

# High tidal volume is associated with the development of acute lung injury after severe brain injury: An international observational study\*

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**Objective:** Although a significant number of patients with severe brain injury develop acute lung injury, only intracranial risk factors have previously been studied. We investigated the role of extracranial predisposing factors, including hemodynamic and ventilatory management, as independent predictors of acute lung injury in brain-injured patients.

**Design:** Prospective multicenter observational study.

**Setting:** Four European intensive care units in university-affiliated hospitals.

**Patients:** Eighty-six severely brain-injured patients enrolled in 13 months.

**Interventions:** None.

**Measurements and Main Results:** All patients with severe brain injury (Glasgow Coma Scale score <9) were studied for 8 days from admission. Ventilatory pattern, respiratory system compliance, blood gas analysis, and hemodynamic profile were recorded and entered in a stepwise regression model. Length of stay in the intensive care unit, ventilator-free days, and mortality were collected. Eighteen patients (22%) developed acute lung injury on day  $2.8 \pm 1$ . They were initially ventilated with significantly

higher tidal volume per predicted body weight ( $9.5 \pm 1$  vs.  $10.4 \pm 1.1$ ), respiratory rate, and minute ventilation and more often required vasoactive drugs ( $p < .05$ ). In addition to a lower  $Pao_2/FiO_2$  (odds ratio 0.98, 95% confidence interval 0.98–0.99), the use of high tidal volume (odds ratio 5.4, 95% confidence interval 1.54–19.24) and relatively high respiratory rate (odds ratio 1.8, 95% confidence interval 1.13–2.86) were independent predictors of acute lung injury ( $p < .01$ ). After the onset of acute lung injury, patients remained ventilated with similar tidal volumes to maintain mild hypocapnia and had a longer length of stay in the intensive care unit and fewer ventilator-free days ( $p < .05$ ).

**Conclusions:** In addition to a lower  $Pao_2/FiO_2$ , the use of high tidal volume and high respiratory rate are independent predictors of acute lung injury in patients with severe brain injury. In this patient population, alternative ventilator strategies should be considered to protect the lung and guarantee a tight  $CO_2$  control. (Crit Care Med 2007; 35:1815–1820)

**KEY WORDS:** acute lung injury; severe brain injury; mechanical ventilation

**D**evelopment of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) occurs in 20% to 25% of patients with isolated brain injury and is associated with a three-fold increased risk of dying or remaining in a vegetative state (1, 2). In patients with brain injury,

a worse global initial brain computed tomography scan findings (1) and lower Glasgow Coma Scale (GCS) score (3, 4) were identified as risk factors for developing ALI/ARDS. Among the extracranial factors, administration of vasoactive drugs and history of drug abuse have been recently identified as independent

predictors of ARDS in patients with traumatic brain injury (TBI) (2).

The presence of pulmonary dysfunction after severe brain injury is attributed both to a massive increase in sympathetic activity (5–7) and to an acute systemic inflammatory response (8, 9). A bimodal distribution of the incidence of ALI/ARDS has been reported with an early peak on days 2–3 and a late peak on days 7–8 after the initiation of mechanical ventilation (10), the latter of which is often related to intercurrent pneumonia (11, 12).

Ventilatory management of brain-injured patients is based on the use of high tidal volumes ( $V_T$ ) to maintain mild hypocapnia ( $Paco_2 \geq 35$  mm Hg) for treatment of intracranial hypertension and low levels of positive end-expiratory pressure (PEEP) to optimize oxygenation while preserving cerebral venous drain-

\*See also p. 1979.

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age (13). This ventilator setting may further exacerbate the pulmonary and systemic inflammatory response in patients with ALI/ARDS (14, 15). Moreover, the use of high  $V_T$  has been recently suggested to be an independent predictor of early ALI/ARDS in patients with "normal" lungs admitted to a general intensive care unit (ICU) (16). Nevertheless, previous clinical trials testing different ventilation strategies for ALI excluded brain-injured patients because of the tight  $CO_2$  control required (14, 15, 17–20). Therefore, the current standard ventilator strategy applied in brain-injured patients and its involvement in the development of ALI/ARDS have never been investigated.

