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Hyperoxemia and Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage

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Abstract

Background: Cerebral vasospasm is a major contributor to disability and mortality after aneurysmal subarachnoid hemorrhage. Oxidation of cell-free hemoglobin plays an integral role in neuroinflammation and is a suggested source of tissue injury after aneurysm rupture. This study sought to determine if patients with subarachnoid hemorrhage and cerebral vasospasm were more likely to have been exposed to early hyperoxemia than those without vasospasm.

Methods: This single-center retrospective cohort study included adult patients presenting with aneurysmal subarachnoid hemorrhage to Vanderbilt University Medical Center between January 2007 and December 2017. Patients with an ICD-9/10 diagnosis of aneurysmal subarachnoid hemorrhage were initially identified (N=441) and subsequently excluded if they did not have intracranial imaging, arterial PaO_2 values, or died within 96 hours post-rupture (N=96). The final cohort was 345 subjects. The degree of hyperoxemia was defined by the highest PaO_2 measured within 72 hours after aneurysmal rupture. The primary outcome was development of cerebral

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vasospasm, which included asymptomatic vasospasm and delayed cerebral ischemia (DCI). Secondary outcomes were mortality and modified Rankin Scale.

Results: 345 patients met inclusion criteria; 218 patients (63%) developed vasospasm. Of those that developed vasospasm, 85 were diagnosed with delayed cerebral ischemia (DCI, 39%). The average patient age of the cohort was 55±13 years, and 68% were female. Ninety percent presented with Fisher Grade 3 or 4 hemorrhage (N=310) while 42% presented as Hunt-Hess Grade 4 or 5 (N=146). In univariable analysis, patients exposed to higher levels of PaO_2 by quintile of exposure had a higher mortality rate and were more likely to develop vasospasm in a dose-dependent fashion (P=0.015 and P=0.019, respectively). There were no statistically significant predictors that differentiated asymptomatic vasospasm from DCI and no significant difference in maximum PaO_2 between these two groups. In multivariable analysis, early hyperoxemia was independently associated with vasospasm (OR=1.15 per 50 mmHg increase in PaO2 [1.03, 1.28]; P=0.013), but not mortality (OR=1.10 [0.97, 1.25]; P=0.147) following subarachnoid hemorrhage.

Conclusions: Hyperoxemia within 72 hours post-aneurysmal rupture is an independent predictor of cerebral vasospasm, but not mortality in subarachnoid hemorrhage. Hyperoxemia is a variable that can be readily controlled by adjusting the delivered FiO_2 and may represent a modifiable risk factor for vasospasm.

Keywords

hyperoxemia; vasospasm; subarachnoid hemorrhage; aneurysm; oxidative stress

Introduction

Subarachnoid hemorrhage (SAH) due to a ruptured intracranial aneurysm accounts for 5% of all strokes in North America[1]. Although the mortality rate associated with aneurysmal SAH has declined over the past few decades, it remains greater than 30%[2]. A major contributor to death and disability after SAH is the development of cerebral vasospasm. In fact, it is estimated that half of the deaths in patients surviving treatment after SAH are attributable to vasospasm. Vasospasm has a spectrum of severity, spanning from asymptomatic patients to those that develop delayed cerebral ischemia (DCI) and infarction. The consequences of vasospasm contribute to high rates of long-term complications and poor quality of life due to significant neurocognitive impairment and loss of independence[3].

Currently there is no effective preventative therapy for cerebral vasospasm. The discovery that nimodipine significantly reduces the occurrence of severe neurologic deficits from vasospasm after SAH was made over 36 years ago and changed practice[4]. However, despite the fact that nearly all SAH patients receive nimodipine, the burden of disability and death from vasospasm persists[3]. In addition to nimodipine, pharmacologic measures to optimize cerebral perfusion by inducing hypertension are routinely utilized after the aneurysm has been secured to ameliorate the effects of vasospasm[5]. Once DCI develops, additional endovascular approaches are commonly employed to aid in delivery of vasodilators or provide restoration of flow in narrowed arterial vessels through cerebral angioplasty[6,7]. These therapies, while important and effective, are not preventative. New insights into the

pathophysiology of cerebral vasospasm after SAH are necessary to develop preventative therapies for this devastating condition.

