

The Association Between Spontaneous Hyperventilation, Delayed Cerebral Ischemia, and Poor Neurological Outcome in Patients with Subarachnoid Hemorrhage

Craig A. Williamson^{1,2} · Kyle M. Sheehan^{1,2} · Renuka Tipirneni^{3,4} · Christopher D. Roark¹ · Aditya S. Pandey¹ · B. Gregory Thompson¹ · Venkatakrishna Rajajee^{1,2}

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Abstract

Background The frequency and associations of spontaneous hyperventilation in subarachnoid hemorrhage (SAH) are unknown. Because hyperventilation decreases cerebral blood flow, it may exacerbate delayed cerebral ischemia (DCI) and worsen neurological outcome.

Methods This is a retrospective analysis of data from a prospectively collected cohort of SAH patients at an academic medical center. Spontaneous hyperventilation was defined by PaCO₂ <35 mmHg and pH >7.45 and subdivided into moderate and severe groups. Clinical and demographic characteristics of patients with and without spontaneous hyperventilation were compared using χ^2 or *t* tests. Bivariate and multivariable logistic regression analyses were conducted to examine the association of moderate and severe hyperventilation with DCI and discharge neurological outcome.

Results Of 207 patients, 113 (55 %) had spontaneous hyperventilation. Spontaneously hyperventilating patients

had greater illness severity as measured by the Hunt–Hess, World Federation of Neurosurgical Societies (WFNS), and SAH sum scores. They were also more likely to develop the following complications: pneumonia, neurogenic myocardial injury, systemic inflammatory response syndrome (SIRS), radiographic vasospasm, DCI, and poor neurological outcome. In a multivariable logistic regression model including age, gender, WFNS, SAH sum score, pneumonia, neurogenic myocardial injury, etiology, and SIRS, only moderate [odds ratio (OR) 2.49, 95 % confidence interval (CI) 1.10–5.62] and severe (OR 3.12, 95 % CI 1.30–7.49) spontaneous hyperventilation were associated with DCI. Severe spontaneous hyperventilation (OR 4.52, 95 % CI 1.37–14.89) was also significantly associated with poor discharge outcome in multivariable logistic regression analysis.

Conclusion Spontaneous hyperventilation is common in SAH and is associated with DCI and poor neurological outcome.

Keywords Stroke · Subarachnoid hemorrhage · Cerebral vasospasm · Hyperventilation · Respiratory alkalosis · Hypocapnia · Brain ischemia

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✉ Craig A. Williamson
craigaw@med.umich.edu

¹ Department of Neurosurgery, University of Michigan, 3552 Taubman Health Care Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA

² Department of Neurology, University of Michigan, Ann Arbor, MI 48109, USA

³ Robert Wood Johnson Foundation Clinical Scholars Program, University of Michigan, Ann Arbor, MI 48109, USA

⁴ Division of General Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

Introduction

Induced hyperventilation is an established, albeit controversial, method for treating acute elevations of intracranial pressure (ICP). While the use of prophylactic-induced hyperventilation is considered an appropriate short-term strategy to treat acute ICP elevations, it has also been associated with worse neurological outcome and greater risk of death when used in patients with traumatic brain injury (TBI) [1, 2]. Much less is known about the frequency and

clinical impact of spontaneous hyperventilation. A small number of prior observational studies found that hyperventilation can occur in response to severe brain injury and may be associated with worse neurological outcomes [3–7]. However, these studies did not attempt to control for confounding factors, such as illness severity and the presence of pneumonia, and did not focus on patients with subarachnoid hemorrhage (SAH).

