PGY-3

**Critical Review Form**

 **Harm**

[Youn CS, Park KN, Kim SH, et al. The Cumulative Partial Pressure of Arterial Oxygen Is Associated With Neurological Outcomes After Cardiac Arrest Treated With Targeted Temperature Management. Crit Care Med. 2018;46(4):e279‐e285.](http://pmid.us/29261569)

**Objectives: "to test the hypothesis that cumulative exposure of hyperoxia is associated with neurological outcome after CA [cardiac arrest]." (e280)**

**Methods: This retrospective, observational study was conducted using prospectively collected data from a database of all post-CA patients maintained by the Seoul St. Mary's Hospital in Seoul, Korea. Adult patients (age 18 years or older) enrolled in the database between January 2009 and December 2016 who resuscitated from out-of-hospital CA (OHCA), were treated with** [**targeted temperature management (TTM)**](https://pmid.us/29239942)**, and had a minimum of four PaO2 measures with a total time interval of at least six hours were eligible for enrollment. Patients exposed to a PaO2 of less than 60 mmHg were excluded. Other exclusion criteria were use of extracorporeal membrane oxygenation (ECMO) during or after resuscitation and death less than 24 hours after ROSC.**

**The primary outcome was poor neurologic outcome at six months after CA, defined as a** [**Cerebral Performance Category score**](https://www.azdhs.gov/documents/preparedness/emergency-medical-services-trauma-system/save-hearts-az-registry-education/cerebral-performance-categories-scale.pdf) **of 3 or more. The exposure (cumulative hyperoxia exposure) was determined by calculating the area under the curve (AUC) of PaO2 via the** [**trapezoidal method**](https://www.khanacademy.org/math/ap-calculus-ab/ab-integration-new/ab-6-2/v/trapezoidal-approximation-of-area-under-curve) **using different cutoff values of hyperoxia (≥ 100, ≥ 150, ≥ 200, ≥ 250, and ≥ 300 mmHg) at different time intervals (0-24, 0-6, and 6-24 hours after ROSC).**

**Out of 290 adults treated with TTM following OHCA during the study period, 187 were eligible for inclusion. There were 77 patients with a good outcome. The median age of those with a good outcome was 47 years and the median age of those with a bad outcome was 57 years. Seventy percent and 67% of the groups were male, respectively.**

