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EDITORIAL

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Hyperoxia following cardiac arrest

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In all manner of acute severe illnesses, oxygen therapy has long been consider as, at worst, harmless, and at best, simple, cheap and highly efficacious. However, there is a large body of accumulating evidence to suggest that hyperoxia is harmful and that mild hypoxaemia may, in fact, be beneficial [1]. At a cellular level, susceptibility to oxygen toxicity appears to be greatest during early reperfusion following ischaemia. Indeed, while our tissues and cells have extensive adaptive mechanisms to hypoxaemia (not least in stimulating local increases in perfusion), they have limited protection from, or adaptation to, hyperoxia.

In all but neonates, hyperoxia is the standard of care both during advanced cardiopulmonary resuscitation (CPR) and in the immediate period (minutes to hours) following the return of spontaneous circulation (RoSC). Over recent years, this dogma has started to be questioned in light of emerging, though somewhat equivocal, evidence from both animal models [2] and retrospective analyses of cardiac arrest registries [3] which suggest an association between the degree and cumulative exposure to hyperoxia, and both short-term mortality and worse neurological outcomes in survivors. Crucially, hyperoxia is frequently accompanied by hyperventilation with consequent and injurious, hypocapnia [4, 5]. Thus, there is biological plausibility for the concept that cardiac arrest and current resuscitation practice subjects patients to a two-hit injury model made worse by hyperoxia (Table 1).

In an attempt to further inform this debate, in an article recently published in *Intensive Care Medicine*, Elmer and colleagues [6] presented a detailed and complex, retrospective statistical analysis of a comprehensive database of post-cardiac arrest patients from a single specialist institution in the US. Their principal and novel aim was to establish the strength of the association between the estimated cumulative exposure to hyperoxia in the first 24 h post-RoSC and three early outcome variables: survival to acute (first) hospital discharge, a basic measure of cognitive function in survivors at (first) hospital discharge, and the severity of multiple organ dysfunction at 24 h following RoSC. Their analysis warrants careful consideration, as not only do they attempt to account for a number of the confounding variables associated with their chosen outcomes but their central tenant of considering cumulative exposure to hyperoxia raises a number of challenging hypotheses.

The data were collected over an 18-month period spanning 2008–2010. The authors screened 232 patients and analysed the data from 184, after excluding those who died in <24 h, those who never required mechanical ventilation or in whom it was discontinued in <24 h, and those with incomplete cardiac arrest data. Forty-three percent of the patients had suffered their cardiac arrest whilst in hospital and 38 % had an initial shockable rhythm. Sixty-six percent received targeted temperature management to 33 °C for the first 24 h.

The authors report that 36 % of their patients were exposed to "severe hyperoxia" (defined by them as a PaO_2 > 300 mmHg) with a mean exposure of 1.4 ± 2.2 h.

Table 1 Theoretical timeline of hypoxic–ischaemic and hyperoxic–reperfusion cellular injury following cardiac arrest

Timeline	PaO_2	CaO_2	DO_2	VO_2	Vasomotor tone	Cellular O_2	Comments
Cardiac arrest	↓	↓	0	↓	Dilated	↓	Assuming sudden cardiogenic aetiology
Chest compressions	Low	Low	Low	Low	Dilated	Low	**First hit:** hypoxic–ischaemic injury
ALS CPR (FiO_2 1.0)	**High**	↑	Low	Low	Constricted (epinephrine hyperoxia hypocapnia)	Low	
RoSC (FiO_2 1.0)	**High**	**Normal**	Normal	High	Constricted	↑	**Second hit:** reperfusion injury exacerbated by vasoconstriction and increased susceptibility to O_2 toxicity
Early post RoSC (FiO_2 1.0)	**High**	**Normal**	Normal	Normal	Constricted	High	
Later post-RoSC	Normal	Normal	Normal	Normal	Normal	Normal	Necrosis, apoptosis and cellular survivors. The latter regain oxidative protection though whether at a diminished, normal or an enhanced level is unknown and probably heterogeneous

Bold highlights the discrepancy between PaO_2, which is principally determined by FiO_2, and CaO_2, which is principally determined by haemoglobin concentration and oxygen saturation

CaO_2 arterial blood oxygen content, *DO_2* global oxygen delivery, *VO_2* global oxygen consumption, *ALS CPR* advanced life support cardiopulmonary resuscitation, *FiO_2* fraction of inspired oxygen, *RoSC* return of spontaneous circulation, ↓ = falling; ↑ = rising

Though it is worth noting that exposure during and in the immediate aftermath of CPR was not included in the analysis; only 43 % of patients had an arterial blood gas analysis in the first hour, and 100 % of patients were receiving a fraction of inspired oxygen of 1.0. Severe hyperoxia was associated with a statistically significant, higher risk of in-hospital mortality in both unadjusted and adjusted analyses. However, it was not associated with early, poorer neurological outcome in survivors. As regards severity of multiple organ dysfunction at 24 h, exposure to "moderate or probable hyperoxia" (defined as PaO_2 101–299 mmHg) was associated with lower SOFA scores than either severe hyperoxia, normoxia or hypoxia. However, it is worth noting that the number of patients in the normoxia and hypoxia categories appears to have been small. Furthermore, the most recent international resuscitation guidelines [7] state, "As soon as the arterial blood oxygen saturation can be measured reliably, by pulse oximeter (SpO_2) or arterial blood gas analysis, titrate the inspired oxygen concentration to achieve an arterial blood oxygen saturation in the range of 94–98 %." On the basis of their analyses, the authors concluded that they consider there to be sufficient equipoise for a randomised control trial of normoxia verses moderate hyperoxia post-cardiac arrest.