Hyperventilation induces cerebral vasoconstriction with a corresponding decrease in cerebral blood flow (CBF) of approximately 2 % for every 1 mmHg (0.13 kPa) decrease in CO₂ [8]. As a result, ICP is lowered but decreased CBF may also lead to cerebral ischemia [9–11]. Because of the substantial risk of delayed cerebral ischemia (DCI), this physiological effect has particular relevance in SAH [12, 13]. To our knowledge, no prior studies have examined the incidence and impact of spontaneous hyperventilation in patients with SAH. Therefore, this study was conducted to determine the frequency of spontaneous hyperventilation in SAH and investigate its association with DCI and neurological outcome. We hypothesized that spontaneous hyperventilation is associated with greater illness severity, DCI, and poor neurological outcome at the time of hospital discharge.

Methods

Study Design

We conducted a retrospective analysis of data from a prospectively collected cohort of patients with SAH. Data were collected by the investigators and extracted from the electronic medical record. Approval for this study was provided by the University of Michigan Institutional Review Board.

Patient Population

All patients with spontaneous SAH admitted to the University of Michigan Neurological Intensive Care Unit (NICU) between January 2010 and March 2014 were identified from a patient registry. The registry was created by active surveillance of all patients admitted to the NICU. SAH was diagnosed by computed tomography (CT) scan and/or the presence of xanthochromia on lumbar puncture. Exclusion criteria included etiology from trauma or arteriovenous malformation and age <18 years.

Clinical Management

All patients were treated in accordance with current guidelines from the Neurocritical Care Society and

American Heart Association [14, 15]. Care was provided by a multidisciplinary team of neurosurgeons and neurointensivists in a dedicated neurological ICU, typically for 14 days. Twenty-four hour access to CT angiography, CT perfusion, and digital subtraction angiography (DSA) was available. All stable patients underwent emergent angiography and, if identified, aneurysms were secured within 24 h by surgical clipping or endovascular coiling. Any signs of hydrocephalus were treated by placement of an external ventricular drain. All patients were treated with nimodipine 60 mg every 4 h unless it was not tolerated due to hypotension despite adjustments in dose and frequency. Transcranial Doppler ultrasounds were performed on all patients for 14 days following the initial hemorrhage. Intravenous fluids were administered to maintain euolemia. Fever was treated aggressively with antipyretics and surface cooling devices. Daily spontaneous breathing trials were performed on all ventilated patients with fraction of inspired oxygen (FiO₂) ≤50 % and positive end expiratory pressure (PEEP) <10. The minimum amount of sedation necessary to prevent ventilator dyssynchrony and patient discomfort was provided. DCI, when present, was treated with additional intravenous fluids and hemodynamic augmentation with vasopressors. If not responsive to initial medical management or if deficits were deemed sufficiently severe, patients underwent emergent angiography and were treated with the intraarterial administration of nicardipine or balloon angioplasty at the discretion of the treating interventionalist.

Clinical Data

Arterial blood gas (ABG) results were reviewed for all subjects. Study subjects had to have at least one ABG that was obtained while not mechanically ventilated, or if mechanically ventilated, the patient had to be breathing above the set respiratory rate or on a pressure support (PS) mode. This was done to exclude instances of iatrogenic hyperventilation. Spontaneous hyperventilation was defined by the presence of at least one ABG with both PaCO₂ <35 mmHg (4.67 kPa) and pH >7.45. Patients were further defined as having severe hyperventilation if they had both PaCO₂ ≤30 mmHg (4.00 kPa) and pH ≥7.50. Patients with hyperventilation not meeting the requirement for severe hyperventilation were considered to have moderate hyperventilation.

Demographic data (age, sex) as well as social and medical history [tobacco use, alcohol abuse, diabetes, hypertension, coronary artery disease (CAD)] were obtained by interview with the patient and/or family on admission. The World Federation of Neurosurgical Societies (WFNS) and Hunt–Hess (HH) scores, both measures of clinical severity ranging from 1 to 5 with 5 indicating the most

severe neurological deficits, were determined by initial clinical examination [16, 17]. Two measures of radiographic severity, the modified Fisher scale (0–4; 0 = no visible hemorrhage, 4 = thick SAH with intraventricular hemorrhage) and Hjidra's SAH sum score (0–42; 0 = no visible hemorrhage, 42 = complete filling of 10 cisterns and fissures and all 4 ventricles) were calculated by the investigators based on the admission head CT [18, 19].