This study set out to test the hypothesis that the use of high  $V_T$  may be associated with an increased risk to develop early ALI/ARDS in patients with severe brain injury. We performed an international prospective observational study in patients with severe brain injury to identify the most powerful independent predictors of ALI/ARDS.

## MATERIALS AND METHODS

An institutional ethics committee approved the research protocol, and informed consent was not required since the study was observational and mandated no deviation from routine medical practice. Data were collected from 86 patients in four European ICUs: S Giovanni Battista Hospital, University of Turin, Italy; Centro Traumatologico Ortopedico, Turin, Italy; Hospital Clinic, Barcelona, Spain; and Western General Hospital, University of Edinburgh, UK, from September 2002 until October 2003. All patients with severe brain injury consecutively admitted were recruited. Inclusion criteria were severe brain injury defined as GCS <9 (3) and age  $18 \geq$  yrs; in addition, patients with severe TBI and spontaneous intracranial hemorrhage (cerebrovascular accident) were recruited if they remained mechanically ventilated for >24 hrs after admission. Exclusion criteria were GCS equal to 3 with fixed and dilated pupils after resuscitation and an ARDS diagnosis within 24 hrs from admission.

**Clinical Management.** All patients were sedated with alfentanil or morphine and propofol or midazolam; if required they were paralyzed with atracurium and ventilated to maintain  $Paco_2$  equal to 35 mm Hg. Arterial, right atrial, and intracranial pressures (ICP) were measured. Hemodynamic goals were ICP <20 mm Hg, cerebral perfusion pressure 60 mm Hg, and central venous pressure 8–10 mm Hg obtained with a moderate, positive fluid balance and catecholamine infusion if required. Specific treatment of intracranial hypertension included cerebrospi-

nal fluid drainage, sedation, and administration of mannitol. Chest radiograph was obtained when required for clinical reasons to define the presence of ALI/ARDS or other abnormalities.

**Study Protocol.** Patients were studied for 8 days from admission to identify the occurrence of early-onset ALI/ARDS (i.e., during the first 72 hrs after the initiation mechanical ventilation). Diagnosis of ALI/ARDS was made according to the American-European Consensus Conference criteria (21), including acute onset,  $PaO_2/FiO_2 < 300$  for ALI (<200 for ARDS) regardless of PEEP level, bilateral and diffuse opacities on anteroposterior chest radiograph, absence of left ventricular failure, or history of lung disease.  $PaO_2/FiO_2 < 300$  was confirmed in three consecutive blood gases. The presence on chest radiograph of lung consolidations, aspiration, and infiltrates was also analyzed. Pneumonia was diagnosed according to standard criteria (22).

The following variables were collected daily and averaged from three values:

1. Ventilatory pattern:  $V_T$ , respiratory rate (RR), minute ventilation ( $\dot{V}_E$ ), applied PEEP, plateau pressure of the respiratory system (Pplat), static compliance of the respiratory system (Cst,rs), blood gas analysis.  $V_T$  was calculated for predicted body weight ( $V_T/PBW$ ):  $PBW$  (kg) = 50 (for men, 45.5 for women) + 0.91 [height/152.4]. Pplat was measured after the end-inspiratory occlusion maneuver of 3–4 secs. Cst,rs was calculated dividing  $V_T$  by the difference between Pplat and applied PEEP.
2. Hemodynamic profile: mean arterial pressure (MAP), ICP, cerebral perfusion pressure (calculated as the difference between MAP and ICP), fluid balance, central venous pressure, use and total dosage of catecholamines.

