Review

The effect of hyperoxia on survival following adult cardiac arrest: A systematic review and meta-analysis of observational studies

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Abstract

Objective: Studies have shown the detrimental effect of hyperoxia in animals with return of spontaneous circulation (ROSC) after cardiac arrest. To maximize the value of existing clinical studies, we performed the systematic review and meta-analysis of human observational studies to examine the effect of hyperoxia on outcomes of post-ROSC patients.

Methods: We searched PubMed and Embase from the inception to October 2013. We selected adult observational studies that compared different levels of partial pressure of arterial oxygen (PaO2) in post-ROSC patients with mortality or neurological status at hospital discharge as outcome. Studies comparing hyperoxia with normoxia only were excluded.

Results: Fourteen studies were identified from 2982 references. Odds ratio (OR) was used as effect estimate. OR was reconstructed if not provided in original articles. Hyperoxia was defined as a PaO2 >300 mmHg. Meta-analysis indicated that hyperoxia appeared to be correlated with increased in-hospital mortality (OR, 1.40; 95% CI, 1.02–1.93; I², 69.27%; 8 studies) but not worsened neurological outcome (OR, 1.62; 95% CI, 0.87–3.02; I², 55.61%; 2 studies). However, the results were inconsistent in subgroup and sensitivity analyses.

Conclusions: Hyperoxia appears to be correlated with increased in-hospital mortality of post-ROSC patients. This result should be interpreted cautiously because of the significant heterogeneity and limited number of studies analyzed. However, because exposure to hyperoxia had no obvious benefits, clinicians should monitor PaO2 closely and titrate oxygen administration cautiously.

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1. Introduction

Cardiac arrest, either out-of-hospital or in-hospital, is a common and lethal emergency condition.1,2 Even if return of spontaneous circulation (ROSC) is achieved, most patients do not survive to hospital discharge.1,2 The high post-ROSC mortality may be attributed to post-cardiac arrest syndrome, which includes anoxic neurological injury, myocardial dysfunction, and systemic ischemic/reperfusion response.3

The 2010 European Resuscitation Council (ERC) Guidelines integrates the post-resuscitation care into the new chain of survival.4 The ERC recommends rapid application of therapeutic hypothermia for post-ROSC patients to improve survival to hospital discharge and neurological outcome because therapeutic hypothermia is thought to mitigate this systemic inflammatory response after ROSC.5

In the search for other modifiable post-ROSC factors that can improve outcomes, the role of supplemental oxygen in the pathogenesis of post-cardiac arrest syndrome has gained increasing attention recently. A meta-analysis of animal studies concluded

1 A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2014.05.021.
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that administration of 100% oxygen in the early post-ROSC period was associated with adverse neurological outcome. The only human randomized controlled trial compared the effects of administering 30% and 100% oxygen to post-ROSC patients. Although this study was not powered to show differences in long-term outcomes, subgroup analysis showed that 100% oxygen was associated with an increased level of neuron-specific enolase, a serum marker of neuronal injury.

It might be difficult to conduct a large-scale randomized controlled trial for examining the influence of high oxygen concentration on post-ROSC patients because of logistical and ethical difficulties. To maximize the value of existing evidence in the literature, we performed a meta-analysis of human observational studies to examine the effects of hyperoxia on outcomes of post-ROSC patients.

2. Methods

2.1. Data sources and searches

We performed this meta-analysis in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Meta-Analysis of Observational Studies in Epidemiology. We searched PubMed and Embase from the inception through October 2013. We did not set any restrictions on publication year or language. We used 2 sets of search terms to represent the primary variable and population of interest. The search terms for the primary variable included “normox,” “hyperox,” and “oxygen.” Then, the search results were cross-checked for the population of interest, using the terms “cardiac arrest” and “cardiopulmonary resuscitation.” To ensure completeness, we also reviewed the references of relevant articles. Pertinent studies were selected by 4 independent reviewers. Discrepancies between the selections by the 4 reviewers were resolved by consensus.