The holy grail of understanding vasospasm pathophysiology has been the identification of a "spasmogen"[8]. The proximate triggering event of vasospasm is the initial deposition of blood in the subarachnoid space[9]. The Fisher scale illustrates a dose-dependent relationship between the amount and pattern of blood and development of vasospasm; however, clot removal or fibrinolysis has not proven to prevent vasospasm[10,11,12]. As such, current research has focused on understanding the 'spasmogenic' nature of the hemorrhage. During clot resolution, extravascular cell-free hemoglobin (CFH) levels rise with the blood breakdown[13]. CFH is a known mediator of inflammation and oxidative tissue injury, which makes it a good candidate "spasmogen"[14,15]. Hyperoxemia increases oxidation of CFH, which has known spasmogenic effects in the pulmonary vasculature, but the effects of hyperoxemia and resultant oxidation of CFH on the cerebral vasculature remains uncertain[16,17,18]. The authors' goal was to test the hypothesis that there was a higher incidence of cerebral vasospasm and mortality for patients with aneurysmal SAH who were exposed to hyperoxemia within 72 hours post-aneurysm rupture compared to those who were not exposed to hyperoxemia.

Methods

Data Source

Patients greater than or equal to 18 years of age with non-traumatic subarachnoid hemorrhage secondary to ruptured aneurysm who presented to Vanderbilt University Medical Center between 2007 and 2017 were identified. Records were obtained from the Synthetic Derivative (SD), which is a de-identified database containing clinical information from the hospital electronic medical record[19]. The SD is not linked to the original medical record and is modified to ensure no identifiers can be traced back to an individual patient. Given the de-identified data source, the study was determined to be exempt by the Vanderbilt Institutional Review Board.

Inclusion and Exclusion Criteria

Patients (N=1,391) were identified by International Classification of Diseases (ICD) codes for nontraumatic subarachnoid hemorrhage. The specific codes were 430 and I60.XX for ICD-9 and ICD-10, respectively. Aneurysmal SAH was confirmed by manual review of each SD record for a computed tomography angiography (CTA) scan and/or a catheter-based angiography procedure which indicated the presence of an aneurysm. Patients who did not have at least one CT of the head or an arterial blood gas in the first 72 hours were excluded. The 72-hour window was selected as vasospasm usually begins on or after post-hemorrhage day three. Time zero was measured from the onset of patient symptoms. Additionally, those who died in the first 96 hours after aneurysmal rupture were excluded from the study as they did not survive long enough to develop vasospasm and thus were unlikely to have a clinical outcome modified by early hyperoxemia. There were 345 patients included in the study (Supplemental Figure I).

Data Collection

Clinical and demographic covariates were identified on the basis of commonly reported risk factors for vasospasm or mortality secondary to aneurysm rupture including age, gender, ethnicity, tobacco use, and Fisher and Hunt-Hess grades[20–22]. Study data were stored in a Research Electronic Data Capture (REDCap) database, which is a secure, web-based application designed to manage clinical data for research studies[23].

Outcome Measures

The primary outcome of this study was the development of cerebral vasospasm, which included both asymptomatic and symptomatic patients. Secondary outcomes studied were mortality and modified Rankin Scale at hospital discharge[24]. Cerebral vasospasm was defined as vasospasm occurring greater than 72 hours after the time of aneurysmal rupture. Vasospasm was defined by an elevated Lindegaard (Li) ratio in the anterior (>3.0) or posterior circulation (>2.0) on transcranial doppler, a report of vasospasm on CTA, MRI with evidence of ischemic stroke, and/or the need for direct intra-arterial therapy for vasospasm in the operating room. Asymptomatic vasospasm was defined by positive transcranial dopplers or CTA but no need for emergent endovascular therapy and no MRI with evidence of infarct. Symptomatic patients, or those with DCI, were defined by the need for emergent intra-arterial therapy and/or MRI with evidence of ischemic stroke. Measures of mortality were confined to in-hospital deaths after the first 96 hours post-aneurysm rupture for reasons previously stated. The primary exposure variable was early hyperoxemia as captured by arterial blood gas analyses completed for clinical reasons. All arterial blood gas results from the first 72 hours after aneurysm rupture were recorded for each patient. The mean number of arterial blood gas analyses in the first 72 hours after aneurysm rupture was 4 ± 3 per patient. The timing of aneurysm rupture was defined by patient-reported symptom onset. PaO_2 was a continuous variable and its maximum value within 72 hours post-aneurysm rupture was used in our analyses. For some analyses, quintiles of maximum PaO_2 in the first 72 hours were compared across the cohort.

