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RESPIRATORY RESPONSE AND NEUROLOGICAL TOLERANCE OF PRONE POSITIONING IN BRAIN-INJURED PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

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ABSTRACT

Background/Objective: Prone positioning is established therapy for moderate-to-severe acute respiratory distress syndrome (ARDS), but its use after acute brain injury remains controversial because it may increase intracranial pressure (ICP). Where invasive ICP monitoring is unavailable, transcranial Doppler (TCD) may provide a non-invasive assessment of cerebral hemodynamic tolerance. We evaluated respiratory and neurological tolerance of proning in brain-injured patients with ARDS.

Methods: We retrospectively studied patients aged ≥16 years who developed ARDS after brain injury in our ICU from January 2020 to March 2023. Patients were grouped by proning exposure. Proning required neurological stability and absence of a pathological TCD pattern, defined as pulsatility index >1.4 with middle cerebral artery diastolic velocity <20 cm/s. TCD and pupillary assessments were repeated twice daily. A pathological pattern suggested intracranial hypertension only after optimization of $PaCO_2$ and invasive arterial blood pressure. The primary outcome was change in PaO_2/FiO_2.

Results: Of 613 brain-injured patients, 29 developed ARDS; 14 were proned and 15 were not. In proned patients, median PaO_2/FiO_2 increased from 133 (62–182) to 222 (185–257), improving in all 14 ($p<0.001$). TCD documentation sufficient to assess cerebral hemodynamic tolerance was available in eight patients: seven had no new pathological pattern and one developed findings suggestive of intracranial hypertension, prompting osmotherapy then external ventricular drainage. No new pupillary abnormality occurred. ICU mortality was 42.9% versus 60.0% (risk ratio 0.71, 95% CI 0.34–1.49; $p=0.47$).

Conclusions: In this selected cohort, prone positioning improved oxygenation without an evident signal of excess neurological intolerance. Serial TCD may be a pragmatic non-invasive adjunct where invasive ICP monitoring is unavailable. The small sample, retrospective single-center design, incomplete TCD data and selection bias preclude causal conclusions; these findings are hypothesis-generating.

Keywords: Prone positioning; Acute brain injury; Acute respiratory distress syndrome; Transcranial Doppler; Intracranial hypertension; Neuromonitoring.

1 INTRODUCTION

The brain and the lung interact through mechanisms that remain incompletely characterized. Acute cerebral injury, whether traumatic or not, triggers a systemic inflammatory response and a catecholamine surge that predispose the lung to injury, while impaired consciousness and disordered neurovegetative control of breathing expose patients to aspiration and ventilator-associated pneumonia. Acute respiratory distress syndrome (ARDS), defined since 2012 by the Berlin criteria [1] and more recently by a new global definition [2], is among the most severe of these complications and is consistently associated with prolonged mechanical ventilation, worse neurological recovery and increased mortality [3–5].

Managing ARDS in a brain-injured patient generates a direct therapeutic conflict. The ventilatory strategies that protect the lung may harm the brain: permissive hypercapnia raises cerebral blood flow and intracranial pressure (ICP), high positive end-expiratory pressure (PEEP) may reduce cerebral venous return and cerebral perfusion pressure, and recruitment maneuvers transiently increase ICP [6,7]. Conversely, the large tidal volumes historically used to protect cerebral perfusion are themselves a recognized cause of lung injury after severe brain trauma [6]. European consensus recommendations acknowledge that this trade-off rests on very limited evidence [7,8].

Prone positioning occupies a particular place in this conflict. The PROSEVA trial established that prolonged prone sessions reduce 28-day and 90-day mortality in severe ARDS [9], and international guidelines recommend the maneuver for a PaO_2/FiO_2 ratio below 150 mmHg [10,11]. Brain-injured patients are largely absent from this evidence base: in a systematic review of 120 studies of prone positioning, 75% excluded them without stated justification [12]. The specific evidence available consists of small series with discordant conclusions. Reinprecht and colleagues observed a significant ICP rise during proning in subarachnoid hemorrhage, yet concluded the maneuver was tolerated because cerebral perfusion pressure was preserved [13]. Roth and colleagues reported a similar increase and judged the oxygenation benefit to outweigh it [14]. Nekludov and Thelandersson described improved cerebral oxygenation, with tolerance depending on intracranial compliance [15,16]. Bernon and colleagues found that intracranial hypertension occurred in every patient whose ICP exceeded 17.5 mmHg before the maneuver [17], and Leppert and colleagues reported comparable limitations after aneurysmal subarachnoid hemorrhage [18].