2.2. Study selection

Studies that were eligible for inclusion (1) compared different levels of partial pressure of arterial oxygen (PaO2) in post-ROSC adult patients; (2) included mortality or neurological status as outcome; and (3) used an observational study design, either a cohort or case–control study with an appropriate control group. Studies only comparing hypoxia with normoxia were excluded.

2.3. Data extraction and quality assessment

In this review, in-hospital mortality was the primary outcome and poor neurologic status (Cerebral Performance Category score of 3–5) at hospital discharge was the secondary outcome. Data were extracted for information on study location, number of participants, setting demographic characteristics of the study population, cardiopulmonary resuscitation (CPR) details, application of therapeutic hypothermia, definition of hyperoxia and hypoxia, mean post-ROSC PaO2, outcomes, and unadjusted/adjusted effect sizes and their corresponding 95% confidence intervals (CIs).

Study quality was assessed using the Newcastle–Ottawa Scale, which rates the quality of observational studies in a standardized format (Supplemental Table 1). When pertinent studies were identified but the required information was not found in the published article, we would attempt to contact the original authors. If an adjusted effect estimate was not available, an unadjusted one was recorded or calculated manually for inclusion in our analysis. If there was more than one effect estimate provided in a study, the effect estimate of the largest cohort was recorded.

2.4. Data synthesis and analysis

We defined hyperoxia as a PaO2 higher than 300 mmHg; hypoxia, as a PaO2 lower than 60 mmHg; and normoxia, as a PaO2 between 60 and 300 mmHg. Odds ratio (OR) was used as an effect estimate for the data synthesis. Other kinds of effect estimates or conclusions would be presented in the results but not synthesized with OR. If PaO2 was analyzed as a continuous variable in the selected studies, we reconstructed the binary OR of hyperoxia versus normoxia or non-hyperoxia by the weighting method based on the numbers of subjects within each of the 3 categories. Data were combined and expressed as a Mantel–Haenszel weighted mean of the ORs, with their associated 95% CIs.

The selection process of effect estimates for the outcome synthesis was as follows: We chose adjusted ORs if possible. If there were no adjusted ORs, unadjusted ORs were used. If there was more than 1 adjusted OR for the same cohort, the most significant OR was used. The influence of this selection process was explored in the sensitivity analysis.

Heterogeneity was quantified by the I^2 statistics and tested with Cochran Q statistics (p < 0.05). For values of I^2 < 50% or p > 0.05, fixed-effects models were chosen; otherwise, random-effects models were used. Meta-regression would be performed for the primary outcome if significant heterogeneity existed. We defined potential relevant covariates a priori, including article type, study setting, comparison groups and timing of exposure to hyperoxia, and tested these covariates one at a time in the meta-regression model. In addition to meta-regression, we reestimated the effect sizes stratified on the same covariates so that they were available as separate estimates in the subgroup analysis. The presence and effect of publication bias were examined using funnel plots for the primary outcome.

The rmeta and metafor packages were used to perform meta-analysis and meta-regression in the R-2.15.3 software (R Foundation for Statistical Computing, Vienna, Austria). In the statistical testing, a 2-sided p < 0.05 was considered statistically significant.

3. Results

3.1. Search results and study characteristics

In the systematic review, we identified 14 observational studies, including 8 full-text articles and 6 abstract-only articles (Fig. 1 and Table 1). All studies were cohort studies and included patients between the years 2000 and 2012, encompassing a total of 49,951 patients.

Six studies used multicenter databases for analysis. Two studies utilized the Project IMPACT database; the later study was a secondary analysis of the previous one and focused on the dose-dependent association between PaO2 and mortality. Three studies utilized ANZICS-APD database with slightly overlapped cohorts: Bellomo et al. included patients between 2000 and 2009; Ihle et al. included patients between 2007 and 2011, focusing only on those with out-of-hospital ventricular fibrillation cardiac arrest; Schneider et al. included patients between 2000 and 2011, mainly studying the effects of abnormal level of carbon dioxide on post-ROSC patients. These two databases were originally designed for critical care registry; therefore, some CPR variables consistent with the Utstein style were not reported, such as cardiac arrest setting and initial arrest rhythm.