Statistical Analysis

Patient characteristics were analyzed by the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. Multivariable logistic regression was performed to determine whether PaO_2 was independently associated with development of vasospasm or mortality. Prespecified potential confounders, including age, gender, ethnicity, tobacco abuse, Fisher grade[10], Hunt Hess grade[25], and minimum $PaCO_2$ within 72 hours of aneurysmal rupture were adjusted in all models. Fisher and Hunt-Hess grades were dichotomized into more and less severe groups. The "more severe" groups were Fisher grades 3 and 4 and Hunt-Hess grades 4 and 5, which is consistent with prior vasospasm studies[26]. Multiple imputation with predictive mean matching was used to impute missing values of covariates in regression models[27]. Among variables used in the multivariable model, there was a negative correlation between minimum $PaCO_2$ and maximum PaO_2. There was a positive correlation between Fisher and Hunt-Hess grades and maximum PaO_2. Although there was correlation among these variables, there was no evidence of multicollinearity when the variance inflation factor was used, indicating that the models are

statistically valid. Two-sided *P* values less than 0.05 were deemed statistically significant. Statistical analysis and graphics were completed using R software Version 3.

Results

Demographics and Clinical Characteristics

There were 345 patients who met inclusion criteria. In total, 218 patients or 63% developed cerebral vasospasm. Overall patient characteristics and a comparative analysis between those with and without vasospasm are found in Table 1. 68% of patients were female (N=234). By univariable analysis, patients who developed vasospasm were younger in age at 52.9±11.9 years versus 57.2±15.2 years (P=0.004). Patients with higher Fisher and Hunt-Hess grades were more likely to develop vasospasm (P=0.003 and 0.035, respectively). There was no significant difference in gender (66% versus 72% female; P=0.325) or tobacco use (61% vs. 50%; P=0.062) between the vasospasm and no vasospasm groups, respectively. Ninety-nine percent of all patients with or without vasospasm received nimodipine therapy (N=342; P=0.788). There was no association between vasospasm and use of open versus endovascular treatment to secure the aneurysm (P=0.283).

Of the 218 patients with vasospasm, 143 met the criteria for asymptomatic vasospasm while 85 (39%) developed delayed cerebral ischemia, as shown in Table 2. There were no statistically significant predictors that differentiated these two groups and no significant difference in maximum PaO_2 between them. Therefore, the primary outcome of cerebral vasospasm included patients who developed DCI in addition to those who developed asymptomatic vasospasm.

Vasospasm and Maximum PaO_2

The highest PaO_2 value in the first 72 hours after aneurysm rupture was significantly higher in patients who went on to develop vasospasm compared to those who did not (232 ± 124 mmHg versus 195 ± 101 mmHg; P=0.012; (Figure 1A). There was an apparent dose-dependent relationship between degree of hyperoxemia as measured by quintile of exposure and risk of vasospasm (Figure 1B). In a multivariable logistic regression for vasospasm controlling for potential confounders (Table 3), higher PaO_2 was associated with a higher risk of vasospasm (OR=1.15 per 50 mmHg increase in PaO_2 [1.03, 1.28]; P=0.013). Variables that were associated with a lower risk of development of vasospasm included non-Caucasian ethnicity (OR=0.51 [0.28, 0.92]; P=0.026), older age (OR=0.97 [0.96, 0.99]; P=0.007), and lower Hunt-Hess grade (OR=0.59 [0.35, 0.98]; P=0.043). All other variables, including Fisher grade, were not significant. (Figure 2)