A feature common to nearly all of these studies is that neurological tolerance was assessed by invasive ICP monitoring. Bernon and colleagues concluded by proposing that intracranial compliance be evaluated before proning, suggesting transcranial Doppler (TCD) for that purpose [17], and Elmaleh and colleagues subsequently used TCD as the primary endpoint of a prospective pilot study in eleven brain-injured patients [12]. TCD is inexpensive, repeatable at the bedside and can provide indirect information on cerebral hemodynamics and the likelihood of intracranial hypertension [19,20]. A recent review of non-invasive ICP estimation emphasizes that such methods are clinically useful surrogates but do not replace invasive ICP measurement [36]. In many intensive care units worldwide, particularly in resource-limited settings, invasive monitoring is not routinely available, and clinicians must decide whether to prone a brain-injured patient without direct ICP measurement.

We therefore reviewed our practice in a Moroccan university intensive care unit where TCD is the only instrumental neuromonitoring modality routinely available and where a reassuring examination is required before prone positioning. Our objective was to evaluate the respiratory response and neurological tolerance of prone positioning in brain-injured patients with ARDS, with particular attention to cerebral hemodynamic tolerance assessed by serial TCD, and to describe outcomes in comparison with patients with ARDS who were not proned.

2 METHODS

2.1 Study design and setting

This was a retrospective observational cohort study conducted in the anesthesiology and intensive care unit (Unit A1) of Hassan II University Hospital, Fez, Morocco, a tertiary referral center. The study period ran from 1 January 2020 to 31 March 2023. The study is reported in accordance with the STROBE statement [21]; the completed checklist is provided as a supplementary file.

2.2 Ethics

Given the retrospective design and the use of anonymized routinely collected data, the requirement for individual informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki.

2.3 Participants

All brain-injured patients aged 16 years or older admitted to the unit during the study period were eligible. Cases were identified through a retrospective keyword search of hospital discharge summaries using the terms “brain injury”, “ARDS” and “prone positioning”, followed by review of the full medical record for group classification and data extraction. Patients younger than 16 years, those managed in the emergency department without transfer to the unit, and those with incomplete records were excluded. Two groups were compared: brain-injured patients who developed ARDS and received at least one prone-positioning session, and those who developed ARDS but were not proned. Patients who did not develop ARDS are described only as a contextual denominator and were not included in the prone versus non-prone comparative analyses.

2.4 Definitions

ARDS was diagnosed on the basis of acute respiratory deterioration with signs of respiratory distress, desaturation and patient–ventilator dyssynchrony, a PaO_2/FiO_2 ratio of 300 mmHg or less on arterial blood gas analysis, and abnormal chest imaging, in the absence of a predominant hydrostatic cause. All proned patients were ventilated with a PEEP of at least 7 cmH_2O, so that the Berlin threshold of 5 cmH_2O [1] was met throughout. Because bilateral opacities were not adjudicated prospectively against the Berlin criteria, we describe our case definition as clinically applied rather than formally validated. The new global definition of ARDS [2] was published after the end of the study period and was not used.

2.5 Transcranial Doppler assessment

TCD examinations were performed at the bedside by the attending intensivist using a 2 MHz pulsed probe through the transtemporal window, insonating both middle cerebral arteries. Systolic, diastolic and mean flow velocities were recorded, and the pulsatility index (PI) was calculated as (systolic velocity - diastolic velocity)/mean velocity. TCD was used as an indirect assessment of cerebral hemodynamics rather than as a direct measurement of ICP. A pathological pattern was predefined as a PI >1.4 together with a middle cerebral artery diastolic velocity <20 cm/s, a combination associated with cerebral hypoperfusion after severe brain injury [19]. Prone positioning was undertaken only when this pathological pattern was absent and the neurological condition was considered stable. During assessment of tolerance, the development of this pattern was interpreted as suggestive of possible ICP elevation or intracranial hypertension only after optimization of $PaCO_2$ and invasively monitored arterial blood pressure, in order to minimize systemic confounding. No patient had an invasive ICP monitor in place specifically for assessment of prone-positioning tolerance at the initiation of proning.

2.6 Prone positioning protocol

Prone positioning was considered when respiratory and hemodynamic parameters failed to improve after deep sedation, recruitment maneuvers and neuromuscular blockade. Before every session, neurological status had to be stable and TCD had to show no pathological pattern as defined above; strict pupillary surveillance and optimal sedation were maintained. Thoracic and iliac bolsters were used systematically. During the session, invasive arterial pressure monitoring was maintained, ventilation was adjusted with close attention to $PaCO_2$, vascular access was secured, pupils were assessed twice daily, TCD was repeated twice daily, and pressure areas were inspected throughout. A new pathological TCD pattern persisting despite correction of $PaCO_2$ and arterial blood pressure was considered a sign of neurological intolerance and prompted treatment and reassessment.

2.7 Data collection and outcomes

Data were extracted from medical records using a standardized case report form and comprised demographic characteristics, comorbidities, mechanism of cerebral injury, time to intensive care admission, Glasgow Coma Scale (GCS) score on admission, pupillary status, hemodynamic and respiratory variables, cerebral and chest imaging, laboratory results, ventilatory management, prone positioning characteristics, adjunctive therapies and outcome.