The definition of hyperoxia varied across the studies. Most of the studies used a cutoff PaO2 value of 300 mmHg to define hyperoxia. Kilgannon et al. and Janz et al. did not set a cutoff point to define hyperoxia and treated PaO2 as a linear continuous
Table 1
Characteristics of the studies identified in the systematic review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study setting (study year)/patient number</th>
<th>Characteristics of cardiac arrest</th>
<th>Timing of the value of PaO2&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Cutoff value/prevalence of hyperoxia</th>
<th>Overall mortality</th>
<th>Comparison group with hyperoxia</th>
<th>Effect estimates</th>
<th>NOS&lt;sup&gt;5&lt;/sup&gt; score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilgannon et al. (2010)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Project IMPACT database (2001–2005)/6326</td>
<td>OHCA&lt;sup&gt;a&lt;/sup&gt;/Shockable rhythm: NA</td>
<td>First PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>300 mmHg/18%</td>
<td>56%</td>
<td>Normoxia</td>
<td>In-hospital mortality: Adjusted OR&lt;sup&gt;2&lt;/sup&gt;: 1.8 (1.5–2.2)</td>
<td>9/9</td>
</tr>
<tr>
<td>Bellomo et al. (2011)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>ANZICS-APD database (2000–2009)/12108</td>
<td>OHCA/ Shockable rhythm: NA</td>
<td>Worst PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>300 mmHg/11%</td>
<td>58%</td>
<td>Normoxia</td>
<td>In-hospital mortality: Adjusted OR: 1.5 (1.3–1.8)</td>
<td>9/9</td>
</tr>
<tr>
<td>Kilgannon et al. (2011)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Project IMPACT database (2001–2005)/4459</td>
<td>OHCA/ Shockable rhythm: NA</td>
<td>Highest PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PaO&lt;sub&gt;2&lt;/sub&gt; was treated as a continuous variable/NA</td>
<td>54%</td>
<td>Normoxia</td>
<td>In-hospital mortality: Adjusted OR: 1.69 (1.56–2.07) (Adjusted OR: 1.24 (1.18–2.31) for a 100 mmHg increase in PaO&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>9/9</td>
</tr>
<tr>
<td>Janz et al. (2012)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Single center (2007–2012)/170</td>
<td>OHCA/ Shockable rhythm: 79%/61%</td>
<td>Highest PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PaO&lt;sub&gt;2&lt;/sub&gt; was treated as a continuous variable/NA</td>
<td>55%</td>
<td>Normoxia</td>
<td>In-hospital mortality: Adjusted OR: 2.53 (1.07–5.96) (Adjusted OR: 1.44 (1.03–2.02) for a 100 mmHg increase in PaO&lt;sub&gt;2&lt;/sub&gt;) Poor neurologic status: Adjusted OR: 2.74 (1.08–6.91) (Adjusted OR: 1.49 (1.03–2.14) for a 100 mmHg increase in PaO&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>9/9</td>
</tr>
<tr>
<td>Ihle et al. (2013)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>VACAR and ANZICS-APD database (2007–2011)/584</td>
<td>OHCA/ Shockable rhythm: both 100%</td>
<td>Worst PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>300 mmHg/6%</td>
<td>41.6%</td>
<td>Normoxia</td>
<td>In-hospital mortality: Adjusted OR: 1.2 (0.52–2.82)</td>
<td>9/9</td>
</tr>
<tr>
<td>Nelskylä et al. (2013)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Single center (2008–2010)/119</td>
<td>OHCA/ Shockable rhythm: 43%/40%</td>
<td>Highest PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>300 mmHg/41%</td>
<td>63%</td>
<td>Non-hyperoxia</td>
<td>In-hospital mortality: Unadjusted OR: 0.76 (0.36–1.61)</td>
<td>7/9</td>
</tr>
<tr>
<td>Roberts et al. (2013)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Single center (2009–2011)/193</td>
<td>OHCA/ Shockable rhythm: 17%/19%</td>
<td>First PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>300 mmHg/24%</td>
<td>74%</td>
<td>Non-hyperoxia</td>
