Acute lung injury in patients with subarachnoid hemorrhage: Incidence, risk factors, and outcome

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Objective: **Pulmonary complications account for significant morbidity and mortality following aneurysmal subarachnoid hemorrhage; however, the effect of acute lung injury is largely unknown. The goal of this study was to determine the incidence of acute lung injury in a large cohort of patients with subarachnoid hemorrhage as well as determine the risk factors for acute lung injury and its effect on mortality and length of stay. Ventilator management was analyzed to determine the proportion of patients with subarachnoid hemorrhage and acute lung injury who a received a low-tidal volume ventilation strategy.**

Design: **Retrospective cohort study.**

Setting: **University-affiliated county hospital in Seattle, WA.**

Patients: **Six-hundred and twenty patients with aneurysmal subarachnoid hemorrhage documented on computed tomography or angiography.**

Interventions: **None.**

Measurements and Main Results: **One-hundred and seventy patients met criteria for acute lung injury (incidence, 27%; 95% confidence interval, 24–31%). On multivariate analysis, severity of illness, clinical grade of hemorrhage, packed red blood cell transfusions, and severe sepsis in the intensive care unit were independently associated with development of acute lung injury. After adjustment for important confounders, development of acute lung injury was associated with a statistically significant increase in hospital mortality (odds ratio, 1.63; 95% confidence interval, 1.03–2.57). Acute lung injury was also independently associated with an increased intensive care unit length of stay (15%, 95% confidence interval, 5–27%). Thirty percent of patients with acute lung injury received low tidal volume ventilation. Patients receiving low tidal volume ventilation had worse oxygenation and higher positive end-expiratory pressure requirements compared with those who did not, but there were no significant differences in arterial pH or Pco_2.**

Conclusions: **Acute lung injury is common in patients with subarachnoid hemorrhage and is independently associated with a worse clinical outcome. Research is needed to determine the causes of acute lung injury in this population and whether these patients are candidates for evidence-based ventilator strategies to reduce mortality. (Crit Care Med 2006; 34:196–202)**

Key Words: subarachnoid hemorrhage; acute lung injury; acute respiratory distress syndrome; intensive care; outcomes research

Aneurysmal subarachnoid hemorrhage (SAH) affects approximately 30,000–40,000 patients per year in the United States, with an estimated mortality rate of 25% in those who survive to hospitalization (1, 2). Increasingly, pulmonary complications such as acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are recognized as significant contributors to the morbidity and mortality that occur as a result of SAH (3). Several small studies have shown pulmonary edema and arterial hypoxemia, two components of ALI, to be significantly associated with poor neurologic outcome (4–6).

Currently, many aspects of ALI in SAH remain poorly understood. Although clinical grade of hemorrhage (Hunt and Hess grade) on presentation has been associated with the development of ALI (5, 7), other relevant clinical predictors have yet to be identified. Additionally, no information exists on how the presence of ALI affects outcomes such as mortality and length of stay. Of note, prior studies of ALI in SAH have not used the standardized North American-European Consensus Conference definition (8), instead relying on arterial hypoxemia alone (6) or arterial hypoxemia in conjunction with nonstandardized chest radiograph findings (5, 7). This makes it difficult to interpret their findings in the context of modern ALI research.

New evidence indicates that a mechanical ventilation strategy involving low tidal volumes and reduced airway pressures can improve survival in ALI (9, 10), making the diagnosis, risk factors, and attributable mortality of ALI in patients with SAH increasingly important. The use of lung-protective ventilation (LPV), however, is often complicated in patients with SAH, who may have high intracranial pressures and may be sensitive to changes in minute ventilation and cerebral perfusion pressure. Because of these perceived risks, many patients with SAH and ALI who are candidates for LPV may not receive it. Consequently, it is important to better understand both the burden of ALI in this population as well as the manner in which these patients receive mechanical ventilation.

The primary aim of this investigation was to determine the incidence of ALI in a cohort of intensive care patients with aneurysmal SAH using the North Ameri-

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Supported, in part, by grants RO1HL67939, T32HL07287, and SCORHL30542 from the National Institutes of Health, Bethesda, MD.

The authors have no financial conflicts of interest to disclose.