Patient complications including pneumonia, neurogenic myocardial injury, systemic inflammatory response syndrome (SIRS), radiographic vasospasm, DCI, and discharge neurological outcome were adjudicated by the investigators. Pneumonia was defined by the decision of the treating physician to complete a full course of antibiotic treatment based on chest X-ray, culture results, and clinical symptoms. Neurogenic myocardial injury was defined by abnormal elevation of troponin and/or the presence of newly impaired ejection fraction (EF <40 %) on echocardiogram [20]. SIRS was identified by the presence of at least 2 of 4 criteria: (1) temperature >38 or <36 °C; (2) pulse >90 beats/min; (3) respiratory rate >20 breaths/min; (4) WBC count >12,000 cells/mm³ or <4000 cells/mm³ [21].

Radiographic vasospasm was defined as the presence of vascular luminal narrowing on angiographic images as determined by the interpreting neuroradiologist. DCI was defined using previously published criteria as either (1) the development of new focal neurological signs or decline in the level of consciousness thought to be due to the presence of ischemia after other etiologies (hydrocephalus, toxic-metabolic abnormality, seizure) had been excluded or (2) the presence of new infarcts on CT or MRI [22]. Outcome at hospital discharge was determined by study staff via direct interview and review of therapy service notes using the modified Rankin scale (mRs) [23]. The mRs ranges from 0 to 6, with 0 representing no neurological deficits and 6 equaling death. A poor discharge outcome was considered to be mRs >3, indicating severe disability or death. Demographic and clinical data were prospectively entered into a database using research electronic data capture (REDCap) tools hosted at the University of Michigan [24].

Statistical Analysis

To compare differences in baseline demographic and clinical characteristics between the groups of patients with and without spontaneous hyperventilation, we used χ^2 test or *t* test, as appropriate. Similar testing was used to compare the groups with and without complete ABG data. We then examined associations between hyperventilation severity and two outcomes—DCI and poor functional outcome (mRs >3)—using bivariate logistic regression. In

addition to demographic factors (age, gender), factors with statistically significant associations in bivariate analysis were included in multivariable logistic regression analysis, and results were expressed as adjusted odds ratios. We used the same multivariable models adjusting for demographic characteristics, SAH severity, etiology, and complications to obtain adjusted predicted probabilities of both DCI and poor functional outcome at different severities of hyperventilation (none, moderate, and severe). To assess final model fit, we used the area under the curve method (C statistic = 0.75 for model with outcome of DCI; C statistic = 0.88 for model with outcome of poor discharge mRs) and the Hosmer–Lemeshow goodness of fit test (both models had *p* > 0.05, suggesting good model fit). We considered a two-sided *p* < 0.05 statistically significant. All analyses were performed using STATA version 13 (Stata Corp, College Station, TX).

Results

Of 317 patients, 207 were included in the final analysis and 110 patients were excluded for not having an eligible ABG. Of the 110 excluded patients, 109 were excluded because they did not have an ABG checked during their hospitalization. None of these patients had required mechanical ventilation. One mechanically ventilated patient did not have an ABG obtained while overbreathing the ventilator, and was also excluded. Overall, 32 of 207 (15.5 %) patients in the study group were mechanically ventilated versus 1 of 110 patients (0.9 %) in the excluded group. Study patients were also older and had greater severity of illness (Supplemental Table 1).

Of the 207 patients eligible for the study, 113 (55 %) had an ABG with both PaCO₂ <35 mmHg and pH >7.45 and were classified as having spontaneous hyperventilation. Forty-nine of the 113 with spontaneous hyperventilation (43.4 %) had an ABG with PaCO₂ ≤30 mmHg and pH ≥7.5 and were determined to have severe spontaneous hyperventilation. The remaining 64 (56.6 %) were considered to have moderate spontaneous hyperventilation.