<td>Poor neurologic status: Adjusted OR: 1.05 (0.45–2.42) Death/failure to be discharged home: Adjusted HR: 1.05 (0.94–1.17)</td>
<td>9/9</td>
</tr>
<tr>
<td>Schneider et al. (2013)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>ANZICS-APD database (2000–2011)/16542</td>
<td>OHCA/ Shockable rhythm: NA</td>
<td>Worst PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>120 mmHg/NA</td>
<td>55.6%</td>
<td>Non-hyperoxia</td>
<td></td>
<td>9/9</td>
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<tr>
<td>Abstract-only studies</td>
<td></td>
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<tr>
<td>Lee et al. (2010)&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Single center (2003–2009)/541</td>
<td>OHCA/ Shockable rhythm: 0%/NA OHCA/ Shockable rhythm: NA/50%</td>
<td>First PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>300 mmHg/10%</td>
<td>NA</td>
<td>Normoxia</td>
<td>In-hospital mortality: Adjusted OR: 2.7 (1.11–6.66) In-hospital mortality: Adjusted HR: 1.75 (0.88–3.49) Adjusted HR: 1.48 (0.64–3.44)</td>
<td>NA</td>
</tr>
<tr>
<td>Rai et al. (2011)&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Single center (2007–2010)/82</td>
<td>OHCA/ Shockable rhythm: NA/50%</td>
<td>NA</td>
<td>300 mmHg/24%</td>
<td>NA</td>
<td>Normoxia</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Tameem et al. (2011)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Draeger Innovian database (2009–2010)/69</td>
<td>OHCA/ Shockable rhythm: NA</td>
<td>First PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>300 mmHg/9%</td>
<td>NA</td>
<td>Normoxia</td>
<td>In-hospital mortality: NA (The results stated that hyperoxia was associated with the lowest mortality in comparison with hypoxia or normoxia)</td>
<td>NA</td>
</tr>
<tr>
<td>Bolduc et al. (2012)&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Single center (NA)/265</td>
<td>OHCA/ Shockable rhythm: NA</td>
<td>NA</td>
<td>300 mmHg/NA</td>
<td>NA</td>
<td>Normoxia</td>
<td>Poor neurologic status: NA (The results stated that hyperoxia was not associated with poor neurologic status in a multivariable regression model)</td>
<td>NA</td>
</tr>
<tr>
<td>Gaierski et al. (2012)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Single center (2000–2007)/190</td>
<td>OHCA/ Shockable rhythm: NA</td>
<td>First PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>300 mmHg/32.1%</td>
<td>70.5%</td>
<td>Normoxia</td>
<td>In-hospital mortality: Unadjusted OR: 0.7 (0.3–1.4) In-hospital mortality: Adjusted OR: 1.18 (1–1.39)</td>
<td>NA</td>
</tr>
<tr>
<td>Pullalarevu and et al. (2012)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Single center (NA)/185</td>
<td>OHCA/ Shockable rhythm: NA</td>
<td>NA</td>
<td>300 mmHg/24.5%</td>
<td>55%</td>
<td>Non-hyperoxia</td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup> NA: not available.
<sup>b</sup> OHCA: out-of-hospital cardiac arrest.
<sup>c</sup> PaO<sub>2</sub>: partial pressure of arterial oxygen.
<sup>d</sup> OR: odds ratio.
<sup>e</sup> This odds ratio was the original effect estimate when PaO<sub>2</sub> was analyzed as a continuous variable.
<sup>f</sup> HR: hazard ratio.
<sup>g</sup> NOS: Newcastle–Ottawa Scale.
variable in the analysis. Schneider et al.25 used a lower cutoff value to define hyperoxia. Most studies sampled PaO2 during the first 24 h after ROSC or admission to intensive care units. The most significant difference in definition was the timing of the representative PaO2 for analysis: 5 studies used the first PaO2,8,24,26,28,30 3 studies used the highest PaO2,20,21,23 and 3 studies used the worst PaO2.18,22,25 The prevalence of hyperoxia according to each definition ranged from 6% to 41% in the post-ROSC patients. The in-hospital mortality ranged from 41.6% to 74%.

