia might be tolerable remains unclear—a research question that could potentially be answered by NIRS technology (15).

A general recommendation to avoid hyperoxia following CA may be too imprecise, as it does not fully consider the different stages of post-CA treatment, or facing the situation of the preclinical setting of OHCA. Further studies to investigate oxygen exposure at different time intervals of critical care attempts or specific CA-related subpopulations (e.g., shockable *vs.* non-shockable rhythms), as well targeting specific cut-offs values are needed (7,15).

In this regard, the ongoing Reoxygenation After Cardiac Arrest II (REOX II; NCT02698826) trial is currently investigating a protocol for FiO_2-optimization in mechanically ventilated post-CA patients with the therapeutic goal of PaO_2 of 60–99 mmHg (based on the target-range that was previously identified by the authors to be associated with the lowest risk of poor outcome). Results are expected in mid-2018, hopefully adding new, conclusive data to the existing portion.

Facing the potential weaknesses of pulse oximetry measurements, early initial and subsequent arterial blood gas sampling in patients after ROSC has to be considered to guide PaO_2 adjustments. For now, current guidelines provide a safe, do-no-harm approach of oxygen titration that should

be followed until an ultimate maximum of 300 mmHg PaO_2.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care 2017;21:90.
2. Sandroni C, D'Arrigo S. Management of oxygen and carbon dioxide pressure after cardiac arrest. Minerva Anestesiol 2014;80:1105-14.
3. Hafner S, Beloncle F, Koch A, et al. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. Ann Intensive Care 2015;5:42.
4. Pannu SR. Too Much Oxygen: Hyperoxia and Oxygen Management in Mechanically Ventilated Patients. Semin Respir Crit Care Med 2016;37:16-22.
5. Soar J, Nolan JP, Böttinger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. Resuscitation 2015;95:100-47.
6. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S465-82.
7. Roberts BW, Kilgannon JH, Hunter BR, et al. Association Between Early Hyperoxia Exposure After Resuscitation From Cardiac Arrest and Neurological Disability: Prospective Multicenter Protocol-Directed Cohort Study. Circulation 2018;137:2114-24.
8. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med 2015;41:2039-56.
9. Pilcher J, Weatherall M, Shirtcliffe P, et al. The effect of hyperoxia following cardiac arrest - A systematic review and meta-analysis of animal trials. Resuscitation 2012;83:417-22.
10. Wang CH, Chang WT, Huang CH, et al. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. Resuscitation 2014;85:1142-8.
11. Ihle JF, Bernard S, Bailey MJ, et al. Hyperoxia in the intensive care unit and outcome after out-of-hospital ventricular fibrillation cardiac arrest. Crit Care Resusc 2013;15:186-90.
12. Helmerhorst HJ, Roos-Blom MJ, Van Westerloo DJ, et al. Association Between Arterial Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Meta-Analysis, and Meta-Regression of Cohort Studies. Crit Care Med 2015;43:1508-19.
13. 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.
14. Nelskylä A, Parr MJ, Skrifvars MB. Prevalence and factors correlating with hyperoxia exposure following cardiac arrest - an observational single centre study. Scand J Trauma Resusc Emerg Med 2013;21:35.
15. Christ M, Von Auenmueller KI, Brand M, et al. Hyperoxia Early After Hospital Admission in Comatose Patients with Non-Traumatic Out-of-Hospital Cardiac Arrest. Med Sci Monit 2016;22:3296-300.
16. 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.
17. Sulzgruber P, Kliegel A, Wandaller C, et al. Survivors of cardiac arrest with good neurological outcome show considerable impairments of memory functioning. Resuscitation 2015;88:120-5.
18. Llitjos JF, Mira JP, Duranteau J, et al. Hyperoxia toxicity after cardiac arrest: What is the evidence? Ann Intensive Care 2016;6:23.
19. Genbrugge C, Eertmans W, Meex I, et al. What is the value of regional cerebral saturation in post-cardiac arrest patients? A prospective observational study. Crit Care 2016;20:327.
20. Schnaubelt S, Sulzgruber P, Menger J, et al. Regional cerebral oxygen saturation during cardiopulmonary resuscitation as a predictor of return of spontaneous circulation and favourable neurological outcome - A review of the current literature. Resuscitation 2018;125:39-47.

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