DOI: 10.1097/01.CCM.0000194540.44020.8E

can-European Consensus Conference definition, to investigate potential risk factors for ALI, and to examine the association of ALI with mortality and length of stay. A secondary aim was to survey ventilation strategies in patients meeting the criteria for ALI to determine the proportion of patients receiving the National Institutes of Health ARDS Network protocol for LPV as a treatment modality, and the relationship between LPV and physiologic variables in this population.

MATERIALS AND METHODS

Study Location and Patients. The study was conducted at Harborview Medical Center, a county teaching hospital with 65 intensive care unit (ICU) beds, affiliated with the University of Washington in Seattle, WA. Harborview Medical Center treats all patients with SAH within the University of Washington hospital system and acts as both a primary point of entry and a secondary referral center for neurosurgery patients in the Seattle area. During the study period, patients were admitted to a dedicated neuro-ICU and managed by the neurosurgery staff with the assistance of intensivists experienced in the care of critically ill neurology and neurosurgery patients.

All patients with aneurysmal SAH admitted between May 1, 1999, and April 30, 2003, were eligible for the study. Cases were retrospectively identified through two separate methods: a) billing records containing the International Classification of Diseases, Ninth Revision (ICD-9) code for SAH (430.0) without a concurrent code for head trauma (959.0, 852.0, 853.0 or 854.0); and b) the computerized patient logs from the hospital's cerebrovascular laboratory, which screens SAH patients for cerebral artery vasospasm on a daily basis. Following patient identification all medical charts were reviewed—patients without aneurysmal SAH documented on either cerebral angiogram or contrast computed tomography were excluded from the study. A subgroup of patients with severe SAH are moribund on admission and die before they have an opportunity to develop ALI. Including these patients in an analysis of risk factors for ALI would bias an analysis of the association of severity of SAH and ALI by informative censoring (11). Consequently, we excluded patients who died within 48 hrs of admission to the hospital. A flowchart documenting patient entry into the study is shown in Figure 1.

Study Design and Variables. The design was a retrospective cohort study using SAH cases identified as explained previously. The presence or absence of ALI had been previously determined from an ongoing hospital ALI registry, in which all ICU patients at Harborview Medical Center are prospectively screened for ALI daily by a trained research nurse. ALI was defined according to the North American-European Consensus Conference definition of acute arterial hypoxemia (ratio of Pao_2 to Fio_2 <300), bilateral infiltrates on chest radiograph, and no clinical evidence of left atrial hypertension (8). ARDS was defined as ALI with a ratio of Pao_2 to Fio_2 <200.

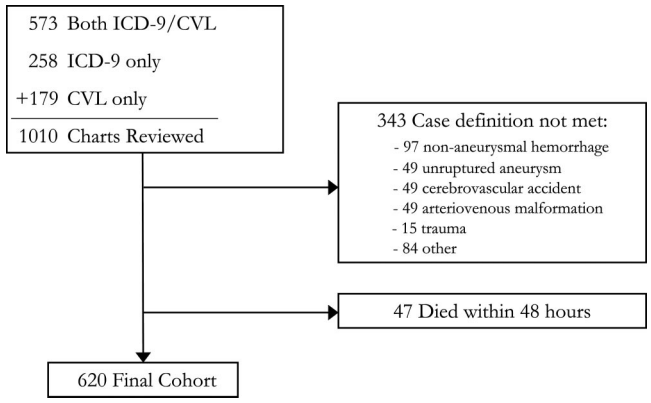

Figure 1. Flowchart of patients into study. *ICD-9*, the patient was identified through the International Classification of Diseases, Ninth Revision, code for subarachnoid hemorrhage; *CVL*, the patient was identified through the hospital's cerebrovascular lab clinical database.

Demographic and clinical variables were abstracted from the electronic medical record, except for ALI, which was taken from the ALI registry as described previously, and clinical grade of hemorrhage and medical comorbidities, which were abstracted from the paper charts. Chart abstractors were blinded as to whether the patient had met criteria for ALI. The Simplified Acute Physiology Score (SAPS) II was used to measure severity of illness (12). Because SAPS II includes points for oxygenation and is therefore collinear with the diagnosis of ALI, oxygenation points were removed from the total SAPS II score to form an adjusted score. Clinical grade of hemorrhage (Hunt and Hess grade) (13) was determined from the admitting physician's initial note. The Glasgow Coma Scale (GCS) was determined by the first neurologic assessment of the admitting nurse and adjusted for intubation when appropriate (14). For those patients who received intracranial pressure (ICP) monitoring, the ICP and cerebral perfusion pressure (CPP) were recorded. ICP and CPP were measured continuously but only recorded by the nurse sporadically; in accordance with nursing protocol, brief transient increases such as those caused by cough or stimulation were not recorded. Only the single highest recorded ICP and lowest recorded CPP were included in the analysis.