The primary outcome was the change in the PaO_2/FiO_2 ratio between the arterial blood gas obtained at the start of the first prone-positioning session and the best value recorded during that session. Secondary outcomes were neurological tolerance; ICU mortality; length of ICU stay; and duration of mechanical ventilation. Neurological intolerance was defined as the development of a pathological TCD pattern (PI >1.4 together with middle cerebral artery diastolic velocity <20 cm/s) despite optimization of $PaCO_2$ and invasive arterial blood pressure, and/or a new pupillary abnormality. TCD findings were interpreted as indirect evidence of possible intracranial hypertension and not as direct ICP measurements.

2.8 Statistical analysis

Continuous variables are reported as means with ranges, except respiratory and blood-gas variables recorded at the start of the first prone-positioning session, which are reported as medians with ranges. Categorical variables are

reported as counts with percentages. Exact individual paired PaO_2/FiO_2 values were no longer retrievable, although the direction of response was documented for each patient; the primary outcome was therefore tested with an exact two-sided sign test on the number of patients whose ratio improved. The proportions of patients who improved were compared between groups using Fisher's exact test. Other proportions were also compared using Fisher's exact test, and risk ratios are presented with 95% confidence intervals calculated by the Katz logarithmic method. A two-sided p value <0.05 was considered significant. Given the small sample size, all comparative analyses are exploratory; no adjustment for confounding or correction for multiple testing was undertaken. Data were managed in Microsoft Excel.