Mortality and Maximum PaO_2

The hospital mortality rate in the included patient population was 15% (N=52). In the multivariable analysis for mortality (Table 2), older age (OR=1.04 per year [1.01, 1.06]; P=0.002) was significantly associated with mortality. Conversely, a higher minimum $PaCO_2$ was associated with better outcomes (OR=0.39 [0.22, 0.69]; P=0.001). Although in univariable analysis maximum PaO_2 was higher in patients who died in hospital (P=0.017, Figure 3A) and there was a dose response relationship between degree of hyperoxemia and

risk of death (Figure 3B), maximum PaO_2 was not a significant predictor of mortality in multivariable analysis after adjusting for potential confounders (OR=1.10 per 50 mmHg [0.97, 1.25]; P=0.147).

Modified Rankin Scale and Maximum PaO_2

Although there was a trend towards an association between higher maximum PaO_2 and lower modified Rankin Scale at discharge, this was not statistically significant (P=0.067, see Supplemental Figure II).

Discussion

Summary of Findings

Our results identify a novel and potentially modifiable risk factor for cerebral vasospasm after subarachnoid hemorrhage. We demonstrate that early hyperoxemia, as measured by maximum PaO_2 within the first 72 hours after aneurysmal rupture, is associated with a higher incidence of cerebral vasospasm. Notably, this finding persisted across the range of severity of SAH and vasospasm. Additionally, the overall degree of hyperoxemia in our study was only moderate, with a mean maximum PaO_2 of 219 mmHg in the study population, consistent with the use of low to moderate levels of supplemental oxygen. In addition to hyperoxemia, ethnicity, age and Hunt-Hess grade were independently associated with cerebral vasospasm, which is consistent with some of the existing literature[28]. Hyperoxemia was also associated with higher hospital mortality in a dose-dependent fashion in univariable analysis, although this association did not remain significant after adjustment for potential confounders.

Hyperoxemia is Common after Aneurysmal Rupture

Ideally, patients with aneurysmal subarachnoid hemorrhage are admitted to a neurologic intensive care unit where a multidisciplinary team can best manage their complex care. The initial focus is to secure the aneurysm by surgical or endovascular means to prevent re-bleeding. As a result, patients are often managed in multiple environments including the operating room, endovascular suite and intensive care unit and are managed by many teams including neuro-intensivists, neuro-anesthesiologists, stroke neurologists and cerebrovascular neurosurgeons. In concert with securing the aneurysm, there is intense attention paid to the key physiological imperative of maximizing cerebral perfusion through careful blood pressure management, often with the institution of induced hypertension using vasoactive support. In addition, the $PaCO_2$ is carefully calibrated through adjustment of the minute ventilation to optimize cerebral perfusion and minimize cerebral ischemia. While blood pressure and $PaCO_2$ are thus monitored closely by teams across all care environments, comparatively little attention has been paid to the PaO_2. Indeed, in this study of over 345 aneurysmal SAH patients, there was wide variability in the maximum PaO_2 measured in the first 72 hours after aneurysm rupture. In fact, patient arterial oxygen levels in our study ranged from approximately 60 to 600mmHg, confirming that PaO_2 is not a parameter that is tightly titrated after SAH. This variability is not unique to aneurysmal SAH and is common across different diagnoses and various intensive care unit settings[29].

Proposed Underlying Mechanism of Hyperoxemia and Vasospasm

Hyperoxemia is defined by excess oxygen content in the arterial blood. In hospital settings, hyperoxemia is caused by administration of excessive supplemental oxygen. While oxygen is critical to survival, supra-physiologic levels can drive damaging cellular responses through generation of reactive oxygen species leading to proinflammatory effects. Reactive oxygen species have been implicated in multiple deleterious processes including cell death[30], cancer[31], and aging[32]. We hypothesize that hyperoxemia in SAH promotes the upregulation of reactive oxygen species through the oxidation of cell-free hemoglobin in the subarachnoid space[33]. Oxidized extracellular hemoglobin subsequently drives lipid and protein oxidation to cause neuronal apoptosis and brain injury[34]. The excess free radicals further stimulate the hypersensitive arterial system to cause vasospasm[35]. In addition to effects on cell-free hemoglobin in the subarachnoid space, other postulated mechanisms of hyperoxemia-induced vasospasm include disrupted mitochondrial respiration, uncoupling of nitric oxide synthase, and disruption of intrinsic oxidative signaling pathways[17,36,37].

