Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating event that accounts for 3% to 5% of all strokes and has a 30-day mortality of 30%. Following survival of the initial event and securing of the aneurysm, the primary contributor of disability and death is cerebral vasospasm, which results in delayed cerebral ischemia (DCI) and infarction. Despite the improvement of intensive care unit (ICU) patient management, widespread use of nimodipine, and development of endovascular approaches for vasospasm treatment, morbidity and mortality associated with cerebral vasospasm persist. The pathophysiology of vasospasm is still only partially understood and precise spasmogenic components of SAH have yet to be established.
Supplemental oxygen is ubiquitous in the acute setting of critically ill patients, including those with aSAH. Oxygen therapy frequently is reflexively used or continued without comprehensive evaluation, and hyperoxemia tends to be tolerated. However, hyperoxemia has been associated with poor outcomes in the setting of ischemic stroke, traumatic brain injury (TBI), and post–cardiac arrest. There is growing literature suggesting an association between early hyperoxemia following aSAH with DCI and poor outcomes.

Several mechanisms connecting hyperoxemia with poor outcomes following aSAH have been proposed. Supraphysiological levels of oxygen result in production of reactive oxygen species (ROS), leading to oxidative stress and cerebral inflammation, neuronal death, blood-brain barrier breakdown, and reduction in cerebral blood flow. This contributes to early brain injury after SAH as well as DCI.

Examining the effects of hyperoxemia on aSAH is critical to improve intensive care of patients with SAH. In this review, we assessed the available clinical literature and conducted a meta-analysis to evaluate the association between hyperoxemia and outcomes in the setting of aSAH.

Methods

A registered protocol was not used for this review. PubMed and Web of Science databases were searched for clinical studies (randomized controlled trials, retrospective or prospective cohort studies, and case series) on September 15, 2021, using the search terms “hyperoxemia OR hyperoxia” AND “subarachnoid hemorrhage OR intracranial hemorrhage.” No publication date restrictions were imposed. Duplicates were removed after review of full texts. Titles, abstracts, and sources cited within full texts were independently screened and reviewed for eligibility by two authors.

Study Selection

Studies that described the relationship between clinical outcomes of patients with aSAH and hyperoxemia exposure were identified based on titles and abstracts. We included review articles, letters and replies, preclinical/animal studies, studies conducted on patients without aSAH, studies that did not report clinical outcomes, and studies that did not report data specific to patients with aSAH. We included studies independent of the definition of hyperoxemia exposure.

Data Extraction and Outcome Definitions

All data were extracted independently by a single author (J.A.) and then reviewed for accuracy by a second author (P.M.). Baseline characteristics extracted included patient age, sex, maximum PaO₂, aneurysm location (anterior vs posterior), World Federation of Neurosurgical Societies grade, Fisher grade, and Hunt and Hess grade. All relevant reported outcome data were extracted, including crude data and reported effect sizes (ESs). The reported outcome measures included neurological outcome, incidence of vasospasm and/or DCI, and mortality. ESs were reported as odds ratios or risk ratios. Included studies defined poor neurological outcome at, or 3 months after, discharge based on modified Rankin Scale scores of 3 or 4 to 6, or Glasgow Outcome Scale scores < 3. If reported, mortality was given as in-hospital mortality or mortality at 3 months. Authors typically defined vasospasm and/or DCI with transcranial Doppler ultrasonography, CTA, or imaging results combined with need for therapy. We constructed mortality or poor neurological outcome as a combined outcome by pooling unadjusted or adjusted ESs of either reported mortality or poor neurological outcome. If a study reported both outcomes, poor neurological outcome was used preferentially. If the authors reported quartiles/quantiles of PaO₂ rather than hyperoxia exposure as a binary measure, we opted to use 200 mm Hg as the threshold for hyperoxia, as this most closely aligned with existing oxygen bands used by the included studies. If the authors made a distinction between normoxia and hypoxemia cohorts, we used only the normoxia cohort as the reference.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics version 28 (IBM Corp.). Available patient demographics of included studies were pooled as a weighted average and pooled standard deviation. Baseline characteristics reported as a median and IQR were converted to mean and standard deviation on the assumption of normal distribution. Aggregate patient demographic information was used if SAH-specific information was not available. Bias and quality of all included studies were assessed using the Downs and Black checklist. Meta-analysis was conducted for reported ESs that describe the relationship between hyperoxemia and various reported outcomes. Pooling of crude data or ESs was computed using the restricted maximum likelihood random-effects model for binary variables. ESs were computed as an odds ratio with 95% confidence interval. Meta-analyses of unadjusted or adjusted ES were constructed into forest plots. Adjusted ESs were pooled as reported without modification. We analyzed study heterogeneity using Cochran’s Q and I² test. Significant heterogeneity was defined as both a Q value with p < 0.10 and the I² value exceeding 50%. Statistical significance was defined as p < 0.05.