Cerebral artery vasospasm was determined from the highest cerebral artery flow velocities measured on routine screening transcranial Doppler examinations, obtained daily on each ICU patient except neurologically morbid patients and those with no clinical suspicion of vasospasm. These were classified into none, mild, moderate, and severe according to predefined criteria (15). No data on symptomatic vasospasm were available. Patients with vasospasm were administered hypervolemic, hypertensive, hemodilution ("triple-H") therapy at the discretion of the treating physician. The triple-H protocol was as follows: for mild vasospasm, intravenous fluid (IVF) was administered at a rate of 150–200 mL/hr; for moderate vasospasm, IVF was titrated to a central venous pressure of 10–12 cm H_2O or a pulmonary artery occlusion pressure of 12–14 mm Hg with a systolic blood pressure >140, using intravenous phenylephrine if necessary; for severe vasospasm, IVF was titrated to a central venous pressure of 12–14 mL H_2O or a pulmonary artery occlusion pressure of 14–16 mm Hg with a systolic blood pressure >160 mm Hg, using intravenous phenylephrine if necessary. We defined triple-H on the basis of fluid administration (daily IVF >4.0 L) and blood pressure (systolic blood pressure >140 mm Hg) in the setting of vasospasm documented by transcranial Doppler. Sepsis and organ failures during the ICU stay were determined according to recent consensus conference definitions (16). For the purposes of the sepsis definition, clinical suspicion of infection was defined as the administration of an antibiotic for purposes other than surgical or neurologic drain prophylaxis. Since a large proportion of patients had some neurologic dysfunction at baseline, severe sepsis was defined as sepsis plus two or more organ failures.

For patients meeting criteria for ALI, ventilation variables and arterial blood gas measurements were collected on days 1, 3, and 7 of ALI. For the ventilation variables, the lowest tidal volume, lowest plateau pressure, and highest positive end-expiratory pressure on a given day were recorded. For blood gas measurements, only values associated with the lowest pH and highest partial pressure of carbon dioxide were recorded. To determine whether patients with ALI received LPV, delivered tidal volume was divided by the predicted body weight obtained from the patients height and gender (10)—for patients in which no height was recorded (18 patients), the actual body weight was used. A patient was consid-

Table 1. Patients with subarachnoid hemorrhage characterized according to presence of acute lung injury (ALI)

	ALI (n = 170)	No ALI (n = 450)	*p* Value
Age, yrs	55 ± 15	55 ± 14	.48
Female gender, %	62	68	.12
SAPS II	46 ± 16	35 ± 17	<.001
Adjusted SAPS II[a]	44 ± 14	34 ± 15	<.001
GCS, %			
3–5	38	16	<.001
6–13	33	26	
14–15	29	58	
Hunt and Hess grade	3.3 ± 1.1	2.7 ± 1.2	<.001
Mechanical ventilation, %	100	70	<.001
Duration of mechanical ventilation, median (IQR), in days	14 (10–20)	8 (0–13)	<.001
Primary management, %			
Operative	71	78	.04
Endovascular	24	15	
Neither	6	7	
Maximal ICP, mm Hg[b]	48 ± 26	41 ± 23	.002
Minimal CPP, mm Hg[c]	45 ± 17	52 ± 17	<.001
Vasospasm, %			
None	33	29	.49
Mild-moderate	51	51	
Severe	16	20	
Hypervolemic, hypertensive, hemodilution therapy, %	67	62	.32
Underwent pulmonary artery catheterization, %	64	45	<.001
Renal failure in ICU, %[d]	8	2	.001
Sepsis, %	88	54	<.001
Severe sepsis, %	13	02	<.001

SAPS, Simplified Acute Physiology Score; GCS, Glasgow Coma Scale; IQR, interquartile range; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

[a]SAPS II with oxygenation points removed; [b]highest sustained ICP observed throughout intensive care unit stay; [c]lowest sustained CPP observed throughout intensive care unit stay; [d]creatinine >1.9. Data are presented as % or mean ± SD unless otherwise specified.

ered to have received LPV either if the lowest delivered tidal volume was ≤6 mL/kg of predicted body weight on a given day or if it was ≤8 mL/kg of predicted body weight and the lowest plateau airway pressure was ≤30 cm H_2O, according to the most conservative tidal volumes allowed in the ARDS Network's published protocol (10).