Clinical characteristics of patients with spontaneous hyperventilation are compared to those without spontaneous hyperventilation in Table 1. Those with spontaneous hyperventilation had significantly higher incidence of both DCI (43.4 vs. 18.1 %, *p* < 0.001) and poor discharge outcome (68.5 vs. 41.8 %, *p* < 0.001). There were no significant differences in age, gender, medical comorbidities, method of aneurysm treatment, and aneurysm location. However, spontaneously hyperventilating patients were significantly more likely to have an aneurysmal etiology (86.7 vs. 75.5 %, *p* = 0.03), higher mean WFNS

(3.2 vs. 2.5, $p = 0.007$), and HH (3.5 vs. 2.9, $p = 0.001$) scores, and were more likely to experience radiographic vasospasm (34.6 vs. 10.5 %, $p < 0.001$), pneumonia (38.1 vs. 14.9 %, $p < 0.001$), neurogenic myocardial injury (38.9 vs. 22.3 %, $p = 0.01$), and SIRS (66.4 vs. 42.6 %, $p = 0.001$).

In bivariate analysis, we found that patients with moderate hyperventilation had almost three times the odds of DCI [odds ratio (OR) 2.9, 95 % confidence interval (CI) 1.40–6.00], and patients with severe hyperventilation had over 4 times the odds of DCI (OR 4.35, CI 2.02–9.37), compared to patients without spontaneous hyperventilation (Table 2). Other factors significantly associated with DCI were WFNS (OR 1.31, CI 1.10–1.56), SAH sum score (OR 1.07, CI 1.04–1.10), neurogenic myocardial injury (OR 2.17, CI 1.27–3.70), SIRS (OR 6.01, CI 3.37–10.72), and pneumonia (OR 4.14, CI 2.28–7.50). Relative to aneurysmal etiology, perimesencephalic SAH had a significant inverse association with DCI (OR 0.05, CI 0.01–0.40).

Additionally, severe hyperventilation was strongly associated with poor discharge outcome (OR 9.30, CI 3.58–24.14), while the association with moderate hyperventilation was not statistically significant (OR 1.69, CI 0.88–3.25). Other factors significantly associated with poor discharge outcome were age (OR 1.04, CI 1.02–1.06), WFNS (OR 3.32, CI 2.60–4.24), SAH sum score (OR 1.09, CI 1.06–1.12), SIRS (OR 9.96, CI 5.84–16.98), pneumonia (OR 6.32, CI 3.32–12.04), and DCI (OR 3.96, CI 2.27–6.92). Relative to aneurysmal etiology, perimesencephalic SAH was less likely to be associated with poor discharge outcome (OR 0.09, CI 0.03–0.29).

In addition to age and gender, all factors significantly associated with DCI in the bivariate analysis were included in a multivariable logistic regression model (Table 3). After adjusting for WFNS, SAH sum score, etiology, pneumonia, and SIRS, only moderate (OR 2.49, CI 1.10–5.62) and severe (OR 3.12, CI 1.30–7.49) spontaneous hyperventilation remained significantly associated with DCI. Similarly, in addition to age and gender, all factors significantly associated with poor discharge outcome in bivariate analysis were included in a multivariable logistic regression model of poor discharge outcome (Table 4). After adjusting for WFNS, SAH sum score, pneumonia, and DCI, severe spontaneous hyperventilation remained significantly associated with poor discharge outcome (OR 4.52, CI 1.37–14.89). Other covariates with significant associations include age (OR 1.05, CI 1.02–1.08), WFNS (OR 2.47, CI 1.78–3.42), and SIRS (OR 2.76, CI 1.10–6.89).