Results

Our initial search identified 102 records. After screening of titles and abstracts, 10 full-text articles were reviewed for eligibility (Fig. 1). A total of 7 studies were included for analysis.

Table 1 shows basic characteristics of the 7 included studies published between 2014 and 2021 (n = 2602 patients). All were retrospective, single- or multicenter observational studies. All studies, with one exception, adjusted reported outcomes of interest for severity of illness. The period of data collection ranged from 1996 to 2018 and the cohort size of each study ranged from 196 to 936 patients. Included studies evaluated for hyperoxia exposure at the time of ICU admission or in the first 24 hours, 72 hours, or 6 days following admission. There was significant heterogeneity in the methodology used to evaluate hyperoxia exposure. Four studies used single PaO₂ values to assess for hyperoxemia, while 3 studies used time-
weighted averages (TWAs) of PaO₂.\textsuperscript{14–16} Table 2 shows the baseline demographic characteristics of the included studies. The mean pooled age of included patients was 58.8 years (SD 14.4 years), and 54.8% of patients were female.

Table 3 shows the crude outcome data and adjusted ESs extracted from the included studies; there was significant heterogeneity in the types of reported outcomes among them. Five of the 7 selected studies reported neurological outcome at, or 3 months after, hospital discharge.\textsuperscript{12,14–17} Five studies reported DCI or cerebral vasospasm,\textsuperscript{12–16} with 3 of these 5 studies performing multivariate analysis for this outcome measure.\textsuperscript{13–15} Three of the 7 studies reported mortality at 3 months or at discharge,\textsuperscript{1,13,16} with 2 performing multivariate analysis for this outcome.\textsuperscript{13,16}

**Pooled Analysis**

The included studies were pooled for further analysis. All were retrospective, single- or multcenter observational studies. Meta-analysis of unadjusted outcome data showed that hyperoxemia was associated with worse neurological outcome (OR 2.26, 95% CI 1.66–3.07; p < 0.001; Fig. 2A), increased likelihood of mortality or poor neurological outcome measured as a combined endpoint (OR 2.36, 95% CI 1.87–2.97; p < 0.001; Fig. 2B), and DCI (OR 1.91, 95% CI 1.31–2.78; p < 0.001; Fig. 2C). Meta-analysis of adjusted ESs showed the same relationship for neurological outcome (OR 1.28, 95% CI 1.07–1.55; p = 0.01; Fig. 3A) and mortality or poor neurological outcome measured as a combined endpoint (OR 1.17, 95% CI 1.11–1.23; p <
## Table 1: Basic characteristics of included studies

| Authors & Year | Data Collection | Region | Period | Intubation Status | Hyperoxia Exposure Measurement | Time Point | Threshold | Outcome Measures | Total No. of Pts (normoxia/hyperoxia) | Summary of Results |
|----------------|-----------------|--------|--------|------------------|---------------------------------|------------|-----------|------------------|-------------------------------------|-------------------|
| Rincon et al., 2014 | Retrospective, multicenter | US | 2003–2008 | Mechanically ventilated | Single PaO$_2$ | Time of ICU admission | >300 mm Hg | In-hospital mortality | 936 (383/135) | Higher in-hospital mortality |
| Jeon et al., 2014 | Retrospective, single center | US | 1996–2011 | Mechanically ventilated | TWA PaO$_2$ | Until development of DCI, or until postbleed day 6 | >173 mm Hg (upper quartile) | DCI, neurological outcome at 3 mos | 252 (188/64) | Increased risk of DCI & poorer neurological outcome |
| Lång et al., 2016 | Retrospective, multicenter | Finland | 2004–2012 | Mechanically ventilated | TWA PaO$_2$ | 1st 24 hrs of ICU admission | >150 mm Hg | Neurological outcome at 3 mos, in-hospital mortality | 432 (192/104) | Hypoxia & hyperoxia were not associated with poor neurological outcome |
| Li et al., 2019 | Retrospective, single center | Hong Kong | 2011–2016 | Either | Single PaO$_2$ | 1st 24 hrs of ICU admission | >200 mm Hg | Neurological outcome at 3 mos, in-hospital mortality, length of stay | 244 (205/39) | Poor neurological outcome at 3 mos |
| Yokoyama et al., 2019 | Retrospective, single center | Japan | 2009–2018 | Mechanically ventilated | Single PaO$_2$ | 1st 24 hrs of ICU admission | >120 mm Hg | Neurological outcome at discharge, DCI | 196 (13/183) | Unfavorable neurological outcomes in pts with H&K grades I–III |
| Fukuda et al., 2021 | Retrospective, single center | Japan | 2011–2017 | Either | TWA PaO$_2$ | 1st 24 hrs (hyperacute phase) & between 1st 24 hrs & postbleed day 6 (acute phase) | Continuous | Neurological outcome at discharge, DCI | 197 (150/47) | Increased risk of DCI & poorer neurological outcome with higher TWA PaO$_2$ in the hyperacute phase |
| Reynolds et al., 2021 | Retrospective, single center | US | 2007–2017 | Either | Single PaO$_2$ | 1st 72 hrs of ICU admission | Continuous | Cerebral vasospasm, neurological outcome at discharge, in-hospital mortality | 345 (NA) | Higher risk of vasospasm, but not in-hospital mortality or outcome at discharge |

