Effects of hyperoxemia on aneurysmal subarachnoid hemorrhage outcomes: a systematic review and meta-analysis

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OBJECTIVE In recent years, hyperoxemia in the intensive care unit has received attention as potentially contributing to negative outcomes in the setting of cardiac arrest, ischemic stroke, and traumatic brain injury. The authors sought to evaluate whether hyperoxemia contributes to worse outcomes in the setting of aneurysmal subarachnoid hemorrhage (aSAH) and to summarize suggested pathophysiological mechanisms.

METHODS A systematic literature review was conducted without date restrictions on the PubMed and Web of Science databases on September 15, 2021. All studies that assessed the relationship between patients treated for aSAH and hyperoxemia were eligible independent of the criteria used to define hyperoxemia. All nonclinical studies and studies that did not report outcome data specific to patients with aSAH were excluded. A total of 102 records were found and screened, resulting in assessment of 10 full-text studies, of which 7 met eligibility criteria. Risk of bias was assessed using the Downs and Black checklist. A meta-analysis on the pooled 2602 patients was performed, and forest plots were constructed. Additionally, a review of the literature was performed to summarize available data regarding the pathophysiology of hyperoxemia.

RESULTS The included studies demonstrated an association between hyperoxemia and increased morbidity and mortality following aSAH. The criteria used to determine hyperoxemia varied among studies. Pooling of univariate data showed hyperoxemia to be associated with poor neurological outcome (OR 2.26, 95% CI 1.66–3.07; $p < 0.001$), delayed cerebral ischemia (DCI) (OR 1.91, 95% CI 1.31–2.78; $p < 0.001$), and increased incidence of poor neurological outcome or mortality as a combined endpoint (OR 2.36, 95% CI 1.87–2.97; $p < 0.001$). Pooling of multivariable effect sizes showed the same relationship for poor neurological outcome (OR 1.28, 95% CI 1.07–1.55; $p = 0.01$) and poor neurological outcome and mortality as a combined endpoint (OR 1.17, 95% CI 1.11–1.23; $p < 0.001$). Additionally, review of preclinical studies underlined the contribution of oxidative stress due to hyperoxemia to acute secondary brain injury and DCI.

CONCLUSIONS Reported outcomes from the available studies have indicated that hyperoxemia is associated with worse neurological outcome, mortality, and DCI. These findings provide a general guideline toward avoiding hyperoxemia 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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KEYWORDS aneurysmal subarachnoid hemorrhage; hyperoxemia; oxidative stress; vasospasm

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%.^{1,2} 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.³ 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.³ The pathophysiology of vasospasm is still only partially understood and precise spasmogenic components of SAH have yet to be established.^{4,5}

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; DCI = delayed cerebral ischemia; ES = effect size; ICU = intensive care unit; ROS = reactive oxygen species; TBI = traumatic brain injury; TWA = time-weighted average.

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Supplemental oxygen is ubiquitous in the acute setting during the treatment of critically ill patients, including those with aSAH. Oxygen therapy frequently is reflexively used or continued without comprehensive evaluation,⁶ and hyperoxemia tends to be tolerated.⁷ However, hyperoxemia has been associated with poor outcomes in the setting of ischemic stroke, traumatic brain injury (TBI), and post-cardiac arrest.^{8–11} There is growing literature suggesting an association between early hyperoxemia following aSAH with DCI and poor outcomes.^{11–17}

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.¹⁸ 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 excluded 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^{11,13–17} or risk ratios.¹² 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/quintiles of PaO₂^{12,14} 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.¹¹ Bias and quality of all included studies were assessed using the Downs and Black checklist.¹⁹ 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 reported 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,¹¹ 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 admission¹¹ or in the first 24 hours,^{12,14,16,17} 72 hours,¹³ or 6 days¹⁵ following admission. There was significant heterogeneity in the methodology used to evaluate hyperoxia exposure. Four studies used single PaO₂ values to assess for hyperoxemia,^{11–13,17} while 3 studies used time-

FIG. 1. PRISMA flowchart depicting PubMed and Web of Science literature search.

weighted averages (TWAs) of PaO₂.^{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.^{12,14–17} Five studies reported DCI or cerebral vasospasm,^{12–16} with 3 of these 5 studies performing multivariate analysis for this outcome measure.^{13–15} Three of the 7 studies reported mortality at 3 months or at discharge,^{1,13,16} with 2 performing multivariate analysis for this outcome.^{13,16}

Pooled Analysis

The included studies were pooled for further analysis. All were retrospective, single- or multicenter 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; $p < 0.001$; Fig. 3B).