Figure 1 shows the predicted probability of DCI for patients with different hyperventilation status, after controlling for age, gender, WFNS, SAH sum score, etiology, pneumonia, and SIRS. The adjusted predicted probability

of DCI was 18.5 % for patients with no hyperventilation, 39.1 % for those with moderate hyperventilation, and 50.0 % when severe hyperventilation was present. Compared to patients with no hyperventilation, patients with moderate and severe spontaneous hyperventilation were significantly more likely to experience DCI ($p = 0.003$ and $p < 0.001$, respectively). Figure 2 shows the adjusted predicted probability of poor discharge outcome for patients by hyperventilation status, after adjusting for age, sex, WFNS, SAH sum score, pneumonia, and DCI. The adjusted predicted probability of poor discharge outcome was 42.2 % for patients with no hyperventilation, 54.8 % for those with moderate hyperventilation, and 86.4 % when severe hyperventilation was present. Compared to patients with severe hyperventilation, patients with no and moderate spontaneous hyperventilation were significantly less likely to experience a poor discharge outcome ($p < 0.001$ for both comparisons). The difference in adjusted predicted probability for patients with moderate compared to no spontaneous hyperventilation did not reach the pre-specified threshold of statistical significance ($p = 0.05$).

Discussion

In this retrospective analysis of a prospectively collected database of SAH patients admitted to an academic neurological ICU, we found that spontaneous hyperventilation was common and independently associated with DCI and poor discharge outcome. These results suggest a novel and potentially clinically relevant relationship between spontaneous hyperventilation, DCI, and functional outcome. To our knowledge, this is the first study to detect an association between spontaneous hyperventilation and DCI. It is also the first study to demonstrate a relationship between spontaneous hyperventilation and neurological outcome in a dedicated population of SAH patients. Our results are consistent with previous studies that have shown increased mortality in TBI patients treated with induced hyperventilation [1].

The exact mechanism of the association between spontaneous hyperventilation and DCI is unclear. It may be explained by the marked decrease in CBF that is triggered by hypocapnia. However, the observational nature of this study limits inferences about causality. Another important potential mediator of hyperventilation after SAH is the SIRS. SIRS is common after SAH, and our data and other studies suggest that it is associated with poor neurological outcome and may have an association with DCI [25, 26]. However, inclusion of SIRS in both multivariable logistic regression models did not affect the strength of the associations with spontaneous hyperventilation.

Table 1 Demographic and clinical characteristics of study subjects

	Spontaneous hyperventilation <i>n</i> = 113	No hyperventilation <i>n</i> = 94	<i>p</i>
Age	57.3 (13.9) ^a	58.3 (12.8)	0.62
Female	71 (62.8 %) ^b	70 (74.5 %)	0.07
Hypertension	65 (57.5 %)	60 (63.8 %)	0.36
Diabetes	15 (13.3 %)	18 (19.2 %)	0.25
CAD	16 (14.2 %)	8 (8.5 %)	0.21
Tobacco use	59 (52.2 %)	40 (42.6 %)	0.17
Alcohol abuse	21 (18.6 %)	13 (13.8 %)	0.36
Pneumonia	43 (38.1 %)	14 (14.9 %)	<0.001
Neurogenic myocardial injury	44 (38.9 %)	21 (22.3 %)	0.01
SIRS	75 (66.4 %)	40 (42.6 %)	0.001
Treatment			
Coil	49 (48.0 %)	34 (44.7 %)	0.06
Clip	40 (39.2 %)	22 (29.0 %)	
None	13 (12.8 %)	20 (26.3 %)	
Etiology			
Aneurysm	98 (86.7 %)	71 (75.5 %)	0.03
Perimesencephalic	3 (2.7 %)	11 (11.7 %)	
Unknown	12 (10.6 %)	12 (12.8 %)	
Aneurysm location			
Acomm	33 (34.7 %)	27 (38.6 %)	0.50
Pcomm	20 (21.1 %)	12 (17.1 %)	
MCA	17 (17.9 %)	9 (12.9 %)	
Basilar	10 (10.5 %)	7 (10.0 %)	
PICA	5 (5.3 %)	6 (8.6 %)	
ICA	6 (6.3 %)	2 (2.9 %)	
Ophthalmic	2 (2.1 %)	1 (1.4 %)	
Pericallosal	2 (2.1 %)	6 (8.6 %)	
WFNS	3.2 (1.4)	2.5 (1.5)	0.007
Hunt–Hess	3.5 (1.0)	2.9 (1.2)	0.001
Modified Fisher	3.0 (0.7)	3.0 (0.8)	0.74
SAH sum score	24.4 (9.3)	22.0 (10.8)	0.09
Radiographic vasospasm	36 (34.6 %)	9 (10.5 %)	<0.001
DCI	49 (43.4 %)	17 (18.1 %)	<0.001
Discharge mRs > 3	74 (68.5 %)	38 (41.8 %)	<0.001