All aspects of this investigation were approved by the University of Washington's Human Subjects Research Committee.

Statistical Analysis. Values are expressed as mean ± SD or frequency (percent). Statistical comparisons are between patients with and without ALI or between patients with ALI who did and did not receive LPV. Bivariate analysis of continuous variables was performed using an unpaired Student's *t*-test for normally distributed variables or the Wilcoxon rank-sum test for nonnormally distributed variables. Comparisons of categorical variables were performed using a chi-square test or Fisher's exact test, as appropriate.

Logistic regression was used to perform multivariate analyses of factors associated with the development of ALI and factors associated with hospital mortality. Linear regression was used to compare hospital and ICU length of stay in patients with and without ALI. To satisfy the normality assumption of linear regression and improve model fit, length of stay was log-transformed before entering the model. After model fitting, the β estimates were back-transformed and are therefore reported as percent change in length of stay associated with ALI. Linear regression models were checked with residual vs. fitted plots and standardized normal probability plots to evaluate model fit. In all multivariate analyses, candidate variables were determined *a priori* and retained in the model only if they acted as confounders of the risk estimate of another variable (>10% change in estimates) or were statistically significant. Statistical significance was tested using a likelihood ratio test for logistic regression or a partial F test for linear regression. In the case of collinearity between covariates (e.g., Hunt and Hess grade and GCS, or ICP and CPP), the variables determined to be the most clinically important (Hunt and Hess grade and ICP) were retained in the model. Clinically relevant interaction terms and quadratic terms were tested and included in the model if statistically significant.

Since not all patients received intracranial pressure monitoring, there were a significant number of missing values for ICP and CPP (33 patients, 5% of total). To avoid dropping these patients from the multivariate analysis, missing values were imputed using the median and modal values as well as multiple imputation with regression techniques (17). None of these methods significantly changed the risk estimates compared with the complete case analysis and the final analyses are presented using multiple imputation.

Data analysis was performed using Stata 8.2 (StataCorp, College Station, TX). All tests were two-tailed, and $p \leq .05$ was considered significant.

RESULTS

Six-hundred and twenty patients with aneurysmal SAH were admitted during the study period and survived >48 hrs. Of those, 170 met criteria for ALI at some point during their ICU stay, for an overall incidence of 27% (95% confidence interval, 24–31%). Median time to development of ALI was 3 days (interquartile range, 2–6 days). There was no difference in the median time to ALI among ALI patients who died (3 days) and those who survived (4 days, $p = .30$). Of the 170 patients meeting criteria for ALI, 112 patients met criteria for ARDS (18% of total; 95% confidence interval, 15–21%).

Demographic characteristics and ICU complications for patients with and without ALI are given in Table 1. Groups were similar with regard to age, gender, and percent receiving operative management. Patients with ALI tended to have higher severity of illness scores, a lower GCS, and worse Hunt and Hess grade on admission. ALI patients also tended to have a higher maximum ICP and a lower minimum CPP during their ICU stay. ALI patients were more likely to meet criteria for sepsis and severe sepsis. There were no differences in frequency of vasospasm as measured by screening transcranial Doppler examinations, nor was there a difference in use of triple-H therapy. The 47 patients excluded due to early mortality were similar in age (55 ± 15 yrs) and gender (68% female) to the rest of the cohort. Ninety-six percent of those excluded had a GCS of 3–5, and 91% had a poor clinical grade (Hunt & Hess grade of 4 or 5). Only one excluded patient received operative treatment.

Table 2 shows the multivariate analysis of factors associated with development of ALI. Increasing severity of illness, increasing Hunt and Hess grade, severe

Table 2. Multivariate analysis for factors associated with development of acute lung injury (ALI) in patients with subarachnoid hemorrhage[a]

Variable	Adjusted OR	95% CI	*p* Value
SAPS II[b]	1.03	1.02–1.05	<.001
Hunt and Hess grade[c]	1.23	1.01–1.48	.035
Severe sepsis	2.96	1.22–7.17	.016
PRBC transfusions[d]	2.73	1.66–4.50	<.001

OR, odds ratio; CI, confidence interval; SAPS, simplified acute physiology score; PRBC, packed red blood cell.