The patients of hyperoxia were compared with those of normoxia in 10 studies18,26–30 or with those of non-hyperoxia in another 3 studies23,24,31. Most studies used multivariable analysis, controlling for different variables, except 3 studies23,28,30 Nelskylä et al.23 mainly studied factors correlating with hyperoxia exposure in post-ROSC patients but also provided crude mortality by oxygenation status for manual calculation. All the full-text studies achieved similarly high Newcastle–Ottawa Scale scores (Supplemental Table 1). These full-text studies were well-conducted but they might still suffer from the inherent bias of retrospective observational studies, such as unmeasured confounding factors.

Four studies25,27–29 were not pooled in meta-analysis because there were no crude data for manual calculation of OR: two studies25,27 provided hazard ratios only; two studies28,29 did not provide any effect estimates (Fig. 1). Therefore, only the remaining 10 studies were synthesized.

3.2. Quantitative data synthesis

Nine studies reported in-hospital mortality (Table 1).18–22,26,30,31 Binary adjusted ORs were calculated by published data from the study by Kilgannon et al.20 and Janz et al.21; unadjusted OR was calculated from the published data by Nelskylä et al.23 Bellomo et al.19 provided 2 ORs, one of which was a less significant estimate when disease severity (Acute Physiology and Chronic Health Evaluation score) was considered in the regression model. Kilgannon et al. also provided 2 ORs of the similar cohort from Project IMPACT database18,20 because they conducted a secondary analysis50 of the previous study18 with a slightly different hypothesis and definition of hyperoxia.

The pooled results showed that hyperoxia was significantly associated with in-hospital mortality but that heterogeneity was
high (OR, 1.40; 95% CI, 1.02–1.93; I², 69.27%; Fig. 2 and Table 2). The meta-regression indicated that article type (p = 0.001), study setting (p = 0.003) and comparison groups (p = 0.003) were significant factors causing heterogeneity while timing of exposure to hyperoxia was not. The effect sizes stratified on the these covariates indicated that the pooled results of studies of full-text articles, multicenter databases, or comparisons between hyperoxia and normoxia showed more significant detriments by hyperoxia with decreased heterogeneity (Table 2).

The sensitivity analysis showed that either using adjusted effect estimates only or substituting alternative less-significant ORs in the synthesis would not shift the summary estimate or heterogeneity significantly (Table 2).

Two studies provided adjusted ORs for neurological status at hospital discharge.21,24 Roberts et al.24 primarily examined the relationship between post-ROSC partial pressure of carbon dioxide and neurological outcome but also provided OR for hyperoxia in their sensitivity analysis. The pooled results showed that post-ROSC hyperoxia was not significantly associated with poor neurological outcome at hospital discharge (OR, 1.62; 95% CI, 0.87–3.02; I², 55.61%; Fig. 3 and Table 2).