**Clinical Predictors of ALI/ARDS.**  $V_T$ , RR,  $\dot{V}_E$ ,  $Paco_2$ , Pplat, Cst,rs,  $FiO_2$ , PEEP, and  $PaO_2/FiO_2$  data were expressed as mean value; fluid balance as cumulative value of the first 24 hrs; use of vasoactive drugs as the percentage of patients who required vasoactive support at any time before ALI/ARDS onset and total dosage required; aspiration, lung contusion, and pneumonia as the percentage of patients who developed these complications at any time before ALI/ARDS onset. All variables significantly different between patients with and without ALI/ARDS were entered in the stepwise regression model.

**Ventilatory and Hemodynamic Management After ALI/ARDS Development.** All variables recorded for patients with ALI/ARDS at the day of its onset were compared with the variables of patients who did not develop ALI/ARDS in the corresponding day. Chest radiograph data were obtained according to the clinical management protocol. Chest radiographs were performed using a standardized setting and scored by two investigators blinded to the patient's clinical course for the presence of alveolar consolidation in any of

the four quadrants. To assess the level of agreement in the radiologic diagnosis of ALI/ARDS, we calculated a chance-corrected agreement, using the  $k$  statistic (23).

**Outcome Assessment.** ICU length of stay was calculated up to 28 days, and patients who died before were considered as having the maximum value. Ventilator-free days (VFD) represent a composite outcome that incorporates both mortality and duration of mechanical ventilation (death = no VFD); therefore, VFD was defined as the number of days alive and free from mechanical ventilation between study enrollment and day 28. Mortality was assessed at ICU discharge.

**Statistical Analysis.** Continuous data are presented as mean  $\pm$  SD or median and range. Comparisons of continuous and categorical data between groups were performed using the unpaired Student's  $t$ -test or Mann-Whitney and Fisher's exact test, respectively, and were considered significant for  $p < .05$ . To evaluate the effect of more than one predictor on the occurrence of ALI/ARDS, a stepwise regression model with backward elimination was selected (significant level for inclusion  $\alpha = .1$  and significant level for odds ratio estimation  $\alpha = .05$ ). For stepwise regression power analysis, a sample size of 80 observations was calculated to be necessary to detect an odds ratio of 0.3 with a 95% power at a .05 significance level (SAS Institute, Cary, NC).

## RESULTS

Demographic data of the 82 patients included in the study are shown in Table 1. Early ALI/ARDS occurred in 18 (22%) on day  $2.8 \pm 1$ . At admission, chest radiograph was negative for ARDS in 82 patients, while four patients were excluded because of the presence of ALI/ARDS within 24 hrs. The  $k$  coefficient representing the agreement between the two raters to judging bilateral infiltrates present or absent was equal to 0.66 (SE = 0.19).

In the TBI group, the initial diagnosis was isolated head injury in 26, while 18 had other systemic injuries. There was no difference in ALI/ARDS incidence among cerebrovascular accident (21%), isolated TBI (15%), and polytrauma (33%) patients. Incidence of aspiration, lung contusion, and pneumonia (within 72 hrs from mechanical ventilation) was not different in the two groups. There were no differences in age and severity of injury between patients with and without ALI/ARDS, while most of the patients in the ALI/ARDS group were male ( $p < .005$ , Table 1).

**Baseline Ventilatory and Hemodynamic Management.** Patients who subsequently developed ALI/ARDS were initially ventilated with significantly higher

Table 1. Demographic data of the patient population

Patient Characteristics	Control (n = 64; 78%)	ALI/ARDS (n = 18; 22%)	p Value
Age, yrs, mean ± SD	45 ± 18	49 ± 14	.34
Gender, n, M/F	37/27	17/1	.004
Kind of injury TBI/CVA, n	34/30	10/8	.99
GCS, mean ± SD	6 ± 2	6 ± 3	.54
SAPS II, mean ± SD	39 ± 14	45 ± 12	.11
Aspiration, n (%)	3 (5)	3 (16)	.11
Pneumonia, n (%) <sup>a</sup>	3 (3)	1 (5)	.99
Lung contusion, n (%)	8 (13)	4 (22)	.45
ALI/ARDS onset day	NA	2.8 ± 1	NA

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; TBI, traumatic brain injury; CVA, cerebrovascular accident; GCS, Glasgow Coma Scale score at admission after resuscitation; SAPS, Simplified Acute Physiology Score.