[a]Model includes all of the listed variables—severe sepsis and PRBC transfusions were only counted if they occurred prior to the onset of ALI. Hosmer-Lemeshow goodness-of-fit test for model: $p = .053$; [b]odds ratio for every one-unit increase in SAPS II. Oxygenation points have been removed from SAPS II to avoid collinearity with ALI. Age points were included and as such age was not included as a separate covariate; [c]odds ratio for every one-unit increase in clinical grade; [d]odds ratio for every unit of PRBC per day in intensive care unit.

Table 3. Factors associated with mortality in patients with subarachnoid hemorrhage: Regression model includes all listed variables

	Bivariate Analysis		Multivariate Analysis[a]	
Variable	OR	95% CI	OR	95% CI
SAPS II[b]	1.08	1.06–1.09	1.05	1.03–1.07
Hunt and Hess grade[c]	2.73	2.24–3.33	1.85	1.48–2.31
Maximal ICP[d]	1.03	1.02–1.04	1.02	1.01–1.03
Severe sepsis	3.14	1.53–6.44	1.54	0.66–3.60
ALI	3.11	2.12–4.57	1.63	1.03–2.57

OR, odds ratio; CI, confidence interval; SAPS, simplified acute physiology score; ICP, intracranial pressure.

[a]Hosmer-Lemeshow goodness-of-fit test for model: $p = .79$; [b]odds ratio for every one-point increase in SAPS II. Oxygenation points have been removed from SAPS II to avoid colinearity with ALI. Age points were included and as such age was not included as a separate covariate; [c]odds ratio for every one-point increase in clinical grade; [d]odds ratio for every one-point increase in maximal ICP.

Table 4. Percent increase in intensive care unit (ICU) and hospital length of stay (LOS) associated with development of acute lung injury using linear regression

	Unadjusted		Adjusted[a]	
	% Change	95% CI	% Change	95% CI
ICU LOS, days	30	19–41	15	5–27
Hospital LOS, days	15	3–27	7	−3–17

[a]Multivariate analysis adjusting for severity of illness (Simplified Acute Physiology Score [SAPS] II), SAPS II squared, Hunt and Hess clinical grade, vasospasm, and sepsis using linear regression of log-transformed length of stays. R-square for models: 0.42 (ICU LOS) and 0.38 (hospital LOS).

sepsis, and packed red blood cell transfusions were independently associated with increased odds of developing lung injury. Intracranial pressure and vasospasm were tested in the model and found not to be statistically significantly associated with ALI when examined in combination with other factors. We also examined ventilator strategies before ALI onset to determine whether patients who subsequently developed lung injury were ventilated with higher tidal volumes, which may precipitate ALI (18). There were no significant differences in tidal volumes before ALI onset on days 1, 3, and 7 of ventilation in patients who did and did not develop ALI (data not shown).

Crude mortality in the cohort was 42% in those meeting criteria for ALI and 19% in those not meeting criteria for ALI. Bivariate and multivariate analyses of factors associated with mortality are given in Table 3. After adjustment for factors known to be associated with mortality (severity of illness, clinical grade, intracranial pressure, and severe sepsis), development of ALI was independently associated with a increase in the odds of death. A similar multivariate analysis was performed with ARDS as the covariate instead of ALI—in this model the risk estimates did not appreciably change from those of the model examining ALI (data not shown). Table 4 shows the results of linear regression with log-transformed ICU and hospital length of stay as the response variables. On multivariate analysis, ALI was associated with a 15% increase in ICU length of stay and a 7% increase in hospital length of stay, although the increase in hospital length of stay did not achieve statistical significance.

Of the 170 patients meeting criteria for ALI, 51 received LPV at some point on days 1, 3, or 7 of diagnosis (30%, 95% confidence interval 23–37%). In considering baseline characteristics, there were no differences between patients with ALI who did receive LPV and those who did not with respect to mean age (absolute difference 0.5 yrs, 95% CI for difference −4.3 to 5.4), mean SAPS II score (absolute difference 1.31, 95% CI for difference, −3.8 to 6.5), or mean Hunt and Hess grade (absolute difference 0.12, 95% CI for difference −0.26 to 0.50). Comparisons of ventilation variables and arterial blood gas measurements for patients who did and did not receive LPV are shown in Table 5. Despite the large differences in tidal volumes (approximately 3 mL/kg of predicted body weight), there were no significant differences in plateau airway pressure. This suggests that there was poorer lung compliance in the group who received LPV, although this could also be due to increased positive end-expiratory pressure in this group. Importantly, there were also no significant differences in the measured arterial pH or Pco_2, except on day 1 of ALI where the difference in pH, although small, was statistically significant.