H&K = Hunt and Kosnik; NA = not available; pts = patients; TWA PaO$_2$ = time-weighted average of PaO$_2$.

* The hyperoxia cohort was defined as having a TWA PaO$_2$ > 200 mm Hg within the first 24 hours.
emia due to the generation of ROS. Supraphysiological levels of oxygen result in production of ROS, leading to oxidative stress, cerebral inflammation, neuronal death, blood-brain barrier breakdown, and reduction in cerebral blood flow. Oxidative stress has been associated with poor outcomes following ischemic stroke, TBI, and post–cardiac arrest.

Several mechanisms connecting hyperoxemia with poor outcomes following aSAH have been proposed. These include acute effects of oxidative stress on early brain injury and effects of hyperoxemia on DCI. Following acute brain injury, disruption of cellular respiration results in increased production of ROS that overwhelm the antioxidant systems and contribute to secondary brain injury. Indeed, it has been found that even healthy patients exposed to hyperoxia transiently develop increased ROS burden, lipid peroxidation, and reduced nitric oxide metabolites. Moreover, hyperoxemia promotes oxidation of extravascular cell-free hemoglobin, which is known to be proinflammatory in the setting of SAH and has been associated with vasospasm of the pulmonary arteries. It is also believed that ROS may be involved with NLRP3 inflammasome activation and upregulation of oxidized low-density lipoprotein (LDL) and its receptor, lectin-like oxidized LDL receptor-1. Both are currently being studied for their potential roles in the development of DCI.

**Discussion**

Administration of supplemental oxygen constitutes the default approach in the acute setting for critically ill patients. Here, we investigated the effects of hyperoxia on outcomes after aSAH. We systematically identified 7 retrospective clinical studies and performed a meta-analysis, which showed an association between hyperoxia and the risk of poor neurological outcome, mortality, and DCI. Our results underline the need for judicious oxygen supplementation in the acute setting after aSAH.

While hypoxia is often the immediate concern where brain injury is concerned, oxygen itself cannot be considered a benign agent. The potential pulmonary toxicity of oxygen has been well described. The brain is one of the first organs to experience the effects of hyperoxemia due to the generation of ROS. Supraphysiological levels of oxygen result in production of ROS, leading to oxidative stress, cerebral inflammation, neuronal death, and upregulation of oxidized low-density lipoprotein (LDL) and its receptor, lectin-like oxidized LDL receptor-1. Both are currently being studied for their potential roles in the development of DCI.

0.001; Fig. 3B), but showed no significant association with DCI (OR 1.47, 95% CI 0.81–2.67; p = 0.20; Fig. 3C). The pooling of multivariate odds ratios for DCI was marked by significant heterogeneity.