3 RESULTS

3.1 Cohort characteristics

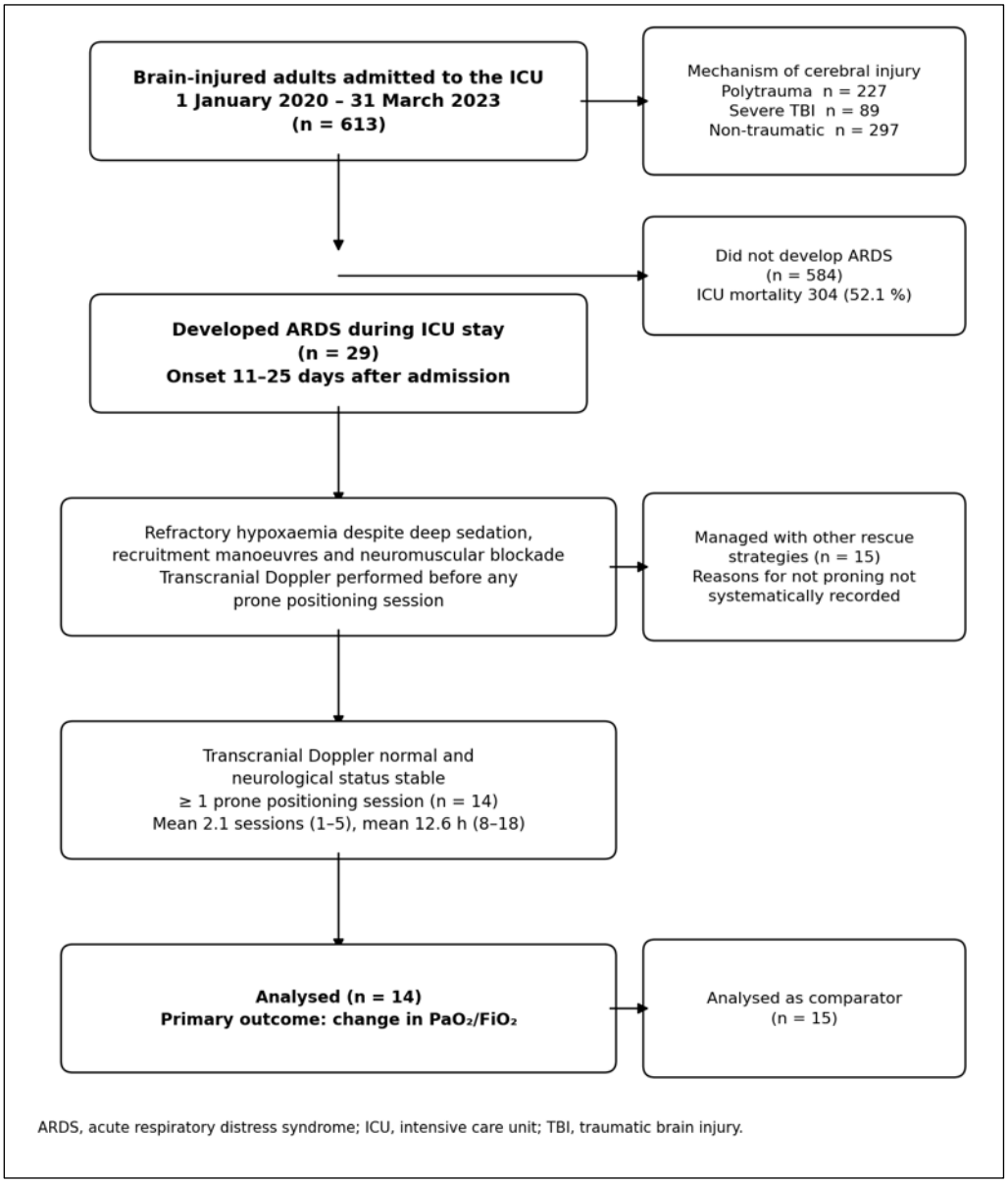

Figure 1: Study flow diagram. ARDS, acute respiratory distress syndrome; ICU, intensive care unit; TBI, traumatic brain injury.

During the study period, 613 brain-injured patients were admitted: 227 in the context of polytrauma, 89 following severe traumatic brain injury and 297 with non-traumatic cerebral injury. Twenty-nine developed ARDS during their stay. Of these, 14 received at least one prone positioning session and 15 were managed with other rescue strategies, namely protective ventilation, recruitment maneuvers, neuromuscular blockade and inhaled nitric oxide. The study flow is shown in Figure 1.

Table 1: Baseline characteristics of the study groups.

Characteristic	No ARDS (n = 584)	ARDS + PP (n = 14)	ARDS, no PP (n = 15)	p value
Age, years				
Mean (range)	—	33 (17–57)	—	—
17–25, n (%)	—	2 (14.3)	6 (40.0)	—
26–35, n (%)	—	5 (35.7)	5 (33.3)	—
36–45, n (%)	—	2 (14.3)	2 (13.3)	—
46–55, n (%)	—	3 (21.4)	1 (6.7)	—
≥ 56, n (%)	—	2 (14.3)	1 (6.7)	—
Mechanism of cerebral injury				
Polytrauma, n (%)	227 (38.9)	7 (50.0)	—	—
Severe traumatic brain injury, n (%)	89 (15.3)	1 (7.1)	—	—
Non-traumatic, n (%)	297 (50.9)	6 (42.9)	—	—
Road traffic collision, n (%)	—	8 (57.1)	—	—
Admission status				
GCS ≤ 8, n (%)	120 (20.5)	11 of 29 pooled (37.9)		0.035
GCS 9–13, n (%)	352 (60.3)	15 of 29 pooled (51.7)		—
GCS 14–15, n (%)	112 (19.2)	3 of 29 pooled (10.3)		—
Time to ICU admission 6–24 h, n (%)	167 (28.6)	15 of 29 pooled (51.7)		0.012
Cerebral CT abnormal on admission, n (%)	—	29 of 29 pooled (100)		—
ARDS at diagnosis				
Days from admission to ARDS, range	—	11–25 (pooled)		—
SpO_2 at diagnosis, mean %	96	79 (pooled)		—
Ventilator dyssynchrony, n (%)	—	29 of 29 pooled (100)		—
PaO_2/FiO_2, median (range)	—	133 (62–182)	151 (65–240)	—
PaO_2/FiO_2 < 150 mmHg, n (%)	—	13 (92.9)	—	—
Tracheostomy during stay, n (%)	—	64 % (pooled)		—

Values are n (%) unless otherwise stated. Where a variable was recorded only for the 29 patients with ARDS as a whole, the pooled figure is given and spans both ARDS columns. Em dashes indicate variables not recorded for that group. p values compare patients with and without ARDS (Fisher's exact test). ARDS, acute respiratory distress syndrome; CT, computed tomography; GCS, Glasgow Coma Scale; ICU, intensive care unit; PP, prone positioning.

Among the 14 proned patients, the mean age was 33 years (range 17–57), 7 were admitted after polytrauma, 1 after severe traumatic brain injury and 6 after a non-traumatic cerebral insult; road traffic collisions accounted for 8 cases and an abrupt unexplained impairment of consciousness for 5. The 15 non-proned patients were younger, 11 of 15 being under 36 years compared with 7 of 14 among proned patients. Across the 29 patients with ARDS, 8 had no medical, surgical or toxicological history, 6 were hypertensive and 3 diabetic. Cerebral computed tomography was abnormal on admission in every patient and half had multiple concomitant lesions; among the lesions identified, subarachnoid hemorrhage was the most frequent (26%), followed by subdural hematoma and cerebral contusion (21% each),

extradural hematoma and intraparenchymal hemorrhage (11% each), and cerebral abscess and intracerebral calcification (5% each). Baseline characteristics are summarized in Table 1.