CAD coronary artery disease, SIRS systemic inflammatory response syndrome, Acomm anterior communicating artery, Pcomm posterior communicating artery, MCA middle cerebral artery, PICA posterior inferior cerebellar artery, ICA internal carotid artery, WFNS World Federation of Neurosurgical Societies score, SAH subarachnoid hemorrhage, DCI delayed cerebral ischemia, mRs modified Rankin scale

^a Continuous variables are displayed as mean (standard deviation)

^b Categorical variables are displayed as *n* (%)

It is also possible that severe brain injury and/or DCI directly induce hyperventilation, similar to the phenomenon of central neurogenic hyperventilation. Although case reports of central neurogenic hyperventilation are largely restricted to patients with infiltrating brain tumors

[27–29], it has been described in a variety of other disease entities [30–32]. There is extensive cortical inhibitory input into the brainstem respiratory centers [33]. This has led some to hypothesize that severe brain injury may induce hyperventilation by disrupting this cortical inhibition,

Table 2 Factors associated with delayed cerebral ischemia and poor discharge outcome

	Delayed cerebral ischemia			Poor discharge outcome		
	OR	95 % CI	<i>p</i>	OR	95 % CI	<i>p</i>
Hyperventilation						
None	Ref			Ref		
Moderate	2.90	1.40–6.00	0.004	1.69	0.88–3.25	0.11
Severe	4.35	2.02–9.37	<0.001	9.30	3.58–24.14	<0.001
Age	1.02	1.0–1.04	0.10	1.04	1.02–1.06	<0.001
Female gender	1.19	0.68–2.09	0.55	1.58	0.95–2.62	0.08
WFNS	1.31	1.10–1.56	0.003	3.32	2.60–4.24	<0.001
SAH sum score	1.07	1.04–1.10	<0.001	1.09	1.06–1.12	<0.001
Etiology						
Aneurysm	Ref					
Perimesencephalic	0.05	0.01–0.40	0.004	0.09	0.03–0.29	<0.001
Unknown	0.36	0.12–1.07	0.07	1.42	0.65–3.12	0.38
Neurogenic myocardial injury	2.17	1.27–3.70	0.005	0.94	0.58–1.53	0.80
Tobacco use	1.37	0.82–2.31	0.23	1.00	0.63–1.58	1.00
SIRS	6.01	3.37–10.72	<0.001	9.96	5.84–16.98	<0.001
Pneumonia	4.14	2.28–7.50	<0.001	6.32	3.32–12.04	<0.001
DCI	–			3.96	2.27–6.92	<0.001

OR odds ratio, CI confidence interval, WFNS World Federation of Neurosurgical Societies score, SAH subarachnoid hemorrhage, Ref reference category, SIRS systemic inflammatory response syndrome, DCI delayed cerebral ischemia

Table 3 Multivariable logistic regression model of factors associated with delayed cerebral ischemia