DISCUSSION

In a large cohort of patients with aneurysmal SAH, more than one quarter of patients met criteria for ALI using the modern consensus conference definition. Development of ALI was associated with a 63% increase in the odds of death and a longer ICU length of stay on multivariate analysis. These results demonstrate that ALI not only is common in patients with SAH but also is independently associated with a poor clinical outcome.

Table 5. Ventilation variables of patients with acute lung injury (ALI) receiving lung protective ventilation on days 1, 3, and 7 of ALI compared with those who did not

	Received Lung-Protective Ventilation (n = 51)	Did Not Receive Lung-Protective Ventilation (n = 119)	*p* Value
Tidal volume, mL/kg/PBW			
Day 1	7.3 ± 1.5	10.0 ± 1.2	<.001
No. of patients	48	91	
Day 3	6.8 ± 1.6	9.8 ± 1.2	<.001
No. of patients	43	68	
Day 7	6.8 ± 1.7	9.8 ± 1.2	<.001
No. of patients	25	29	
Plateau pressure, cm H_2O			
Day 1	22 ± 6	21 ± 5	.42
No. of patients	48	93	
Day 3	23 ± 5	22 ± 5	.58
No. of patients	42	69	
Day 7	23 ± 7	24 ± 6	.77
No. of patients	25	30	
PEEP, cm H_2O			
Day 1	8.4 ± 5.0	5.5 ± 2.7	<0.001
No. of patients	51	112	
Day 3	10.0 ± 6.3	6.5 ± 3.2	0.001
No. of patients	46	79	
Day 7	10.4 ± 5.9	7.7 ± 4.8	0.08
No. of patients	27	52	
P/F ratio, mm Hg/%			
Day 1	158 ± 74	195 ± 63	.003
No. of patients	51	112	
Day 3	172 ± 68	221 ± 76	<.001
No. of patients	46	79	
Day 7	218 ± 89	220 ± 71	.94
No. of patients	27	52	
Arterial pH			
Day 1	7.41 ± 0.08	7.44 ± 0.05	.01
No. of patients	51	112	
Day 3	7.43 ± 0.07	7.45 ± 0.04	.07
No. of patients	46	79	
Day 7	7.42 ± 0.08	7.45 ± 0.06	.24
No. of patients	27	52	
Arterial P_{CO_2}, mm Hg			
Day 1	38 ± 8	36 ± 6	.08
No. of patients	51	112	
Day 3	37 ± 7	36 ± 7	.43
No. of patients	46	79	
Day 7	40 ± 8	39 ± 7	.74
No. of patients	27	52	

PBW, predicted body weight; PEEP, positive end-expiratory pressure; P/F, ratio of Pa_{O_2} to F_{IO_2}. Total numbers of patients may not be consistent due to missing values.

Currently, little is known about the etiology of ALI in SAH. Several mechanisms have been postulated, including aspiration, infection, and neurogenic pulmonary edema (3). Neurogenic pulmonary edema may result from catecholamine surges resulting in direct endothelial damage (19, 20) or from pulmonary venous and arterial hypertension and subsequent hydrostatic edema (21, 22). In the present study, factors known to be associated with ALI in other populations, such as sepsis and red cell transfusion (23), were shown to be risk factors in SAH as well. This indicates that a certain proportion of patients with SAH likely develop ALI as a consequence of the complications of ICU care such as infection or need for transfusion. Even after controlling for these risk factors, however, clinical grade of hemorrhage persisted as a strong independent predictor of development of ALI. This may indicate that some proportion of lung injury is due to neurologic factors such as altered mental status with subsequent aspiration, which is known to cause ALI, or true neurogenic pulmonary edema. Future studies of ALI in SAH, in which cardiac filling pressures are analyzed and lung inflammation is measured with bronchoalveolar lavage, may be able to better determine the cause of lung injury in this population.