<sup>a</sup>Pneumonia diagnosed within 72 hrs from mechanical ventilation. Boldface, significant values ( $p < .05$ ).

Table 2. Baseline ventilatory and hemodynamic variables in the patient population

Variable	Control (n = 64, 78%)	ALI/ARDS (n = 18, 22%)	p Value
Vt/PBW, mL/kg	9.5 ± 1.0	10.4 ± 1.1	.001
RR, min <sup>-1</sup>	12.7 ± 1.3	14.2 ± 2.1	.0006
$\dot{V}_E$ , L/min <sup>-1</sup>	7.6 ± 1.4	9.6 ± 1.4	<.0001
Paco <sub>2</sub> , mm Hg	34.8 ± 3.5	38.2 ± 4.2	.001
Pplat, cm H <sub>2</sub> O	16.7 ± 3.2	20.2 ± 3.8	.0003
Cst,rs, mL/cm H <sub>2</sub> O	49.4 ± 12.1	45.4 ± 10.2	.30
PEEP <sub>appl</sub> , cm H <sub>2</sub> O	3.7 ± 2.8	4.2 ± 3.7	.50
Fio <sub>2</sub> , %	41 ± 11	50 ± 12	.001
PaO <sub>2</sub> /Fio <sub>2</sub>	371 ± 88	263 ± 76	.0001
MAP, mm Hg	89 ± 10	90 ± 12	.89
ICP, mm Hg	14 ± 8	13 ± 7	.78
Cumulative balance, mL	50 (-3710 to 4614)	420 (-3000 to 5939)	.14
CVP, mm Hg	8.3 ± 2.6	8.5 ± 2.6	.75
Vasoactive drugs, %	67	94	.03

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; Vt/PBW, tidal volume per predicted body weight; RR, respiratory rate;  $\dot{V}_E$ , minute ventilation; Pplat, plateau pressure; Cst,rs, static compliance of the respiratory system; PEEP<sub>appl</sub>, applied positive end-expiratory pressure; MAP, mean arterial pressure; ICP, intracranial pressure; CVP, central venous pressure.

Data are presented as mean ± SD or median (range). Boldface, significant values ( $p < .05$ ).

Table 3. Multivariate stepwise regression analysis with backward elimination of demographic and treatment variables

Variable	p Value	Odds Ratio	95% CI
Mean Vt/PBW	.008	5.45	1.54–19.24
RR	.013	1.80	1.13–2.86
PaO <sub>2</sub> /Fio <sub>2</sub>	.004	0.98	0.98–0.99

CI, confidence interval; Vt/PBW, tidal volume per ideal body weight; RR, respiratory rate. The OR for Vt/PBW is per unit increase.

Vt/PBW, RR, and  $\dot{V}_E$  compared with the control group ( $p < .001$ ; Table 2). Despite the use of higher  $\dot{V}_E$ , a significantly higher level of Paco<sub>2</sub> was obtained suggesting an early impairment in CO<sub>2</sub> clearance. Actual Vt in the control group was significantly lower than in patients who developed ALI/ARDS (606 ± 83 mL vs. 698 ± 98 mL;  $p < .0005$ ). Pplat was significantly higher in patients who later

developed ALI/ARDS, and Cst,rs tended to be lower while similar levels of PEEP were applied to optimize oxygenation. A higher level of Fio<sub>2</sub> was required from admission, and PaO<sub>2</sub>/Fio<sub>2</sub> was significantly lower in patients who later developed ALI/ARDS ( $p < .01$ ). Cumulative fluid balance, MAP, ICP, cerebral perfusion pressure, and central venous pressure were not significantly different be-

tween groups before ALI/ARDS onset. Vasoactive support was required more often in patients who later developed ALI/ARDS ( $p < .05$ ; Table 2) with following total dosage: mean value of dopamine 4378 ± 5226 vs. 5947 ± 5431 (median 1200 [0–21,600] vs. 5280 [0–19,344])  $\gamma$ /kg/day and noradrenaline 56 ± 115 vs. 80 ± 157 (median 0 [0–576] vs. 0 [0–552])  $\gamma$ /day in control and ALI/ARDS groups, respectively.