Hyperoxemia Associates with Neurologic Morbidity

Hyperoxemia has been associated with adverse clinical outcomes in other clinical conditions. For example, in animal models, hyperoxemia can precipitate acute lung injury when the fraction of inspired oxygen (F_{IO2}) exceeds 0.7 through generation of high levels of reactive oxygen species that overwhelm natural antioxidant defenses in the lung and cause destruction of cellular structures[38]. Hyperoxemia in premature infants with exposure to mean PaO_2 values of 107.3 ± 59.3 mmHg has been correlated with compromised long-term neurodevelopmental outcomes[39]. In post-cardiac arrest patients, hyperoxemia is associated with higher mortality rate and worse Cerebral Performance Category Scale at hospital discharge among survivors[40], while studies of hyperoxemia in the setting of stroke and traumatic brain injury studies have yielded mixed results[41,42]. Several recent clinical studies have attempted to examine whether any association exists between blood oxygen levels and outcomes following SAH, with varying results. A study by Yokoyama et al suggested that hyperoxemia, defined categorically as $PaO_2 > 120$ mmHg, within the first 24 hours in an intensive care unit is associated with worse neurological disability defined as modified Rankin Scale at hospital discharge in patients with mild-to-moderate SAH[43]. Another study by Lång et al similarly examined arterial oxygen levels during the first 24 hours in an intensive care unit; this study did not demonstrate any association between oxygen levels and Glasgow Outcome Scale or mortality[44]. Both studies were potentially limited by their short observation windows since vasospasm most commonly occurs at least 72 hours post-SAH. A study by Jeon et al suggested an association between sustained hyperoxemia and delayed cerebral ischemia along with poor 3-month neurological outcomes in long-term mechanically ventilated patients; however, this publication was biased toward a more severely ill patient population than our study[18]. To our knowledge, this is the first study to demonstrate an independent association between early hyperoxemia and cerebral vasospasm in patients presenting with SAH of varying degrees of severity.

Study Limitations

The principal limitations of this study are attributable to its retrospective nature at a single academic center. Further prospective human studies at multiple institutions are required. The inclusion and exclusion criteria may limit the generalizability of the findings. Patients who died within the first 96 hours were excluded from this study since early death would preclude development of cerebral vasospasm, potentially confounding the analysis. Although exclusion of early deaths may have shifted the analysis to include less severely ill patients, the spectrum of Hunt-Hess grades was widely distributed across the cohort, thereby including patients of all hemorrhage severities. The requirement for an arterial blood gas analysis in the first 72 hours may have excluded less severely ill patients whose respiratory status could be managed without blood gas monitoring. Less severely ill patients may also have presented later than 72 hours after initial symptom onset, thereby excluding them from the study since no PaO_2 values would have been obtained prior to hospital presentation. Conversely, since hyperoxemia is an iatrogenic phenomenon, the study inclusion criteria may introduce bias toward the more severely ill, mechanically ventilated patients. In attempts to mitigate this fact, hemorrhage severity scores and PaCO2 values were controlled for in the multivariable analyses. Lastly, we elected to use the highest PaO_2 value in the first three days after hemorrhage as an index of hyperoxemia, but this reflects a single data point in time and is not representative of duration of time spent at this elevated value. All arterial blood gases were obtained for clinical reasons and thus the timing and number of blood gases was not standardized. A continuous measurement of oxygenation including time spent at each elevated value would provide a more accurate measurement of hyperoxemia, but this data was not available retrospectively. Despite these limitations, the study includes a diverse patient population across varying degrees of hemorrhage severity and multiple PaO_2 measurements, which are reflective of a “real-world” sampling pattern.