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| **Critical Review Form: Harm** |
| Guide | Comments |
| **Are the results valid?** |
| **Did experimental and control groups being the study with a similar prognosis?** |
| Did the investigators demonstrate similarity in all known determinants of outcome; did they adjust for differences in the analysis? | Yes and no. This study did not divide the cohort into two groups (exposure and non-exposure), but rather looked at the association between outcomes and a continuous spectrum of AUCs for various PaO2 cutoff values at various time intervals. It would therefore not be possible to compare groups with respect to various determinants of outcome. The authors did utilize [logistic regression](https://www.cdc.gov/nchs/tutorials/dietary/Advanced/EstimatePrevalence/Info3.htm) to control for several known confounders to attempt to isolate the effect of PaO2 on the outcome of interest. |
| Were exposed patients equally likely to be identified in the two groups? | N/A. Patients were not divided into groups, rather all patients who survived for at least 24 hours following OHCA were enrolled via a prospective database. It seems unlikely that eligible patients would not have been identified and included in this study. |
| **Did experimental and control groups retain a similar prognosis after the study started?** |
| Were the outcomes measured in the same way in the groups being compared? | Yes. 6-month neurologic outcome was assessed for all patients included in the study in the same manner.Ideally, all patients in the study would have had PaO2 measurements at the same time intervals for the first 24 hours of their hospital stay, but this does not seem to be the case. For enrollment, subjects were only required to have at least 4 measurements with an overall time interval of at least 6 hours; where measurements were missing, the AUC calculation was imputed to account for missing data points (the calculated total area was divided by the time and the multiplied by 24). The authors do not specify how many patients were missing data points and required imputation and which data points were missing. |
| Was follow-up sufficiently complete? | Purportedly yes. The prospective database used in this study should contain appropriate follow-up information for all subjects, and the authors do not specifically mention any loss to follow-up. |
| **What are the results?** |
| How strong is the association between exposure and outcome? | * Prior to adjustment by logistic regression, the AUCs for time intervals 6-12, 12-18, and 18-24 hours did not differ significantly between those with good and those with poor outcomes for any PaO2 cutoff values.
	+ The AUCs within 6 hours after ROSC did differ significantly between outcome groups for cutoff values of 200, 250, and 300 mmHg, but did not differ for cutoff values of 100 or 150 mmHg.
* Following adjustment for confounders (initial rhythm, witness status, and time from collapse to ROSC), increasing PaO2 cutoffs were associated with increasing odds ratios for poor neurologic outcome, achieving statistical significance at cutoffs of 200 (OR 1.659, 95% CI 1.194-2.305), 250 (OR 2.082, 95% CI 1.204–3.600), and 300 mmHg (OR 3.969, 95% CI 1.450-10.862).
	+ A similar trend of increasing OR with increased PaO2 cutoff was observed for the 0-6 hour interval, achieving statistical significance at cutoffs of 150, 200, 250, and 300 mmHg.
	+ While a trend of increasing OR with increasing PaO2 was seen in the 6-24 hour interval, statistical significance was not achieved for any cutoff value.
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| How precise is the estimate of the risk? (i.e. what 95% CIs were associated with the results?) | See above. Some of the 95% confidence intervals were fairly wide as some of the subgroups were likely small.  |
| **How can I apply the results to patient care?** |
| Were the study patients and their management similar to those in my practice? | No. This study was conducted entirely in Korea, [where life expectancy is several years longer than in the US](https://www.worldlifeexpectancy.com/south-korea-life-expectancy) and where leading [causes of death](https://www.worldlifeexpectancy.com/south-korea-stroke) are quite different. The prevalence of several key risk factors for cardiovascular disease are much higher in the US (including [diabetes mellitus](https://www.webmd.com/diabetes/news/20040426/diabetes-rates-worldwide#1) and [obesity](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676846/)), and [median age of cardiac arrest patients is higher in Korea than in the US](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4278034/). |
| Was the duration of the follow-up adequate? | Yes. The investigators looked at neurologic outcomes at 6 months, which should be more than adequate. Experts have recommended at least [90-day neurologic outcomes as an appropriate measure for studies of cardiac arrest](https://pubmed.ncbi.nlm.nih.gov/21969010/). |
| What was the magnitude of the risk?  | Following adjustment for several known confounders, there appears to be an increased risk of a poor neurologic outcome at 6 months with a cumulative PaO2 of 200 mmHg or more over the first 24 hours following OHCA, with increasing PaO2 associated with increasing risk. There was no association with increased risk for PaO2 values below 200 mmHg. |
| Should I attempt to stop the exposure? | Yes. Attempts should be made to wean oxygen levels quickly in patients resuscitated following OHCA, with a specific focus on getting the PaO2 below 200 mmHg. This would appear to improve neurologic outcomes at 6 months. |

**Limitations:**

1. **This was an observational study looking at the risk of harm associated with an intervention (oxygen delivery) and was at high risk of** [**selection bias**](http://pmid.us/21491415)**.**
2. **The use of logistic regression (or similar methods) to adjust for the effects of known confounders on the outcome of interest is always limited by the inability to control for** [**unknown confounders**](http://link.springer.com/chapter/10.1007/978-0-387-87959-8_5)**.**
3. **The authors were forced to account for missing variables (initial or final PaO2), but fail to report how many patients were missing these data points.**
4. **This was a single center study conducted in Korea. As pointed out, several considerations may limit the generalizability of these findings to patients in the US (**[**external validity**](http://www.epmonthly.com/archives/features/understanding-external-validity/)**).**

**Bottom Line:**

**This retrospective analysis of prospectively collected data suggests that cumulative hyperoxia over the first 6 and 24 hours of care following resuscitation from OHCA was associated with worsening neurologic outcomes 6 months following arrest. The data also suggest there is a dose response relationship, with increasing PaO2 above 200 mmHg associated with an increased risk of poor outcome.**