**TABLE 2. Demographic and clinical characteristics of included studies**

| Authors & Year | No. of Pts | Mean Age, yrs (SD) | Female Sex, n (%) | Mean Maximum PaO₂ mm Hg (SD) | Anterior Circulation Aneurysm, n (%) | WFNS Grade IV or V, n (%) | Fisher Grade 3 or 4, n (%) | Hunt & Hess Grade III–V, n (%) |
|---------------|-------------|-------------------|-----------------|-----------------------------|-----------------------------------|---------------------------|--------------------------|-------------------------------|
| Rincon et al., 2014¹¹ | 2894*       | 61 (15)           | 1408 (49)       | 274 (148)                   | NA                                | NA                        | NA                       | NA                            |
| Jeon et al., 2014¹⁵ | 252         | 56.7 (13.9)       | 179 (71.0)      | 146.5 (37.0)†              | NA                                | NA                        | NA                       | 199 (79.0)                   |
| Lång et al., 2016¹⁶ | 432         | 56 (11.9)         | 259 (60.0)      | 126.0 (48.4)†              | 367 (85.0)                        | 289 (66.8)                | 392 (90.7)               | 343 (79.4)                   |
| Li et al., 2019¹⁷ | 244         | 57.7 (14.6)       | 155 (63.5)      | 151.2 (62.6)               | 153 (62.7)                        | 107 (43.9)                | 183 (75.0)               | NA                            |
| Yokoyama et al., 201⁰⁻¹² | 196         | 62.7 (16.8)       | 133 (67.9)      | 193 (70.4)†                | NA                                | NA                        | NA                       | NA                            |
| Fukuda et al., 2021¹⁴ | 197         | 62.1 (15.7)       | 133 (67.5)      | NA                          | 105 (53.3)                        | NA                        | NA                       | NA                            |
| Reynolds et al., 2021¹³ | 345         | 54.5 (13.4)       | 234 (67.8)      | 218.8 (117.3)              | NA                                | NA                        | 310 (89.9)               | 240 (69.6)                   |
| Pooled estimate | 4560        | 58.8 (14.4)†      | 2501 (54.8)     | 207.1 (104.8)              | 625/873 (71.6)                    | 396/676 (58.6)            | 816/1029 (79.3)          | NA                            |

WFNS = World Federation of Neurosurgical Societies.

* Study only provided aggregate demographic information for all included patients, including those diagnosed with TBI, intracranial hemorrhage, and SAH.
† Converted to mean (SD) from median and IQR while assuming a normal distribution.
‡ Pooled estimates for continuous variables were given as weighted averages and SDs. Data from studies that provided only aggregate data were weighted for the number of patients within the corresponding SAH cohort.

**TABLE 3. Extracted unadjusted and adjusted outcome data from included studies**

| Authors & Year | Poor Neurological Outcome | DCI or Cerebral Vasospasm | Mortality | Adjusted ES (95% CI) | Adjusted ES (95% CI) | Adjusted ES (95% CI) |
|---------------|---------------------------|---------------------------|-----------|----------------------|----------------------|----------------------|
|               | Hyperoxia | Normoxia |                | Hyperoxia | Normoxia |                | Hyperoxia | Normoxia |                | Hyperoxia | Normoxia |                |
| Rincon et al., 2014¹¹ | NA       | NA       |                | NA       | NA       |                | 80/135    | 139/383   | NA       |               |
| Jeon et al., 2014¹⁵ | 32/18     | 76/76    | 2.30 (1.03–5.12) | 36/28    | 61/127   | 3.16 (1.69–5.92) | NA       | NA       |                |               |
| Lång et al., 2016¹⁶ | 83/21     | 101/91   | 1.09 (0.61–1.97) | 28/108   | 32/160   | NA               | 37/67     | 57/135   | 0.73 (0.38–1.40) |               |
| Li et al., 2019¹⁷  | 27/12     | 95/110   | 3.788 (1.13–12.70) | NA       | NA       |                | NA       | NA       |                |               |
| Yokoyama et al., 201⁰⁻¹² | 48/40     | 42/60    | 1.38 (0.99–1.83) | 17/71    | 10/98    | NA               | NA       | NA       |                |               |
| Fukuda et al., 2021¹⁴ | 25/22     | 57/93    | 1.17 (1.06–1.29) | 16/31    | 26/89    | 1.09 (1.01–1.17) | NA       | NA       |                |               |
| Reynolds et al., 2021¹³ | 25/22     | 57/93    | 1.15 (1.03–1.28) | NA       | NA       |                | NA       | NA       | 1.10 (0.97–1.25) |               |

Values represent the number of patients with outcome/patients without outcome data within the hyperoxia or normoxia cohorts, unless indicated otherwise. We used 200 mm Hg as the threshold for hyperoxia based on the oxygen bands defined within the study and similar thresholds used in other studies.
Furthermore, hyperventilation and hypocapnia have long been known to cause autoregulatory vasoconstriction, decreasing cerebral blood flow by approximately 3% per every millimeter of mercury decrease in PaCO₂. In the setting of SAH, it remains under debate whether this reduction in cerebral blood flow is caused directly by hypoxemia, or indirectly by the resulting hyperventilation and hypocapnia. Interestingly, several retrospective stud-
ies have shown hyperventilation or hypocapnia to be independently associated with worse outcomes after SAH.\textsuperscript{17,38,39} Further studies are needed to investigate hypocapnia in the context of SAH as well as other pathological processes.\textsuperscript{40}