*Predictors of ALI/ARDS Development.*

Among all demographic and clinical variables, the following significantly differed between groups (Table 2) and were initially entered into the stepwise regression model (significant level for inclusion  $\alpha = .1$ ): gender, SAPS, mean Vt/PBW, RR, Pplat, PaO<sub>2</sub>/Fio<sub>2</sub>, Paco<sub>2</sub>, use of vasoactive drugs, and aspiration. The selected model included Vt, RR, and PaO<sub>2</sub>/Fio<sub>2</sub>, whose effects on the development of ALI/ARDS are shown in Table 3.

*Distribution of Mean Tidal Volume.*

The proportion of ALI/ARDS increased with the higher initial Vt settings in a dose-response relationship ( $p < .01$ ). In the days preceding ALI/ARDS, 72% of patients in the ALI/ARDS group were ventilated with mean Vts  $\geq 10$  mL/kg PBW (Fig. 1).

*Ventilatory and Hemodynamic Management After ALI/ARDS Onset.*

After the onset of ALI/ARDS, patients remained ventilated with Vt, RR, and  $\dot{V}_E$  significantly higher than the control group in order to maintain similar levels of Paco<sub>2</sub> (Table 4;  $p < .01$ ). Actual Vt in ALI/ARDS group was significantly higher than in the control group (710 ± 97 mL vs. 620 ± 92 mL). Significantly higher levels of PEEP ( $p < .05$ ) and Fio<sub>2</sub> ( $p < .001$ ) were applied to optimize oxygenation. Cst,rs ( $p < .05$ ) and Pplat ( $p < .0001$ ) were significantly different in the ALI/ARDS group compared with control. Vasoactive support was required more often ( $p < .05$ ) in patients with ALI/ARDS to maintain similar levels of MAP. Fluid balance and central venous pressure were similar in the two groups, while ICP was significantly higher in the ALI/ARDS group (Table 4;  $p < .05$ ).

*Outcome Variables.*

Patients with ALI/ARDS had a significantly longer ICU length of stay and fewer VFD than the control group ( $p < .05$ ; Table 5). Mortality rate in this patient population was 25% and did not vary according to ALI status but did vary according to the initial GCS: Patients with an initial GCS of 3–5 had a 40% mortality rate compared with 15% mortality in patients with initial GCS of 6–8 ( $p < .05$ ).

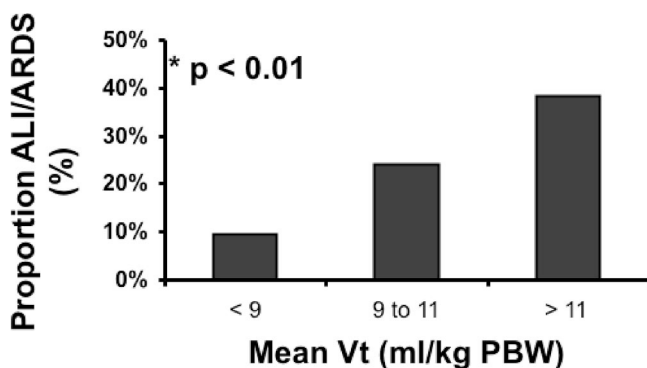


Figure 1. Proportion of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) according to tidal volume ( $V_t$ ).  $V_T < 9$  mL/kg predicted body weight (PBW) ( $n = 21$ );  $V_T 9-11$  mL/kg PBW ( $n = 47$ );  $V_T > 11$  mL/kg PBW ( $n = 14$ ). \*Adjusted  $p$  value from a stepwise regression model (Table 3).