Patients who developed ARDS differed from those who did not in two respects: they were more often admitted late, 15 of 29 reaching the unit between 6 and 24 hours after the insult compared with 167 of 584 ($p = 0.012$), and more often deeply comatose on admission, with a GCS of 8 or less in 11 of 29 compared with 120 of 584 ($p = 0.035$).

3.2 Characteristics of ARDS

ARDS developed between 11 and 25 days after admission, with 14 of the 29 cases arising beyond the twentieth day. Mean oxygen saturation at diagnosis was 79%, compared with 96% in patients without ARDS, and patient–ventilator dyssynchrony was present in all cases. Mechanical ventilation had been instituted within four hours of admission; 27 of the 29 patients were intubated on neurological grounds and 2 on respiratory and hemodynamic grounds, and 64% subsequently underwent tracheostomy. All patients underwent chest radiography. Among the proned patients, archived radiographic images were retrievable for 7: two showed diffuse bilateral perihilar opacities, two bilateral basal consolidation, and three right basal consolidation, with left-sided atelectasis in one of them.

The two ARDS groups differed markedly in the severity of hypoxemia. Among proned patients the PaO_2/FiO_2 ratio was 133 (range 62–182) and 13 of 14 were below the 150-mmHg threshold at which prone positioning is recommended, whereas among non-proned patients the ratio was 151 (range 65–240). Respiratory and blood-gas variables at the start of the first prone session are given in Table 2: ventilation was lung-protective, with a median tidal volume of 6.4 mL/kg predicted body weight and a median PEEP of 8 cmH_2O, and arterial carbon dioxide tension was close to normal at a median of 43 mmHg (range 35–75).

Table 2: Respiratory and arterial blood-gas variables at the start of the first prone positioning session.

Variable	Median (range), n = 14
PaO_2/FiO_2, mmHg	133 (62–182)
Set PEEP, cmH_2O	8 (7–12)
Tidal volume, mL	450 (360–550)
Tidal volume, mL/kg predicted body weight	6.4 (5.2–7.3)
FiO_2, %	63 (30–100)
Set respiratory rate, breaths/min	28 (16–30)
pH	7.35 (7.10–7.55)
PaO_2, mmHg	80 (55–150)
$PaCO_2$, mmHg	43 (35–75)
Arterial lactate, mmol/L	1.6 (0.5–3.0)

PEEP, positive end-expiratory pressure.

3.3 Delivery of prone positioning and neurological surveillance

Patients received a mean of 2.1 prone-positioning sessions (range 1-5); session duration ranged from 8 to 18 hours, with a mean of 12.6 hours. The decision to prone was taken 4-12 hours after the diagnosis of ARDS, after failure of deep sedation, recruitment maneuvers and neuromuscular blockade, and in every case after a TCD examination without the predefined pathological pattern. All proned patients received isotonic saline and vasoactive support, predominantly noradrenaline, together with sedation and antiepileptic prophylaxis. External ventricular drainage was performed in two patients during the ICU stay and decompressive craniectomy in one. Details are given in Table 3.

Table 3: Delivery of prone positioning, oxygenation response and neurological tolerance.

Variable	Proned patients (n = 14)
Delivery	
Number of sessions, mean (range)	2.1 (1–5)
Session duration, hours, mean (range)	12.6 (8–18)
Time from ARDS diagnosis to first session, hours	4–12
Normal transcranial Doppler before every session, n (%)	14 (100)
Thoracic and iliac bolsters, n (%)	14 (100)
Vasopressor support, n (%)	14 (100)
Sedation and antiepileptic prophylaxis, n (%)	14 (100)
Oxygenation response	
PaO_2/FiO_2 before proning, median (range)	133 (62–182)
PaO_2/FiO_2 during proning, median (range)	222 (185–257)
Patients with any improvement, n (%)	14 (100); $p < 0.001$
Neurological monitoring and tolerance	
Transcranial Doppler during session, times/day	2
Pupillary assessment during session, times/day	2
Patients with TCD documentation sufficient for tolerance assessment, n (%)	8 (57.1)
New pathological TCD pattern suggestive of intracranial hypertension, n (% of evaluable patients)	1 (12.5)
No new pathological TCD pattern, n (% of evaluable patients)	7 (87.5)
External ventricular drainage, n (%)	2 (14.3)
Decompressive craniectomy, n (%)	1 (7.1)

TCD was used as a non-invasive surrogate of cerebral haemodynamic status and did not directly measure ICP. A pathological TCD pattern was defined as PI >1.4 together with middle cerebral artery diastolic velocity <20 cm/s; during proning it was considered suggestive of possible intracranial hypertension only after optimisation of $PaCO_2$ and invasive arterial blood pressure. No patient had invasive ICP monitoring in place specifically for assessment of prone-positioning tolerance at the start of proning. The p value for the oxygenation response is an exact two-sided sign test on the number of patients whose ratio improved. ARDS, acute respiratory distress syndrome; ICP, intracranial pressure; PI, pulsatility index; TCD, transcranial Doppler.