Overall, the mechanisms described suggest that normoxia and normocapnia should be targeted when managing patients with SAH and that hyperoxemia may lead to worse secondary injury and DCI. As expected, due to the
underlying pathophysiological mechanisms described, the retrospective studies available in the literature have suggested an association between hyperoxia and the risk of poor neurological outcome, mortality, and DCI.

There remains considerable debate in the literature about what constitutes hyperoxemia. Correspondingly, there was significant heterogeneity in the methodology used to measure hyperoxemia exposure. Four studies used single PaO₂ measurements to determine hyperoxia exposure, while 3 used TWAs. TWA PaO₂ measurements may provide an advantage in that many instances of hyperoxia in the ICU may be transient, and, unlike single PaO₂ measurements, TWA PaO₂ is not affected by the frequency of measurements. Additionally, TWA PaO₂ has been statistically correlated to single PaO₂ measurements in a previous study that investigated hyperoxia in the setting of TBI.

The predetermined thresholds for hyperoxia exposure among included studies ranged from 120 mm Hg PaO₂ to 300 mm Hg PaO₂. In the study by Fukuda et al., the median values of 24-hour TWA PaO₂ in the DCI and unfavorable outcome groups were 186 (range 141–213) mm Hg and 176 (range 154–205) mm Hg, respectively. This very closely approximates the 173–mm Hg PaO₂ threshold used to define hyperoxia exposure by Jeon et al. Reynolds et al. also reported that the mean maximum PaO₂ ± SD in patients who experienced vasospasm was 232 mm Hg ± 124.1 mm Hg. In contrast, the threshold PaO₂ values used by Yokoyama et al. and Lâng et al. were much lower at 120 mm Hg and 150 mm Hg, respectively. This may partially explain the variability in results. Importantly, these results suggest that the threshold for hyperoxia that contributes to worse outcomes may lie within the region of 175 mm Hg to 200 mm Hg. It remains unclear whether this effect is dominated by acute or persistent exposure to hyperoxia, although most findings have focused on the initial 24-hour period. To our knowledge, there currently remains no laboratory data to help guide what should be defined as hyperoxia in the setting of SAH. Even animal models have not shown agreement for what degree of hyperoxia, if any, may be deleterious with respect to reperfusion injury.

DCI was found to be associated with hyperoxia after pooling of univariate ESs. However, the meta-analysis of adjusted ES for DCI was characterized by significant heterogeneity. This may be partially explained by differences in patient cohorts. The patients within the cohort of the study by Jeon et al. were mechanically intubated, and thus more likely to be severely ill (Table 1). In contrast, the studies by Fukuda et al. and Reynolds et al. did not exclude nonintubated patients. Correspondingly, the latter studies reported modest ESs relative to the former.

These findings indicate that hyperoxia in the early periods of ICU admission for SAH is associated with worse outcomes, possibly more pronounced with lower-grade hemorrhages. However, the heterogeneity of the study findings weakens this assertion. Furthermore, it remains less clear how this would translate to clinical practice and what thresholds of PaO₂ or TWA PaO₂ should be used to guide therapy. There remains a need for prospective studies with greater control of PaO₂ levels to further investigate the effects of hyperoxemia on SAH outcomes.

Limitations

The limitations of this work include the retrospective nature of all included studies and the significant heterogeneity of the study findings with respect to hyperoxia exposure criteria and reported outcomes with mixed availability of crude and adjusted data. Additionally, a majority of the studies were performed at a single center with large ranges of maximum PaO₂, within each cohort, reducing the external validity of the studies’ findings. While most included studies performed multivariate analysis to account for confounders, residual confounders are an inherent risk of retrospective analysis.

Conclusions

In accordance with the findings on ischemic stroke, TBI, and post–cardiac arrest, the literature review and meta-analysis conducted here suggests that hyperoxemia may worsen the outcome of patients with aSAH. This is attributed to acute effects of oxidative stress on early brain injury and effects of hyperoxia on DCI. While these findings provide a general guideline toward avoiding hyperoxia in the acute setting of aSAH, further studies are needed to determine the optimal ventilation and oxygenation parameters for acute management of this patient population.

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