![Fig. 2. Forest plot for odds ratios of in-hospital mortality.](image)

### Table 2

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Included studies</th>
<th>Odds ratio (95% confidence interval)</th>
<th>p, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>18,19,21–23,26,30,31</td>
<td>1.40 (1.02–1.93)</td>
<td>69.27</td>
</tr>
<tr>
<td><strong>Subgroup analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Article type (full text versus abstract)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-text studies</td>
<td>18,19,21–23</td>
<td>1.59 (1.41–1.80)</td>
<td>32.56</td>
</tr>
<tr>
<td>26,30,31</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Abstract-only studies</td>
<td></td>
<td>1.18 (1.01–1.39)</td>
<td>66.97</td>
</tr>
<tr>
<td>Study setting (multicenter database versus single center)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicenter database studies</td>
<td>18,19,22</td>
<td>1.61 (1.42–1.82)</td>
<td>31.50</td>
</tr>
<tr>
<td>21,23,26,30,31</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Single-center studies</td>
<td></td>
<td>1.19 (1.02–1.39)</td>
<td>65.66</td>
</tr>
<tr>
<td>Comparison groups (hyperoxia versus normoxia or nonhyperoxia)</td>
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<td></td>
</tr>
<tr>
<td>Studies comparing hyperoxia with normoxia</td>
<td>18,19,21,22,26,30</td>
<td>1.61 (1.43–1.81)</td>
<td>28.13</td>
</tr>
<tr>
<td>Studies comparing hyperoxia with non-hyperoxia</td>
<td>23,31</td>
<td>1.16 (0.98–1.36)</td>
<td>20.91</td>
</tr>
<tr>
<td>Timing of exposure to hyperoxia</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>First PaO₂ in the initial 24-h post-ROSC period</td>
<td>18,26,30</td>
<td>1.52 (0.31–7.47)</td>
<td>73.50</td>
</tr>
<tr>
<td>Worst PaO₂ in the initial 24-h post-ROSC period</td>
<td>19,22</td>
<td>1.49 (1.27–1.75)</td>
<td>0</td>
</tr>
<tr>
<td>Highest PaO₂ in the initial 24-h post-ROSC period</td>
<td>21,23</td>
<td>1.36 (0.0007–2800.82)</td>
<td>76.64</td>
</tr>
<tr>
<td><strong>Sensitivity analysis</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Studies with adjusted estimates</td>
<td>18,19,21,22,26,31</td>
<td>1.54 (1.16–2.04)</td>
<td>66.78</td>
</tr>
<tr>
<td>All studies with two alternative less-significant estimates*</td>
<td>19–23,26,30,31</td>
<td>1.32 (0.98–1.79)</td>
<td>67.81</td>
</tr>
<tr>
<td><strong>Poor neurological outcome at hospital discharge</strong></td>
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<tr>
<td>All studies</td>
<td>21,24</td>
<td>1.62 (0.87–3.02)</td>
<td>55.61</td>
</tr>
</tbody>
</table>

* Two less-significant odds ratios provided by Bellomo et al.19 and Kilgannon et al.20 were substituted in the synthesis.
analysis stratified by the timing of exposure was performed, the result should be interpreted cautiously because of the limited number of studies.

The meta-regression indicated that article type (full text versus abstract), study setting (multicenter database versus single center) and comparison groups (hyperoxia versus normoxia or non-hyperoxia) were significant variables causing heterogeneity. Data in the abstract that are inconsistent with or absent from the article’s body are common, even in published articles of large-circulation general medical journals. The accuracy of the unpublished abstract could not be further verified. In current systematic review, most of the unpublished abstracts showed no significant association between hyperoxia and adverse outcomes. Although funnel plot did not reveal obvious asymmetry, publication bias might still be a concern.

The main advantage of the database analysis was the huge sample size, which enabled the researchers to control numerous confounders in the statistical analysis. Nonetheless, the 2 well-maintained databases (Project IMPACT and ANZICS-APD) were originally designed from the perspective of critical care. Some important variables in Utstein style, such as cardiac arrest setting, CPR duration, and initial arrest rhythm, were not recorded in these databases. In a pediatric cohort, Bennett et al. noticed that cardiac arrest setting and initial arrest rhythm might be more significantly associated with adverse outcomes than hyperoxia. Therefore, in adult studies, these uncontrolled important variables for post-ROSC prognosis might have also caused the differences in the pooled results between the multicenter database and single-center studies.