3.4 Oxygenation response

Every proned patient improved both the PaO_2/FiO_2 ratio and oxygen saturation (14 of 14; exact sign test $p < 0.001$). The ratio rose from 133 (range 62–182) before the maneuver to 222 (range 185–257) during it, an improvement apparent from the first session and persisting after the patient was returned supine. Among the 15 patients who were not proned, 8 improved their ratio with alternative strategies — four with recruitment maneuvers, three with inhaled nitric oxide combined with deep neuromuscular blockade and one with recruitment maneuvers alone — but the overall gain was smaller, from 151 (range 65–240) to 190 (range 115–210), and 10 of the 15 subsequently showed a renewed fall in the ratio. The proportion of patients whose ratio improved was therefore higher with prone positioning than with alternative rescue strategies (14 of 14 versus 8 of 15; Fisher's exact $p = 0.006$). The oxygenation response in both groups is shown in Figure 2.

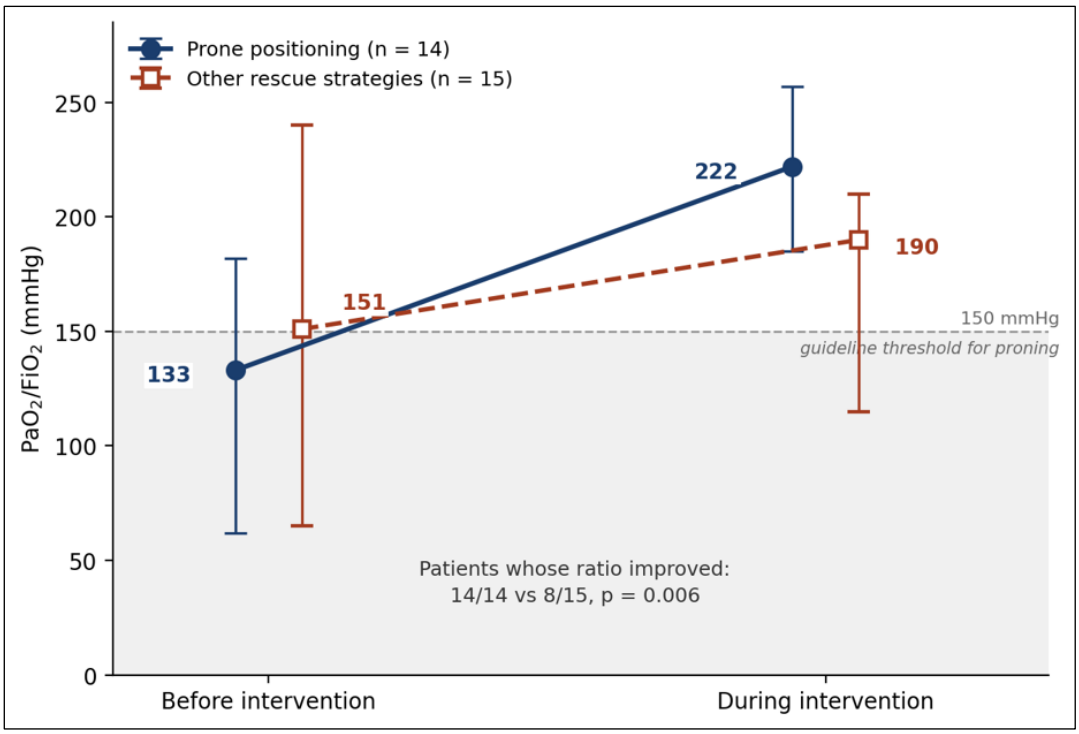

Figure 2: PaO_2/FiO_2 before and during the intervention in patients who received prone positioning and in those managed with other rescue strategies. Points are medians and bars show the full observed range. The dashed line marks the 150 mmHg threshold at which prone positioning is recommended by international guidelines. Exact individual paired values were not retrievable; comparison of response rates therefore uses the documented direction of change for each patient.

3.5 Neurological tolerance

Neurological tolerance was assessed by TCD and pupillary examination, each repeated twice daily during prone-positioning sessions. TCD documentation sufficient to characterize cerebral hemodynamic tolerance was retrievable for 8 of the 14 proned patients. Seven had no new pathological TCD pattern. One patient developed a PI >1.4 together with a diastolic velocity <20 cm/s despite optimization of $PaCO_2$ and invasive arterial blood pressure; this was interpreted clinically as suggestive of possible intracranial hypertension. Osmotherapy was administered and, because the abnormality persisted, external ventricular drainage was subsequently performed. No patient developed a new pupillary abnormality during a session, and no session was interrupted for neurological reasons. In the 15 non-proned patients, available records did not show a clear between-group difference in documented surrogate evidence of intracranial hypertension; this comparison is descriptive because serial numerical TCD data were not systematically available.

