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Editorial

Delivering oxygen after cardiac arrest — A breath of life or death?

Hypoxic ischaemic encephalopathy is the main determinant of outcome following cardiac arrest with around two-thirds of deaths attributed to devastating neurological injury.[1] While the detrimental effects of hypoxaemia are well established the implications of variable degrees of hyperoxaemia following restoration of circulation remain a matter of debate. Hyperoxaemia may contribute to neuronal damage by increased production of reactive oxygen species leading to lipid peroxidation of cell membranes and increased intracellular oxidative stress with protein oxidation and apoptosis.[2,3] In addition, cerebral vasoconstriction, reduced cerebral blood flow, seizures and increased levels of biomarkers for neuronal damage[4] as well as increased myocardial injury[5] have been associated with hyperoxaemia.[6] A recent systematic review and meta-analysis reported lower mortality with intra-arrest hyperoxaemia but increased mortality with post-arrest hyperoxaemia.[7] The evidence is overall limited by many small study cohorts, overwhelmingly retrospective, observational study designs, heterogeneous study populations including both in-hospital and out-of-hospital cardiac arrest and variability in post-resuscitation care such as utilisation of hypothermia and revascularisation procedures.

Current guidelines recommend that the maximal feasible inspired oxygen concentration is used during cardiopulmonary resuscitation and that the inspired oxygen concentration is titrated to maintain an arterial blood oxygenation in the range of 94–98% as soon as it can be monitored reliably.[8,9]

The retrospective cohort study by Humaloja et al. in this issue of Resuscitation[10] included both out-of-hospital and in-hospital adult cardiac arrest patients admitted to Helsinki University Hospital between 2005 and 2013. The associations between the arterial partial pressure of oxygen (PaO_2) on the first recorded blood gas analysis obtained within two hours of return of spontaneous circulation and the neurological outcome and mortality one year later were investigated by multivariable logistic regression. Similar to earlier studies, severe hyperoxaemia was defined as a PaO_2 above 40 kPa (300 mmHg) and in addition the authors investigated any associations with moderate hyperoxaemia (PaO_2 16–40 kPa, 120–300 mmHg), normoxaemia (8–16 kPa, 60–120 mmHg) and hypoxaemia ($<$8 kPa, 60 mmHg). A total of 1100 patients, using imputation for missing data (an aggregate proportion of 14% across all data variables), were analysed of which 11% had severe hyperoxaemia and 37% moderate hyperoxaemia. In the adjusted analyses the odds ratio and its 95% confidence interval for poor neurological outcome (Cerebral Performance Category 3–5) compared to normoxaemia was 0.89 (95% CI 0.56–1.42), for severe hyperoxaemia and 1.07 (0.80–1.45) for moderate hyperoxaemia. The corresponding odds ratios for mortality were 0.76 (0.45–1.24) and 0.94 (0.69–1.27) for severe and moderate hyperoxaemia, respectively. The lack of associations between hyperoxaemia and neurological outcome remained after testing for interactions with co-variates such as type of initial rhythm, location of cardiac arrest and time to return of spontaneous circulation. The authors concluded that there was no association between short-term early hyperoxaemia and long-term outcomes.

The study by Humaloja et al. is based on a large cohort with uniform treatment algorithms including target temperature management at 32–34 °C. Notwithstanding, it arguably suffers from the same limitations as many previous investigations including a registry based, retrospective design with heterogeneous causes and circumstances for cardiac arrest at a single institution. The adverse effects of hyperoxaemia arise from increased oxidative cellular stress that relates to the oxygen concentration. Whether short but transient severe hyperoxaemia in the immediate post-resuscitation period carries the same relevance as prolonged but extended moderate hyperoxaemia following admission to the intensive care unit is unclear. In the systematic review by Patel et al. the timing of arterial blood gas analyses spanned a wide time period with most studies focusing on the first 24 h.[7] In an exploratory substudy of the Target Temperature Management trial, Ebner et al. investigated the association between hyperoxaemia (progressive oxygen and time-weighted oxygen levels and maximum oxygen difference) over the first 37 h following return of spontaneous circulation in 869 out-of-hospital cardiac arrest patients, starting at admission to hospital.[11] No association was found between hyperoxaemia and poor neurological outcome (Cerebral Performance Category 3–5) six months after cardiac arrest. An observational, prospective study with protocolised time points for arterial blood gas sampling at one and six hours following return of spontaneous circulation after in- and out-of-hospital cardiac arrest was recently reported.[12] Data on mechanical ventilation, inspired oxygen fraction and arterial oxygen saturation were also collected and allowed for time-weighted variables to be evaluated for the first six hours. The study cohort comprised 280 patients and demonstrated an association between hyperoxaemia above PaO_2 $>$40 kPa/300 mmHg and poor neurological outcome (modified Rankin Scale $>$3, i.e. range between moderate severe disability to death) with a 3% increased risk for every hour of hyperoxaemia.

The conflicting evidence for the association between hyperoxaemia and patient centred, clinical outcomes illustrate the need for more rigorously conducted studies with prospective experimental

designs in more homogenous populations and separating pre-hospital versus in-hospital oxygen delivery and targets. Study enrolment and titration of oxygen in the pre-hospital setting pose significant challenges. While a previous study questioned the feasibility,[13] the PROXY[14] and EXACT[15] protocols show promise to conduct such much needed studies.

The delivery of oxygen to sustain brain function is determined not only by oxygen levels but also by perfusion pressure and vascular resistance, influenced by mean arterial pressure and carbon dioxide levels, as governed by cerebrovascular autoregulatory capacity. The author's research group has previously published important results in regard to the multifactorial determinants of oxygenation and while the primary outcome was a short-term change in neuron specific enolase, the results for six-months neurological outcome as a secondary endpoint were consistent with the present findings.[16,17]

Investigating the association between blood oxygen levels and long term outcomes is further complicated by the risk factors and confounders in the intervening time period that are rarely reported with sufficient detail. The interactions between trajectories of neuro-cognitive recovery from hypoxic ischaemic encephalopathy[18] and neurocognitive decline as a result from cardiovascular disease and age[19] are complex. A one year follow up period as in the study by Humaloja et al. is important and should be reported in detail to capture nuances of quality of life in addition to neurological recovery.

The debate on oxygen delivery after cardiac arrest continues and we look forward to the results of ongoing clinical trials with bated breath.

Conflict of interest

None.

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