For the comparison groups, hyperoxia was compared with normoxia or non-hyperoxia. It has been well established that hypoxia is associated with worse outcomes. In a pediatric study, Ferguson et al. noted that the detrimental effect of hypoxia on post-ROSC mortality might be even greater than that of hyperoxia. Therefore, if patients with hypoxia were included in the non-hyperoxia groups for comparison with hyperoxia, the estimated effect size might be biased to the null, as observed in the subgroup analysis.

The sensitivity analysis showed that the summary effect estimates were inconsistent. This variation was mainly caused by the study by Bellomo et al. Bellomo et al. tested the robustness of the relationship between hyperoxia and in-hospital mortality through multiple testing with different controlled variables or statistical models. When disease severity was considered in the regression analysis, the effect estimates became less significant.

In the secondary outcome analysis, post-ROSC hyperoxia was not significantly associated with poor neurological outcome. Nonetheless, this pooled result of neurologic outcome should be further verified because of the small number of included studies.

Laboratory studies suggest that formation of reactive oxygen species results in elevated brain lipid peroxidation, impaired cerebral oxidative energy metabolism, and increased neurological degeneration. Despite the presence of this plausible biological explanation, the inherent limitation of an observational study design would lead to an association only rather than a causal relationship between hyperoxia and adverse outcomes. Therefore, this relationship might also be alternatively explained by other unmeasured confounders. For example, the occurrence of post-ROSC hyperoxia might imply that these patients receive less frequent invasive monitoring during this fragile period while physicians are less willing to adjust the concentration of inspired oxygen on the basis of pulse oximetry alone, which might be unreliable because of decreased peripheral perfusion. As reported by Nelskylä et al., delay in ICU admission was associated with post-ROSC hyperoxia. Therefore, post-ROSC hyperoxia might also just be a surrogate of clinical care quality; that is, patients who were not exposed to hyperoxia received more frequent invasive monitoring and adjustment of oxygen supplement.

In summary, post-ROSC hyperoxia appeared to be correlated with increased in-hospital mortality. The 2010 ERC guidelines recommend that rescuers titrate oxygen administration to the lowest level required to maintain the arterial oxyhemoglobin saturation at 94–98% and avoid potential oxygen toxicity, if appropriate equipment is available. Although our results did not consistently demonstrate the harmful effects of hyperoxia and suffered from significant heterogeneity, use of a high oxygen concentration showed no obvious benefits for post-ROSC patients. Future prospective clinical trials might further be focused on finding techniques for emergency responders to safely and effectively taper oxygen concentration and avoid hypoxia at the same time.

4.1 Limitations

First, we were unable to contact several authors for original data. We reconstructed the binary OR using the data published by Kilgannon et al. and Janz et al., which might have introduced some inaccuracies. To maximize the existing data, we chose to use the reconstructed effect estimates rather than exclude these studies. Secondly, there was some overlapping population studied by Bellomo et al. (ANZICS-APD database year 2000–2009) and Ihle et al. (ANZICS-APD database year 2007–2011). This overlapping accounted for only a minority of total population in the meta-analysis. Therefore, we kept both in data synthesis. Thirdly, the definition of hyperoxia was not consistent in each included study, including the timing/duration of exposure to hyperoxia and threshold of hyperoxia. However, because of the inherent limitations of meta-analysis, impact of these factors could only be fully investigated in future observational studies, especially in a prospective design. Finally, in spite of the high quality of included studies, these studies were all observational in design and could only establish
an association rather than a causal relationship between hyperoxia and adverse outcomes.

5. Conclusions

Hyperoxia appears to be correlated with increased in-hospital mortality of post-ROSC patients. This result should be interpreted cautiously because of the significant heterogeneity and limited number of studies included in the analysis. However, because exposure to hyperoxia had no obvious benefits, clinicians should monitor PaO₂ closely and titrate the oxygen administration cautiously.

Conflict of interest statement

The authors declare no conflicts of interest or sources of funding for this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2014.05.021.

References