	OR	95 % CI	<i>p</i>
Hyperventilation			
None	Ref		
Moderate	2.49	1.10–5.62	0.03
Severe	3.12	1.30–7.49	0.01
Age	1.00	0.98–1.03	0.81
Female gender	1.50	0.71–3.17	0.29
WFNS	0.86	0.66–1.13	0.28
SAH sum score	1.03	0.99–1.08	0.11
Etiology			
Aneurysm	Ref		
Perimesencephalic	0.50	0.06–4.44	0.53
Unknown	0.44	0.13–1.51	0.19
Neurogenic myocardial injury	1.37	0.67–2.79	0.39
Pneumonia	1.54	0.70–3.40	0.29
SIRS	2.18	0.95–4.98	0.07

OR odds ratio, CI confidence interval, WFNS World Federation of Neurosurgical Societies score, SAH subarachnoid hemorrhage, Ref reference category, SIRS systemic inflammatory response syndrome

thereby “releasing” brainstem respiratory centers and triggering hyperventilation [34]. Theoretically, in the case of DCI this process could become self-reinforcing because hyperventilation would further decrease CBF, consequently triggering more hyperventilation.

Although the causal nature of the association between spontaneous hyperventilation, DCI, and neurological outcome is uncertain, some may consider therapeutic interventions to minimize hyperventilation. In fact, induced hypercapnia has recently been proposed as an acute

Table 4 Multivariable logistic regression model of factors associated with poor discharge outcome (mRS >3)

	OR	95 % CI	<i>p</i>
Hyperventilation			
None	Ref		
Moderate	1.30	0.52–3.24	0.58
Severe	4.52	1.37–14.89	0.01
Age	1.05	1.02–1.08	0.001
Female gender	1.87	0.78–4.45	0.16
WFNS	2.47	1.78–3.42	<0.001
SAH sum score	1.00	0.95–1.04	0.84
Etiology			
Aneurysm	Ref		
Perimesencephalic	0.85	0.14–5.22	0.86
Unknown	2.12	0.56–7.96	0.27
Pneumonia	1.19	0.44–3.22	0.73
SIRS	2.76	1.10–6.89	0.03
DCI	1.95	0.80–4.78	0.14

OR odds ratio, CI confidence interval, WFNS World Federation of Neurosurgical Societies Score, SAH subarachnoid hemorrhage, Ref reference category, SIRS systemic inflammatory response syndrome

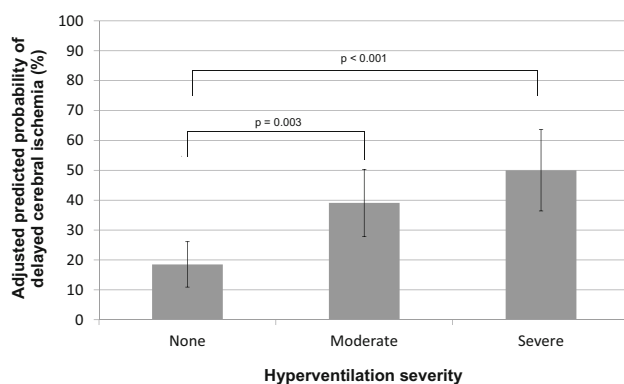


Fig. 1 The adjusted predicted probability of DCI was 18.5 % for patients with no hyperventilation, 39.1 % for those with moderate hyperventilation, and 50.0 % when severe hyperventilation was present. Error bars show 95 % confidence intervals. Compared to those with no hyperventilation, the probability of DCI was significantly increased in patients with moderate ($p = 0.003$) and severe ($p < 0.001$) hyperventilation. There was no significant difference between patients with moderate and severe hyperventilation ($p = 0.23$)

treatment for DCI [35]. Unfortunately, in spontaneously breathing patients, therapeutic options are limited. Hypocarbica-induced cerebral vasoconstriction is mediated by nitric oxide [36]. Consequently, nitric oxide donors currently being tested for treatment of SAH-induced vasospasm may also mitigate the effects of hyperventilation, but this has not been tested [37]. Adding dead space to the ventilator circuit can sometimes reduce hypocapnia. Sedation with opioids can also be effective, but may interfere with monitoring of the patient's neurological status [38, 39]. The use of neuromuscular blockade is typically