TABLE 1. Basic characteristics of included studies

Authors & Year	Data Collection	Region	Period	Intubation Status	Hyperoxia Exposure			Outcome Measures	Total No. of Pts (normoxia/hyperoxia)	Summary of Results
					Measurement	Time Point	Threshold			
Rincon et al., 2014 ¹¹	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 ¹⁵	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 ¹⁶	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 w/ poor neurological outcome
Li et al., 2019 ¹⁷	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 ¹²	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 w/ H&K grades I–III
Fukuda et al., 2021 ¹⁴	Retrospective, single center	Japan	2011–2017	Either	TWA PaO ₂	1st 24 hrs (hyperacute phase) & btwn 1st 24 hrs & postbleed day 6 (acute phase)	Continuous	Neurological outcome at discharge, DCI	197 (150/47)*	Increased risk of DCI & poorer neurological outcome w/ higher TWA PaO ₂ in the hyperacute phase
Reynolds et al., 2021 ¹³	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 PaO₂ = time-weighted average of PaO₂.* The hyperoxia cohort was defined as having a TWA PaO₂ > 200 mm Hg within the first 24 hours.

TABLE 2. Demographic and clinical characteristics of included studies

Authors & Year	No. of Pts	Mean Age, yrs (SD)	Female Sex, n (%)	Mean Maximum PaO ₂ , 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., 2014 ¹¹	2894*	61 (15)	1408 (49)	274 (148)	NA	NA	NA	NA
Jeon et al., 2014 ¹⁵	252	56.7 (13.9)	179 (71.0)	146.5 (37.0)†	NA	NA	199 (79.0)	233 (92.5)
Lång et al., 2016 ¹⁶	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., 2019 ¹⁷	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., 2019 ¹²	196	62.7 (16.8)	133 (67.9)	193 (70.4)†	NA	NA	NA	NA
Fukuda et al., 2021 ¹⁴	197	62.1 (15.7)	133 (67.5)	NA	105 (53.3)	NA	NA	NA
Reynolds et al., 2021 ¹³	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)	1084/1273 (85.2)	816/1029 (79.3)

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.

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.

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 therapy has been well described.²⁰ The brain is one of the first organs to experience the effects of hyperoxemia due to the generation of ROS.^{21,22} 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.¹⁸ Oxidative stress has been associated with poor outcomes in the setting of ischemic stroke, TBI, and post-cardiac arrest.^{8–11}

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.^{13,23} 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.^{23,24} Indeed, it has been found that even healthy patients exposed to hyperoxia transiently develop increased ROS burden, lipid peroxidation, and reduced nitric oxide metabolites.²⁵ 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.^{23,26,27} It is also believed that ROS may be involved with NLRP3 inflammasome activation^{28,29} and upregulation of oxidized low-density lipoprotein (LDL) and its receptor, lectin-like oxidized LDL receptor-1.^{30–32} Both are currently being studied for their potential roles in the development of DCI.