Conclusions

In patients with aneurysmal subarachnoid hemorrhage, hyperoxemia is common within the first 72 hours after aneurysm rupture and is an independent predictor of cerebral vasospasm. Since hyperoxemia is readily measured and can be eliminated by titration of the level of supplemental oxygen, it may be an easily modifiable risk factor for cerebral vasospasm. Larger prospective studies are needed to validate the clinical significance of this finding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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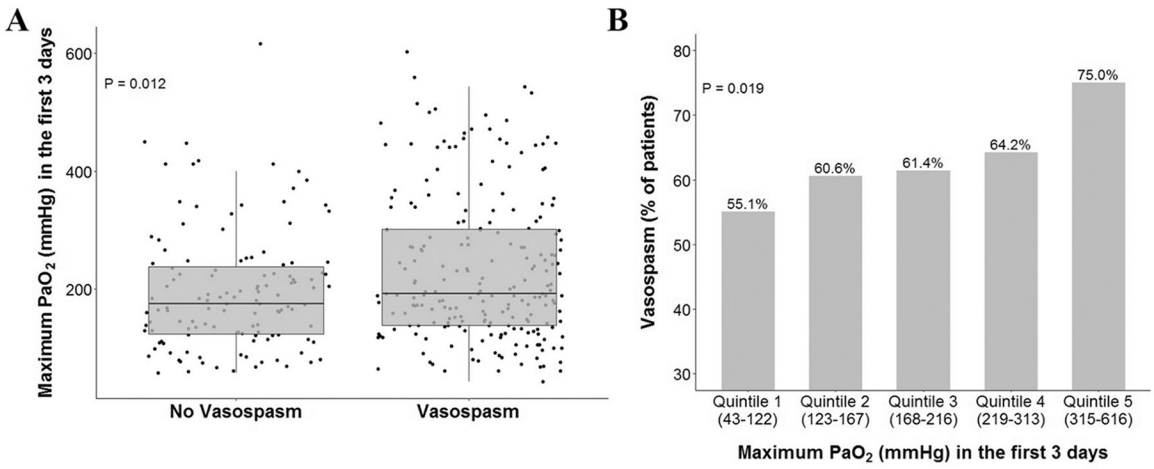


Figures 1A and 1B. Maximum PaO_2 and vasospasm.

(A) Maximum PaO_2 is significantly higher in patients who subsequently develop cerebral vasospasm in unadjusted analysis (P=0.012 by Kruskal-Wallis test). (B) Maximum PaO_2 exhibited behavior similar to a dose-dependent effect on vasospasm. (P = 0.019 by linear-by-linear test).