Our study demonstrated that ALI occurring after SAH is independently associated with increased mortality and prolonged length of stay, suggesting that recognition and treatment of ALI in patients with SAH could possibly improve clinical outcome. Recent publications have demonstrated that a mechanical ventilation strategy using low tidal volumes and reduced end-expiratory pressures reduces mortality in patients with ALI (24). The largest of these studies, conducted by the National Heart Lung and Blood Institute's ARDS Network, resulted in a 22% reduction in the risk of death in patients ventilated with 6 mL/kg of predicted body weight compared with 12 mL/kg of predicted body weight (10). Currently it is unknown whether this impressive risk reduction can be extended to patients with SAH and ALI. Patients with increased ICP were excluded from the ARDS Network tidal volume trial, making it unlikely that many patients with SAH participated.

In the present cohort, less than one third of patients meeting criteria for ALI received low tidal volume ventilation. This could be due to a variety of reasons (25), including poor recognition of the syndrome, concerns about patient comfort, or concerns about safety, especially regarding hypoventilation and subsequent effects on ICP and cerebral blood flow (26). Patients who received LPV in our cohort received increased positive end-expiratory pressure and may have had worse lung compliance, suggesting that they had more severe lung injury. The fact that they received lower tidal volumes could therefore reflect either that the treating clinician believed they were more likely to benefit from LPV or that their disease severity made ALI easier to recognize. Patients receiving LPV also had poorer oxygenation, which either may have been due to more severe lung injury or may have been a result of the LPV strategy itself, which can result in a lower Pa_{O_2}/F_{IO_2} ratio (10). Interestingly, there was no significant difference in arterial P_{CO_2} among patients who did or did not receive LPV. This provides some preliminary evidence that low tidal volumes might possibly be implemented without affecting minute ventilation and P_{CO_2} (and, by extension, ICP). Since our study was observational and nonprotocolized, we were unable to directly address this hypothesis—more comprehensive

The results of this study indicate that development of acute lung injury is a common complication of subarachnoid hemorrhage and is independently associated with a poor clinical outcome.

physiologic studies are needed in which arterial blood gases and ICPs are followed as tidal volumes are lowered. If LPV is indeed feasible in this population, it could mean a significant reduction in mortality for patients with SAH.

Our study has a several limitations. Most important, we were not able to collect systematic data on left ventricular filling pressures such as central venous or pulmonary artery occlusion pressures. Consequently, it is possible that some patients diagnosed with ALI actually had high-pressure pulmonary edema. High-pressure edema, stemming from either acute cardiac dysfunction (27), pulmonary venous constriction (28), or hypervolemic therapy for vasospasm (29), may have a different clinical effect than ALI, thus affecting our risk estimates. Our screeners, however, were trained to evaluate patients for high-pressure edema using clinical data and filling pressures when available—patients with evidence of high filling pressures were not included in the ALI registry. There were also no differences between groups in the frequency of triple-H therapy. It is likely, therefore, that few patients with pulmonary edema due to high pressure were diagnosed with ALI.

Another limitation is that our cohort was composed of patients from a single academic center, and therefore our results may not easily generalize. Harborview Medical Center, however, cares for a wide range of patients with SAH, including both local patients who present acutely to our emergency room and patients referred for tertiary care. Additionally, the overall mortality rate in this study was comparable to other large multiple-center reports (1, 30), making it likely that this cohort is representative of the population at large.

Finally, this study did not examine neurologic outcome (such as the Glasgow Outcome Scale) following SAH. Prior reports have shown that development of pulmonary edema after SAH is associated with worse neurologic outcome (5, 6)—our study did not have data on long term follow-up to address this question in ALI. Despite this, mortality and length of stay are relevant patient-centered outcomes in SAH. Moreover, a large proportion of the poorer neurologic outcome associated with pulmonary edema after SAH is due to those who have died and thus have a Glasgow Outcome Scale of 1 (on a scale from 1 to 2). Given the increased proportion of deaths in those with ALI in the present study, it is likely that similar results would have been found had we obtained longer follow-up.

CONCLUSIONS

The results of this study indicate that development of ALI is a common complication of SAH and is independently associated with a poor clinical outcome. Future studies are needed to delineate the causes of ALI in SAH and to determine whether patients with SAH are candidates for evidence-based ventilator strategies proven to reduce mortality in lung-injured patients.

ACKNOWLEDGMENTS

The authors would like to thank Colleen Douville, RVT for assisting with the availability of the Harborview Medical Center Cerebrovascular Laboratory database.

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