Table 4. Ventilatory and hemodynamic variables after the onset of ALI/ARDS

Variable	Control ( $n = 64$ ; 78%)	ALI/ARDS ( $n = 18$ ; 22%)
$V_T$ /PBW, mL/kg	$9.6 \pm 1.4$	$10.6 \pm 1.5^a$
RR, $\text{min}^{-1}$	$12.4 \pm 1.6$	$15.2 \pm 5.1^a$
$\dot{V}_E$ , L/ $\text{min}^{-1}$	$7.6 \pm 1.9$	$10.4 \pm 3.2^a$
$\text{Paco}_2$ , mm Hg	$34.5 \pm 4.3$	$35.2 \pm 5.3$
Pplat, cm $\text{H}_2\text{O}$	$16.8 \pm 3.6$	$22 \pm 3.5^a$
Cst,rs, mL/cm $\text{H}_2\text{O}$	$52 \pm 15$	$45 \pm 8^a$
PEEP <sub>appl</sub> , cm $\text{H}_2\text{O}$	$4.4 \pm 3.2$	$6.3 \pm 4.2^a$
$\text{FiO}_2$ , %	$35 \pm 10$	$60 \pm 10^a$
$\text{PaO}_2/\text{FiO}_2$	$365 \pm 95$	$150 \pm 36^a$
MAP, mm Hg	$94 \pm 14$	$92 \pm 12$
ICP, mm Hg	$13.5 \pm 7.2$	$17.1 \pm 5.3^a$
Daily balance, mL	$-450$ ( $-4400$ to $2915$ )	$-506$ ( $-1700$ to $2250$ )
CVP, mm Hg	$8.9 \pm 3.2$	$10.3 \pm 4.2$
Vasoactive drugs, %	57	89 <sup>b</sup>

ALI, acute lung injury; ARDS, acute respiratory distress syndrome;  $V_T$ /PBW, tidal volume per predicted body weight; RR, respiratory rate;  $\dot{V}_E$ , minute ventilation; Pplat, plateau pressure; Cst,rs, static compliance of the respiratory system; PEEP<sub>appl</sub>, applied positive end-expiratory pressure; MAP, mean arterial pressure; ICP, intracranial pressure; CVP, central venous pressure.

<sup>a</sup>Unpaired  $t$ -test: control vs. ALI/ARDS,  $p < .001$ ; <sup>b</sup>Fisher's exact test: control vs. ALI/ARDS,  $p < .05$ . Data are presented as mean  $\pm$  SD or median and range.

Table 5. Outcome data of the patient population

Patient Characteristics	Control ( $n = 64$ , 78%)	ALI/ARDS ( $n = 18$ , 22%)
VFD	16 (0-25)	11 (0-21) <sup>a</sup>
ICU LOS	$20 \pm 10$	$25 \pm 8^b$
Mortality, %	22	28

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; VFD, ventilator-free days up to 28 days; ICU LOS, intensive care unit length of stay up to 28 days.

<sup>a</sup>Mann-Whitney: control vs. ALI/ARDS,  $p < .05$ ; <sup>b</sup>unpaired  $t$ -test: control vs. ALI/ARDS,  $p < .05$ . Data are presented as mean  $\pm$  SD or median and range.

## DISCUSSION

Our study shows that in addition to a lower  $\text{PaO}_2/\text{FiO}_2$ , high  $V_T$  and high RR were the most powerful independent predictors of early ALI/ARDS in patients with severe brain injury. After the occurrence of this complication,  $\text{FiO}_2$  and PEEP were increased to guarantee adequate oxygenation to the brain while  $V_T$  was not changed to

protect the lungs but remained significantly higher than control to maintain similar levels of  $\text{Paco}_2$  (mild hypocapnia).