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

Authors & Year	Poor Neurological Outcome			DCI or Cerebral Vasospasm			Mortality		
	Hyperoxia	Normoxia	Adjusted ES (95% CI)	Hyperoxia	Normoxia	Adjusted ES (95% CI)	Hyperoxia	Normoxia	Adjusted ES (95% CI)
Rincon et al., 2014 ¹¹	NA	NA	NA	NA	NA	NA	80/135	139/383	NA
Jeon et al., 2014 ¹⁵	32/18	76/76	2.30 (1.03–5.12)	36/28	61/127	3.16 (1.69–5.92)	NA	NA	NA
Lång et al., 2016 ¹⁶	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., 2019 ¹⁷	27/12	95/110	3.788 (1.13–12.70)	NA	NA	NA	NA	NA	NA
Yokoyama et al., 2019 ¹²	48/40	42/60	1.38 (0.99–1.83)	17/71	10/98	NA	NA	NA	NA
Fukuda et al., 2021 ¹⁴	25/22	57/93	1.17 (1.06–1.29)	16/31	26/89	1.09 (1.01–1.17)	NA	NA	NA
Reynolds et al., 2021 ¹³	NA	NA	NA	NA	NA	1.15 (1.03–1.28)	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.

A. Neurologic outcome

Study	OR	Lower	Upper	p-value	Weight	Weight (%)
Jeon et al ¹⁵	1.78	0.92	3.44	0.09	7.44	18.48
Lang et al ¹⁶	3.60	2.06	6.28	0.00	9.83	24.42
Li et al ¹⁷	2.61	1.25	5.42	0.01	6.20	15.40
Yokoyama et al ¹²	1.89	1.07	3.34	0.03	9.42	23.42
Fukuda et al ¹⁴	1.71	0.88	3.33	0.11	7.36	18.28
Overall	2.26	1.66	3.07	<0.001		

Model: Random-effects model
 Heterogeneity: Tau-squared = 0.02, H-squared = 1.21, I-squared = 0.17
 Homogeneity: Q = 4.40, df = 4, p-value = 0.35
 Test of overall effect size: z = 5.16, p-value <0.001

B. Composite outcome

Study	OR	Lower	Upper	p-value	Weight	Weight (%)
Rincon et al ¹¹	2.55	1.71	3.81	0.00	23.82	32.74
Jeon et al ¹⁵	1.78	0.92	3.44	0.09	8.84	12.15
Lang et al ¹⁶	3.60	2.06	6.28	0.00	12.43	17.09
Li et al ¹⁷	2.61	1.25	5.42	0.01	7.14	9.82
Yokoyama et al ¹²	1.89	1.07	3.34	0.03	11.79	16.21
Fukuda et al ¹⁴	1.71	0.88	3.33	0.11	8.72	11.99
Overall	2.36	1.87	2.97	<0.001		

Model: Random-effects model
 Heterogeneity: Tau-squared = 0.00, H-squared = 1.00, I-squared = 0.00
 Homogeneity: Q = 4.63, df = 5, p-value = 0.46
 Test of overall effect size: z = 7.31, p-value <0.001

C. DCI

Study	OR	Lower	Upper	p-value	Weight	Weight (%)
Jeon et al ¹⁵	2.68	1.50	4.78	0.00	8.21	30.41
Lang et al ¹⁶	1.30	0.74	2.28	0.37	8.58	31.79
Yokoyama et al ¹²	2.35	1.01	5.43	0.05	4.61	17.05
Fukuda et al ¹⁴	1.77	0.84	3.72	0.13	5.60	20.75
Overall	1.91	1.31	2.78	<0.001		

Model: Random-effects model
 Heterogeneity: Tau-squared = 0.03, H-squared = 1.30, I-squared = 0.23
 Homogeneity: Q = 3.39, df = 3, p-value = 0.34
 Test of overall effect size: z = 3.35, p-value <0.001

FIG. 2. Forest plots of individual and pooled unadjusted ORs for poor neurological outcome (A), mortality or poor neurological outcome as a combined outcome measure (B), and incidence of DCI (C). Composite outcome was constructed by pooling the reported unadjusted ORs for either mortality or poor neurological outcome. If a study reported both outcomes, poor neurological outcome was used preferentially. ORs > 1 (right side of plot) indicate a positive association between hyperoxemia and the outcome in question. Pooled ORs were calculated with a random-effects model.