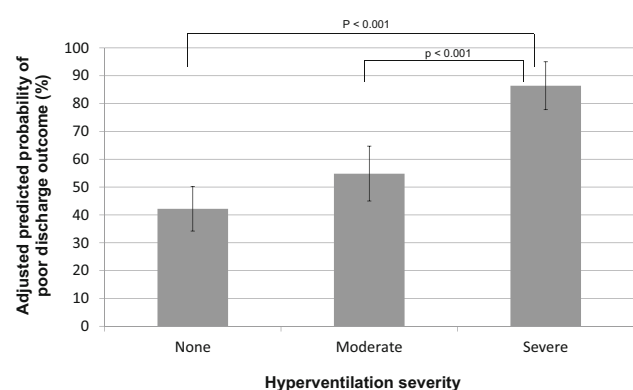


Fig. 2 The adjusted predicted probability of poor discharge outcome was 42.2 % for patients with no hyperventilation, 54.8 % for those with moderate hyperventilation, and 86.4 % when severe hyperventilation was present. Error bars show 95 % confidence intervals. Compared to those with severe hyperventilation, the probability of poor discharge outcome was significantly lower in patients with no ($p < 0.001$) and moderate ($p < 0.001$) hyperventilation. The difference between patients with no and moderate hyperventilation was not statistically significant ($p = 0.05$)

discouraged in critically ill neurological patients because it further compromises the ability to assess neurological status, and neuromuscular blockers significantly increase the risk of adverse effects such as ICU-acquired weakness [40, 41]. Additional study is needed before either modality should be recommended to treat severe spontaneous hyperventilation in SAH. Previous studies have used cerebral oxygenation monitors to show decreased brain oxygen during spontaneous hyperventilation [11]. Invasive or non-invasive cerebral oxygen or blood flow monitors may be particularly useful for measuring treatment efficacy in

future studies. At present, a reasonable treatment approach is to consider low-risk interventions to reduce common triggers of hyperventilation, such as pain and inflammation.

This study has several limitations that should be considered when interpreting the results. First, several patients were excluded from analysis because they did not have an ABG. This selected for a population of patients with greater illness severity, so it is likely that our analysis overestimates the true prevalence of hyperventilation in SAH patients. However, the final cohort was relatively evenly matched between patients with and without hyperventilation, and it is unlikely that excluding these patients had a significant impact on the associations that were identified. Additionally, inclusion in the hyperventilation group only required a single ABG obtained at any time point showing a respiratory alkalosis. Both timing and duration of hyperventilation could influence DCI and neurological outcome, but the current study limits analysis to presence or absence of hyperventilation, rather than timing of onset or cumulative duration.

As this study was conducted at a single academic center, it is possible that these results are not generalizable to all patient populations. However, our institution is a referral center for a wide geographic region, and all care was provided in accordance with standard guidelines. Further, since the study was observational, it may not be possible to account for all confounders mediating an association between hyperventilation, DCI, and poor neurological outcome. Nonetheless, our final regression models include well-established markers of clinical (WFNS) and radiographic (SAH sum score) severity, along with all other factors that were significant in bivariate analysis. Important potential confounders such as infectious and non-infectious triggers of inflammation were accounted for by including pneumonia and SIRS in the final models.

Conclusion

Spontaneous hyperventilation is common in patients with SAH and is significantly associated with DCI and poor neurological outcome at hospital discharge. Further study is needed to determine the pathophysiological underpinnings of this association. Interventions to minimize hyperventilation in SAH patients may be considered, though at present further investigations are needed to determine if they have any beneficial effect on outcome.

Conflict of interest The authors declare that they have no conflict of interest.

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