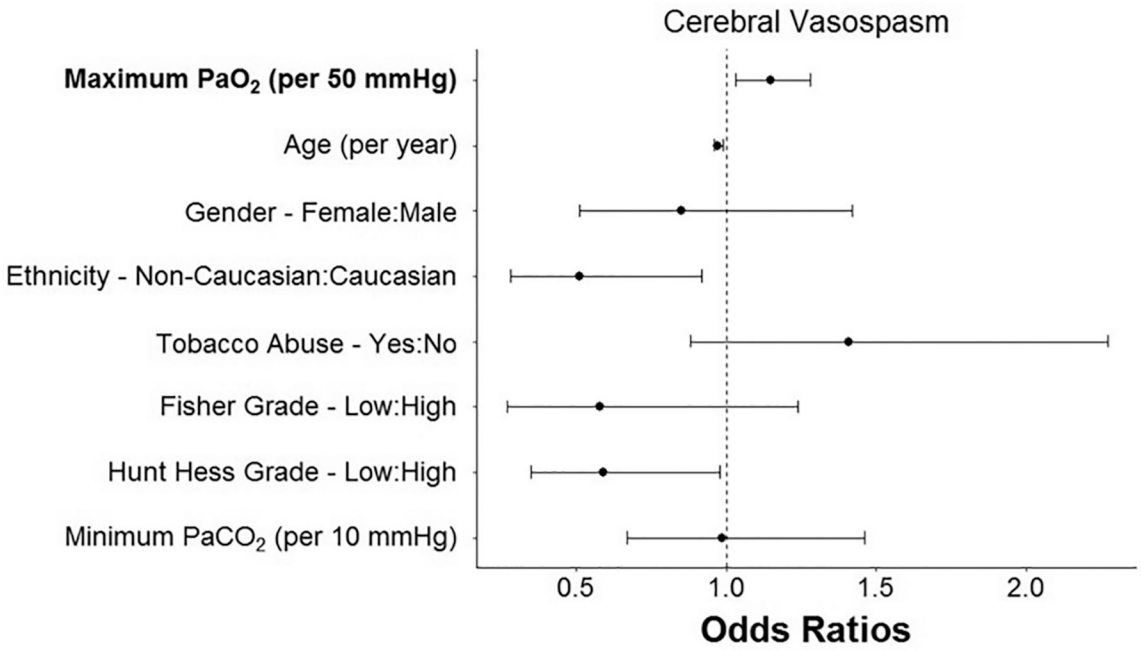
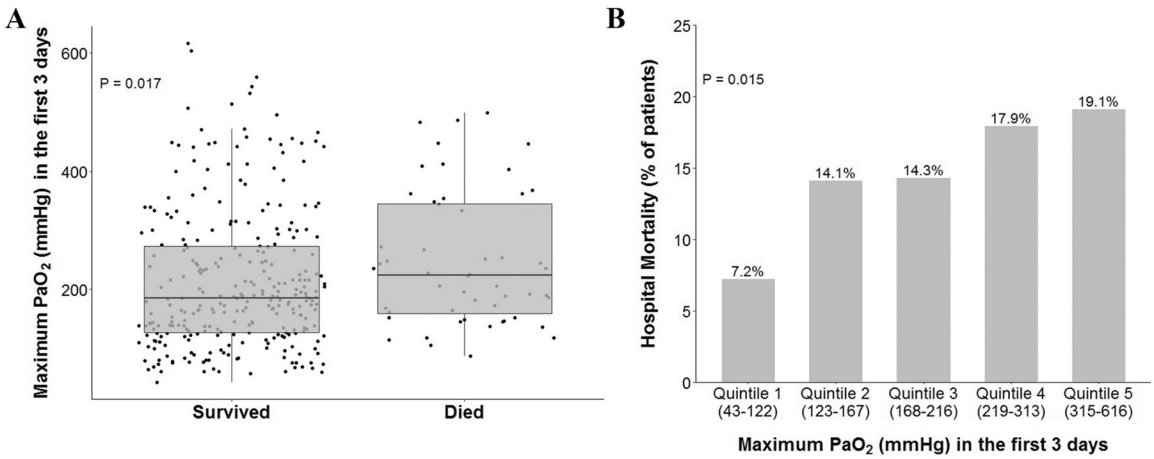


Figure 2. Multivariable analysis for development of vasospasm.

Early hyperoxia was significantly associated with vasospasm controlling for potential confounders.



Figures 3A and 3B. Maximum PaO_2 and mortality.

(A) Maximum PaO_2 is significantly higher in patients who died in hospital in unadjusted analysis (P=0.017 by Kruskal-Wallis test). (B) Maximum PaO_2 exhibited behavior similar to a dose-dependent effect on hospital mortality (P = 0.015 by linear-by-linear test).

Table 1.

Patient demographics and clinical characteristics (N=345).

	All patients (N = 345)	No vasospasm (N = 127)	Vasospasm (N = 218)	p-value
Age in years (mean (SD))	**54.5 (13.4)**	**57.2 (15.2)**	**52.9 (11.9)**	**0.004**
Sex (n (%))				0.325
Female	234 (68)	91 (72)	143 (66)	
Male	111 (32)	36 (28)	75 (34)	
Race (n (%))				
White	269 (78)	92 (72)	177 (81)	0.203
Black	50 (15)	23 (18)	27 (12)	
Other	26 (8)	12 (10)	14 (7)	
Tobacco use (n (%))				0.062
Yes	195 (57)	63 (50)	132 (61)	
No	150 (43)	64 (50)	86 (39)	
Fisher grade (n (%))				**0.003**
1	**6 (2)**	**5 (4)**	**1 (1)**	
2	**29 (8)**	**13 (10)**	**16 (7)**	
3	**57 (17)**	**29 (23)**	**28 (13)**	
4	**253 (73)**	**80 (63)**	**173 (79)**	
Hunt-Hess grade (n (%))				**0.035**
1	**24 (7)**	**10 (8)**	**14 (6)**	
2	**81 (24)**	**40 (32)**	**41 (19)**	
3	**94 (27)**	**35 (28)**	**59 (27)**	
4	**94 (27)**	**25 (20)**	**69 (32)**	
5	**52 (15)**	**17 (13)**	**35 (16)**	
Initial treatment (n (%))				0.283
Endovascular	277 (81)	107 (85)	170 (78)	
Open surgery	59 (17)	16 (13)	43 (20)	
Other	7 (2)	3 (2)	4 (2)	
Nimodipine use (n (%))				0.788
Yes	342 (99)	126 (99)	216 (99)	
No	3 (1)	1 (1)	2 (1)	
Maximum PaO_2 (mean (SD))	**218.8 (117.3)**	**195.4 (101.0)**	**232.4 (124.1)**	**0.005**
Minimum $PaCO_2$ (mean (SD))	34.1 (6.5)	34.8 (6.7)	33.7 (6.3)	0.100