**Main Limitations.** The main limitation of the present study is the observational nature. Consequently, those patients receiving higher  $V_T$ s may have been treated differently from those receiving lower  $V_T$ s in terms of intracranial

hypertension management. Moreover, we cannot exclude the possibility that higher  $V_T$ s were chosen purposefully to correct the underlying gas exchange impairment already present at admission and that this ventilatory setting represented an important "second hit" for the full development of the syndrome. The duration of time that patients were exposed to  $V_T$ s  $> 10$  mL/kg PBW was not recorded: Data were averaged from three values recorded during the day; however, this might have been not enough to measure fluctuations in the ventilator strategy and to determine cumulative exposure to potentially harmful settings.

The incidence of ALI/ARDS in patients with severe brain injury has been reported between 10% and 30% (1, 2, 4, 24). This variability may be explained by patient selection and definition of ALI/ARDS criteria. Using the Lung Injury Score, Gruber et al. (24) reported an incidence of 26% in subarachnoid hemorrhage patients, while authors who used the American-European Consensus Conference criteria (21) reported an incidence of 30% for ALI/ARDS and 10% for ARDS only (1, 2). All of these studies included patients with different severity of injury as suggested by the GCS at admission. When the analysis was restricted to patients with severe TBI (GCS  $< 9$ ), an incidence of 20% and 10% for ALI and ARDS, respectively, was reported (2, 4). However, regardless of the differences in inclusion criteria and ALI/ARDS definition, all previous studies reported an increased mortality associated with the development of ALI/ARDS. In the present study, using the criteria of the American-European Consensus Conference for ALI/ARDS definition (21), we found an incidence of 22%. There were no differences between patients with trauma or cerebrovascular accident in terms of ALI/ARDS incidence. Although the causes of brain injury were different, their severity was similar: They were included only if the GCS was  $< 9$ . However, since the absolute number of cases of ALI/ARDS in the two subgroups (trauma or cerebrovascular accident) may be too low to detect a difference in ALI/ARDS incidence, larger studies are required to confirm this observation. We were interested in studying the independent predictors of early ALI/ARDS (within 72 hrs after mechanical ventilation). Therefore, together with the physiologic and treatment variables, major underlying ALI/ARDS risk factors (aspiration, pneumonia, and lung contu-

sion) were included in the analysis, but only the ventilator settings (Vt and RR) and a lower PaO<sub>2</sub>/FIO<sub>2</sub> remained in the final stepwise regression model. However, the possibility that residual confounding factors were only partially accounted by the logistic procedure because of the small sample size should be considered.

The occurrence of ALI/ARDS was associated with an increased ICU length of stay and a decreased number of VFD while mortality was not significantly different. This result, which is in agreement with results by Treggiari and coworkers (25), may be explained by the fact that in patients with severe brain injury, the effect of ALI/ARDS is obscured by the overall mortality driven by the severity of the brain injury rather than other organ failures.

**Physiologic Rationale.** The presence of pulmonary dysfunction after brain injury is well recognized. In the past, it was attributed to a massive increase in sympathetic activity (7), while recently it has been suggested that a systemic inflammatory response plays an integral role in the development of such injury (9). It has been suggested that after acute brain injury, there is both an increased intracranial production of proinflammatory cytokines resulting in a secondary injury to the brain (26) and the release of proinflammatory mediators into the systemic circulation (27). This is true after both TBI and subarachnoid hemorrhage, suggesting that despite different etiologies of primary injury, the mechanisms of the inflammatory process may be similar (27). Besides, in an experimental model, it was demonstrated that massive brain injury decreases the pulmonary tolerance of subsequent mechanical stress due to mechanical ventilation (28).

Previous studies tried to identify severely brain-injured patients at risk of developing ALI/ARDS. Among the intracranial factors, the presence of midline shift on the first computed tomography scan (2) and lower GCS (1) were the only independent predictors identified. Administration of vasoactive drugs and history of drug abuse were recently reported as extracranial independent predictors of ARDS in patients with severe TBI (2), while the role of ventilatory management has never been evaluated. Guidelines for traumatic brain injury suggest maintaining Paco<sub>2</sub> ≥35 mm Hg for treatment of intracranial hypertension by using high Vt and optimizing oxygenation-preserving cerebral venous drainage by using low levels of PEEP (13). This ventilator