3.6 Outcomes

Table 4: Outcomes of brain-injured patients with ARDS, by exposure to prone positioning.

Outcome	ARDS + PP (n = 14)	ARDS, no PP (n = 15)	Effect estimate
ICU mortality, n (%)	6 (42.9)	9 (60.0)	RR 0.71 (95% CI 0.34–1.49); p = 0.47
ICU length of stay, days, mean (range)	24 (7–49)	25 (5–66)	—
Duration of mechanical ventilation, days, mean	20 (7–49)	22	—

Mortality compared by Fisher's exact test; risk ratio with 95% confidence interval by the Katz logarithmic method. ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; PP, prone positioning; RR, risk ratio.

Intensive care mortality was 42.9% (6 of 14) among proned patients and 60.0% (9 of 15) among those not proned (risk ratio 0.71, 95% CI 0.34–1.49; Fisher's exact p = 0.47). Mortality among the 584 brain-injured patients who did not develop ARDS was 52.1% (304 patients). Mean intensive care stay was 24 days in the proned group (range 7–49), 25

days in the non-proned group (range 5–66) and 18 days in patients without ARDS (range 5–35); corresponding mean durations of mechanical ventilation were 20, 22 and 16 days (Table 4).

4 DISCUSSION

In this single-center retrospective cohort of brain-injured patients with ARDS, prone positioning produced a marked oxygenation response, with improvement documented in all 14 proned patients. The more clinically distinctive observation concerns neurological tolerance: among the eight patients with TCD documentation sufficient for assessment, seven had no new pathological TCD pattern and one developed findings suggestive of possible intracranial hypertension, which required osmotherapy followed by external ventricular drainage. Available records from the non-proned group did not reveal a clearly lower burden of documented surrogate evidence of intracranial hypertension. These findings provide a reassuring signal that prone positioning can be attempted in carefully selected brain-injured patients under neurological surveillance, but they do not establish neurological safety or a causal absence of ICP elevation. Crude ICU mortality was lower in the proned group, but the groups differed substantially at baseline and this comparison is descriptive only.

4.1 Respiratory response in context

The improvement in oxygenation observed in our cohort is consistent with the established physiology and evidence base for prone positioning in ARDS: recruitment of dependent dorsal lung regions, more homogeneous ventilation-perfusion matching, improved secretion drainage and favorable right-ventricular loading conditions [22-24]. A recent systematic review confirms that change in PaO_2/FiO_2 remains the most commonly used physiological definition of response to proning, while also emphasizing that oxygenation response is heterogeneous and should not be equated with a survival effect [35]. In our study, the respiratory response therefore mainly confirms that the maneuver delivered its expected physiological benefit in this particular population; the principal clinical uncertainty is whether that benefit can be obtained without unacceptable cerebral hemodynamic consequences. Lung-protective ventilation was maintained, with a median tidal volume of 6.4 mL/kg predicted body weight and median PEEP of 8 cmH_2O. The median $PaCO_2$ was 43 mmHg, an important consideration because hypercapnia can increase cerebral blood flow and ICP.

4.2 Neurological tolerance and the role of transcranial Doppler

Our neurological findings sit at the more reassuring end of a discordant literature. Reinprecht and colleagues documented a significant ICP rise during proning in patients with subarachnoid hemorrhage but concluded that the maneuver was tolerated when cerebral perfusion pressure was preserved [13]. Roth and colleagues likewise observed an ICP increase during 8-hour prone sessions and judged the oxygenation gain to outweigh it [14]. Thelandersson and colleagues showed that tolerance depends on intracranial compliance [16]. Bernon and colleagues found that every patient whose baseline ICP exceeded 17.5 mmHg developed intracranial hypertension during proning, whereas most patients with lower baseline ICP tolerated the maneuver [17]. In our cohort, a new pathological TCD pattern suggestive of possible intracranial hypertension was documented in only one of the eight evaluable proned patients. Because TCD provides a surrogate of cerebral hemodynamics rather than a direct ICP measurement, this observation should be interpreted as a signal of tolerance rather than as proof that ICP remained unchanged.

Selection is likely to explain part of this reassuring signal. In our unit, prone positioning was restricted to neurologically stable patients whose pre-proning TCD did not show the predefined pathological pattern, thereby selecting against marked cerebral hemodynamic compromise. A reassuring TCD cannot, however, prove normal intracranial compliance. The value of TCD in this setting is pragmatic: it is bedside, repeatable and non-invasive, and changes in diastolic flow and pulsatility can alert clinicians to a possible deterioration in cerebral perfusion when invasive ICP monitoring is unavailable [19,20,36]. Our protocol further required correction of $PaCO_2$ and invasively monitored arterial pressure before a pathological TCD was attributed to possible intracranial hypertension, reducing two important physiological confounders. The absence of an obvious excess of documented abnormalities in the non-proned comparator group strengthens the safety signal, but the incomplete and non-randomized nature of the data prevents causal inference. TCD should therefore be viewed as an adjunct for screening and trend monitoring, not as a substitute for invasive ICP measurement.