There are other important limitations in this study. Data regarding well-established factors that affect the outcome variables chosen are not presented. These include: pre-arrest co-morbidities [8]; the cause of the cardiac arrest (specifically cardiogenic verses non-cardiogenic, though initial cardiac rhythm is accounted for and can be considered as a surrogate for this variable); the time from cardiac arrest to first effective CPR and the duration of CPR (time from arrest to RoSC) [9, 10]; the cumulative dose of epinephrine (higher cumulative doses are associated with worse neurological outcome [11]); arterial carbon dioxide data [4, 5]; and the proportion of patients who underwent emergency coronary angiography, with or without intervention [12].

Interpretation of their data is also hampered by the lack of any data on (first) hospital length of stay. In particular, the incidence of "good" neurological outcome (cerebral performance score 1 or 2) at this time point is reported as 5.5 %, which is much lower than larger prospective datasets (15–47 %) [13, 14], albeit that the latter are assessed at 6 months or 1 year.

It is often said that optimal critical care is about attention to detail. Potential and radical innovation in the conduct of advanced CPR is emerging [15, 16] whilst ongoing trials are challenging long-held beliefs and practices (http://www.controlled-trials.com/ISRCTN73485024/). To add to these, we would argue that there is persuasive evidence to conduct trials of advanced CPR using an FiO_2 of 0.21 and aiming for normoxia and mild hypercabia both during CPR and following RoSC, an approach that has already been successfully piloted [17].

Conflicts of interest The authors declare that they have no competing interests.

References

1. Martin DS, Grocott MP (2013) Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med 41:423–432
2. Pilcher J, Weatherall M, Shirtcliffe P, Bellomo R, Young P, Beasley R (2011) The effect of hyperoxia following cardiac arrest—a systematic review and meta-analysis of animal trials. Resuscitation 83:417–422
3. Wang CH, Chang WT, Huang CH, Tsai MS, Yu PH, Wang AY, Chen NC, Chen WJ (2014) The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. Resuscitation 85:1142–1148
4. Vaahersalo J, Bendel S, Reinikainen M, Kurola J, Tiainen M, Raj R, Pettila V, Varpula T, Skrifvars MB (2014) Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. Crit Care Med 42:1463–1470
5. Eastwood GM, Young PJ, Bellomo R (2014) The impact of oxygen and carbon dioxide management on outcome after cardiac arrest. Curr Opin Crit Care 20:266–272
6. Elmer J, Scutella M, Pullalarevu R, Wang B, Vaghasia N, Trzeciak S, Rosario-Rivera BL, Guyette FX, Rittenberger JC, Dezfulian C (2015) The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database. Intensive Care Med 41:49–57. doi:10.1007/s00134-014-3555-6
7. Nolan JP, Soar J, Zideman DA, Biarent D, Bossaert LL, Deakin C, Koster RW, Wyllie J, Bottiger B (2010) European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. Resuscitation 81:1219–1276
8. Ebell MH, Afonso AM (2011) Pre-arrest predictors of failure to survive after in-hospital cardiopulmonary resuscitation: a meta-analysis. Fam Pract 28:505–515
9. Sasson C, Rogers MA, Dahl J, Kellermann AL (2010) Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 3:63–81
10. Bougouin W, Lamhaut L, Marijon E, Jost D, Dumas F, Deye N, Beganton F, Empana JP, Chazelle E, Cariou A, Jouven X (2014) Characteristics and prognosis of sudden cardiac death in greater Paris. Intensive Care Med 40:846–854
11. Callaway CW (2013) Epinephrine for cardiac arrest. Curr Opin Cardiol 28:36–42
12. Zanuttini D, Armellini I, Nucifora G, Grillo MT, Morocutti G, Carchietti E, Trillo G, Spedicato L, Bernardi G, Proclemer A (2013) Predictive value of electrocardiogram in diagnosing acute coronary artery lesions among patients with out-of-hospital-cardiac-arrest. Resuscitation 84:1250–1254
13. Vaahersalo J, Hiltunen P, Tiainen M, Oksanen T, Kaukonen KM, Kurola J, Ruokonen E, Tenhunen J, Ala-Kokko T, Lund V, Reinikainen M, Kiviniemi O, Silfvast T, Kuisma M, Varpula T, Pettila V (2013) Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. Intensive Care Med 39:826–837
14. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Aneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Kober L, Langorgen J, Lilja G, Moller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H (2013) Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 369:2197–2206
15. Yannopoulos D, Segal N, McKnite S, Aufderheide TP, Lurie KG (2012) Controlled pauses at the initiation of sodium nitroprusside-enhanced cardiopulmonary resuscitation facilitate neurological and cardiac recovery after 15 mins of untreated ventricular fibrillation. Crit Care Med 40:1562–1569
16. Yannopoulos D, Segal N, Matsuura T, Sarraf M, Thorsgard M, Caldwell E, Rees J, McKnite S, Santacruz K, Lurie KG (2013) Ischemic post-conditioning and vasodilator therapy during standard cardiopulmonary resuscitation to reduce cardiac and brain injury after prolonged untreated ventricular fibrillation. Resuscitation 84:1143–1149
17. Kuisma M, Boyd J, Voipio V, Alaspaa A, Roine RO, Rosenberg P (2006) Comparison of 30 and the 100 % inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study. Resuscitation 69:199–206