strategy may further exacerbate the pulmonary and systemic inflammatory response in patients with ALI/ARDS (14). Moreover, Gajic et al. (16) showed that the use of high Vt for the first 48 hrs of mechanical ventilation was associated with the development ventilator-induced lung injury in a general ICU patient population with an established inflammatory process, such as aspiration, sepsis, pneumonia, and trauma. Similarly, in patients with severe brain injury, the inflammatory process may be commenced by the primary cerebral injury. Therefore, we hypothesized that the mechanical stretch due to the ventilator strategy proposed for patients with severe brain injury may activate the ventilator-induced lung injury in lungs primed because of the primary cerebral injury.

**Clinical Implications.** In the present study, patients with severe brain injury were ventilated in order to obtain mild hypocapnia and adequate oxygenation as proposed by the guidelines for TBI. In patients who later developed ALI/ARDS, an impaired CO<sub>2</sub> clearance and a lower PaO<sub>2</sub>/FIO<sub>2</sub> were already present in the first 24 hrs. Consequently, compared with the control group, higher levels of Vt and RR were required in the attempt to remove CO<sub>2</sub> while oxygenation was ensured by higher levels of FIO<sub>2</sub> and similar low levels of PEEP. In addition to a lower PaO<sub>2</sub>/FIO<sub>2</sub>, significant risk factors for the development of ALI/ARDS were related to the initial ventilator settings with large Vts and relatively high RR.

Pplat of 30 cm H<sub>2</sub>O is considered the safe limit to protect from ventilator-induced lung injury (29–31). However, reviewing the data of the ARDS network trial, the authors were unable to confirm this threshold and concluded that reduction of Vt from 12 to 6 mL/kg PBW had a beneficial effect regardless of the baseline Pplat (32). In our study, in the group of patients who subsequently developed ALI/ARDS, Cst,rs was similar to the control group, and Pplat, although significantly different in the two groups ( $p < .0005$ ), had an absolute low value ( $20 \pm 3.8$  cm H<sub>2</sub>O), suggesting that the use of large Vts *per se* may be instrumental in the pathogenesis of this syndrome. In our study, levels of PEEP were not different between groups in the first 3 days. Although the role of PEEP settings is more controversial than Vt as a risk factor for development of ventilator-induced lung injury (33), in our study levels of applied PEEP were very low in both groups ( $3.7 \pm 2.8$

vs.  $4.2 \pm 3.7$  cm H<sub>2</sub>O) to allow for a powerful comparison.

The role of hemodynamic management in the development of ARDS after TBI has been recently evaluated. Contant et al. (2) found that the greatest risk of developing ARDS was represented by epinephrine use and history of drug abuse. However, patients who developed ARDS had midline shift on the first computed tomography scan and higher ICP. Due to the retrospective nature of the study, it is difficult to conclude whether these patients were at a higher risk of developing ARDS because they required more aggressive specific treatment (with vasoactive drugs) for intracranial hypertension or if the more severe intracranial hypertension *per se* induced the development of ARDS (7). In our study, severity of the injury was similar at admission but patients who developed ALI/ARDS more often required vasoactive drugs to guarantee adequate cerebral perfusion pressure throughout the study period. Since we did not report the “therapy intensity level” (34), we cannot exclude that the use of vasoactive drugs was associated with the use of higher doses of sedation to treat ICP. Certainly, after ALI/ARDS onset, patients had higher levels of ICP, therefore requiring more aggressive treatment, including vasopressors.

## CONCLUSIONS

We have shown that ALI/ARDS occurred in 20% of patients with severe brain injury and was associated with longer ICU length of stay and fewer VFD. Our data suggest that in addition to a lower PaO<sub>2</sub>/FIO<sub>2</sub>, ventilation with large Vts and relatively high RR represents an important predictor of ALI/ARDS development in patients with severe brain injury. Further studies are required to identify optimal ventilator strategies to protect the lung and maintain a tight a CO<sub>2</sub> control (35).

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