Table 2.

Vasospasm subgroup analysis: asymptomatic versus delayed cerebral ischemia

Total N = 218	**Asymptomatic Vasospasm (n= 143)**	**Delayed Cerebral Ischemia (n=85)**	**p-value**
Age in years (mean (SD))	52.6 (12.3)	53.9 (12.1)	0.438
Race			0.614
White	83 (71)	113 (79)	
Black	23 (20)	19 (13)	
Other	11 (9)	11 (8)	
Sex (n (%))			0.445
Female	97 (68)	52 (62)	
Male	146 (32)	33 (38)	
Tobacco use (n (%))			0.565
Yes	84 (59)	54 (64)	
No	59 (41)	31 (36)	
Fisher grade (n (%))			0.636
1	0 (0)	1 (1)	
2	10 (7)	6 (7)	
3	18 (13)	11 (13)	
4	115 (80)	67 (79)	
Hunt-Hess grade (n (%))			0.217
1	9 (6)	6 (7)	
2	32 (22)	10 (12)	
3	40 (28)	21 (25)	
4	42 (29)	30 (35)	
5	20 (14)	18 (21)	
Initial treatment (n (%))			0.560
Endovascular	110 (78)	68 (80)	
Open surgery	30 (21)	15 (18)	
Other	2 (1)	2 (1)	
Nimodipine use (n (%))			--
Yes	142 (100)	84 (100)	
No	0 (0)	0 (0)	
Maximum PaO_2 (mean (SD))	240.5 (126.9)	213.1 (113.2)	0.102
Minimum $PaCO_2$ (mean (SD))	33.5 (6.4)	33.9 (6.1)	0.659

Table 3.

Multivariable analyses for vasospasm and mortality.

Vasospasm		
Variable	**Odds Ratio [2.5%, 97.5% CI]**	**p-value**
Sex (female)	0.85 [0.51, 1.41]	0.538
Age (years)	**0.97 [0.96, 0.99]**	**0.007**
Tobacco use	1.41 [0.88, 2.27]	0.153
Ethnicity (Non-Caucasian)	**0.51 [0.28, 0.92]**	**0.026**
Fisher grade (low)	0.58 [0.27, 1.23]	0.159
Hunt-Hess grade (low)	**0.59 [0.35, 0.98]**	**0.043**
Minimum $PaCO_2$ (per 10mmHg increase)	0.99 [0.67, 1.45]	0.951
Maximum PaO_2 (per 50mmHg increase)	**1.15 [1.03, 1.28]**	**0.013**
Mortality		
Sex (female)	0.90 [0.44, 1.81]	0.762
Age (years)	**1.04 [1.01, 1.06]**	**0.002**
Tobacco use	0.57 [0.30, 1.08]	0.084
Ethnicity (Non-Caucasian)	0.67 [0.26, 1.71]	0.406
Fisher grade (low)	2.58 [0.88, 7.51]	0.083
Hunt-Hess grade (low)	0.58 [0.29, 1.16]	0.125
Minimum $PaCO_2$ (per 10mmHg increase)	**0.39 [0.22, 0.69]**	**0.001**
Maximum PaO_2 (per 50mmHg increase)	1.10 [0.97, 1.25]	0.147