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.^{33–35} In

the setting of SAH, it remains under debate whether this reduction in cerebral blood flow is caused directly by hyperoxia, or indirectly by the resulting hyperventilation and hypocapnia.^{34,36,37} Interestingly, several retrospective stud-

A. Neurologic outcome

Study	OR	Lower	Upper	p-value	Weight	Weight (%)
Jeon et al ¹⁵	2.30	1.03	5.13	0.04	5.52	4.97
Lang et al ¹⁶	1.09	0.61	1.96	0.77	9.68	8.72
Li et al ¹⁷	3.79	1.13	12.69	0.03	2.53	2.28
Yokoyama et al ¹²	1.38	1.02	1.88	0.04	26.02	23.44
Fukuda et al ¹⁴	1.17	1.10	1.24	0.00	67.28	60.59
Overall	1.28	1.07	1.55	0.01		

Model: Random-effects model
 Heterogeneity: Tau-squared = 0.01, H-squared = 1.40, I-squared = 0.29
 Homogeneity: Q = 7.36, df = 4, p-value = 0.12
 Test of overall effect size: z = 2.63, p-value = 0.01

Forest Plot

B. Composite outcome

Study	OR	Lower	Upper	p-value	Weight	Weight (%)
Jeon et al ¹⁵	2.30	1.03	5.13	0.04	5.97	0.47
Lang et al ¹⁶	1.09	0.61	1.96	0.77	11.18	0.87
Li et al ¹⁷	3.79	1.13	12.69	0.03	2.63	0.21
Yokoyama et al ¹²	1.38	1.02	1.88	0.04	40.68	3.18
Fukuda et al ¹⁴	1.71	1.10	1.24	0.00	980.43	76.67
Reynolds et al ¹³	1.10	0.97	1.25	0.14	237.828	18.60
Overall	1.17	1.11	1.23	<0.001		

Model: Random-effects model
 Heterogeneity: Tau-squared = 0.00, H-squared = 1.00, I-squared = 0.00
 Homogeneity: Q = 8.43, df = 5, p-value = 0.13
 Test of overall effect size: z = 5.57, p-value <0.001

C. DCI

Study	OR	Lower	Upper	p-value	Weight	Weight (%)
Jeon et al ¹⁵	3.16	1.69	5.91	0.00	2.85	26.34
Fukuda et al ¹⁴	1.09	1.01	1.17	0.02	3.99	36.95
Reynolds et al ¹³	1.15	1.03	1.28	0.01	3.97	36.71
Overall	1.47	0.81	2.67	0.20		

Model: Random-effects model
 Heterogeneity: Tau-squared = 0.25, H-squared = 58.48, I-squared = 0.98
 Homogeneity: Q = 11.27, df = 2, p-value = 0.00
 Test of overall effect size: z = 1.27, p-value = 0.20

FIG. 3. Forest plots of individual and pooled adjusted ORs for poor neurological outcome (A), mortality or poor neurological outcome as a combined outcome measure (B), and incidence of DCI (C). Composite outcome was constructed by pooling the reported adjusted ORs for either mortality or poor neurological outcome. If a study reported both outcomes, poor neurological outcome was used preferentially. ORs > 1 (right side of plot) indicate a positive association between hyperoxemia and the outcome in question. Pooled ORs were calculated with a random-effects model.

ies have shown hyperventilation or hypocapnia to be independently associated with worse outcomes after SAH.^{17,38,39} Further studies are needed to investigate hypocapnia in the context of SAH as well as other pathological processes.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.^{8,15,41} 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.⁴²

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.,¹⁴ 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.¹⁵ Reynolds et al.¹³ 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.¹² and Lång et al.¹⁶ 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.⁴³

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).¹⁵ In contrast, the studies by Fukuda et al. and Reynolds et al. did not exclude nonintubated patients.^{14,13} 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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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Mastorakos, Ahn, Chen, Kellogg, Park. Acquisition of data: Mastorakos, Ahn. Analysis and interpretation of data: Mastorakos, Ahn. Drafting the article: Mastorakos, Ahn. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mastorakos. Statistical analysis: Mastorakos, Ahn. Administrative/technical/material support: Mastorakos, Ahn. Study supervision: Mastorakos, Sokolowski.

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