4.3 Deviation from the reference prone positioning protocol

Our sessions were shorter than those used in PROSEVA, in which patients were proned for at least 16 consecutive hours and received a median of four sessions [9]; our patients received a mean of 2.1 sessions lasting 12.6 hours. This reflects local practice in a population in whom cerebral venous drainage and intracranial tolerance were major concerns, but it also means that the intervention differed from the regimen with proven survival benefit in general ARDS. Whether shorter sessions preserve that survival benefit cannot be answered by these data. The degree of reverse Trendelenburg was not systematically recorded, although a head-up prone position is now advocated to facilitate cerebral venous drainage [25], and intra-abdominal pressure was not measured, despite its potential influence on cerebral venous

outflow [26]. Future protocols should specify head elevation, abdominal decompression and session duration prospectively.

4.4 Phenotype of ARDS in our cohort

Twenty-nine of 613 brain-injured patients were identified as having ARDS. We do not present this proportion as an incidence estimate. Case-finding relied on a retrospective keyword search of discharge summaries, without systematic screening of PaO_2/FiO_2 ratios or prospective adjudication of chest imaging, and milder cases are likely to have escaped identification; the figure is far below published estimates of 27% after subarachnoid hemorrhage and 31% in ventilated patients with traumatic brain injury [4,5]. This under-ascertainment is a limitation of the design rather than a finding about our population.

A second observation deserves comment. ARDS occurred late, between the eleventh and twenty-fifth day of admission, with nearly half of cases arising beyond day 20. This is atypical of early neurogenic lung injury and points instead towards ventilator-associated pneumonia as the dominant precipitant, consistent with the prolonged ventilation and the 64% tracheostomy rate we observed. The two patients groups also differed in their route to ARDS: patients who developed the syndrome had been admitted later and were more deeply comatose on arrival, a combination that favors aspiration and nosocomial infection. The distinction matters, because late pneumonia-associated ARDS and early neurogenic ARDS may differ in recruitability and therefore in their response to proning [27]. Prospective work in this population should record the precipitating cause of ARDS explicitly.

Finally, mortality among patients who developed ARDS (51.7%) was virtually identical to that among brain-injured patients who did not (52.1%). The very high baseline mortality in the non-ARDS group reflects a severely injured case-mix, a high proportion of delayed referrals from peripheral hospitals, and the resource constraints of the setting; it limits any inference about the independent prognostic weight of ARDS in this cohort.

4.5 Limitations

This study has major limitations. It is retrospective, single-center and small, with only 14 proned patients, and the analysis was not pre-specified. The two ARDS groups were not comparable at baseline: 13 of 14 proned patients had a PaO_2/FiO_2 ratio <150 mmHg, whereas the median in non-proned patients was 151 mmHg. Proning was reserved for more severe respiratory failure after failure of other strategies, while the requirement for a reassuring pre-proning TCD selected patients without overt cerebral hemodynamic compromise. These opposing selection mechanisms cannot be disentangled. The reasons why the 15 comparator patients were not proned were not systematically recorded, so residual confounding by neurological severity is unavoidable. TCD is an indirect surrogate rather than a direct measure of ICP; serial numerical velocities and PI values were not consistently archived, and documentation sufficient for neurological tolerance assessment was available in only 8 of 14 proned patients. Monitoring was intermittent rather than continuous, no invasive ICP reference was available for validation, and no standardized long-term neurological outcome was recorded. Exact individual paired PaO_2/FiO_2 values were not retrievable, so the primary outcome could be tested only from the documented direction of change. Chest imaging was not prospectively adjudicated against the Berlin criteria and archived images were retrievable for only half of the proned patients. No adjustment for confounding was possible. Consequently, our data support only a hypothesis-generating signal of feasibility and neurological tolerance; they cannot establish that prone positioning does not increase ICP or worsen neurological outcome. Prospective multicenter studies with standardized TCD acquisition, continuous or invasive ICP monitoring where indicated, and validated neurological outcomes are needed.

Abbreviations

- ARDS, acute respiratory distress syndrome;
- CI, confidence interval;
- CT, computed tomography;
- GCS, Glasgow Coma Scale;
- ICP, intracranial pressure;
- ICU, intensive care unit;
- MCA, middle cerebral artery;
- PEEP, positive end-expiratory pressure;
- PI, pulsatility index;
- PP, prone positioning; RR, risk ratio;
- STROBE, Strengthening the Reporting of Observational Studies in Epidemiology;
- TBI, traumatic brain injury;
- TCD, transcranial Doppler;
- Vd, diastolic velocity.

5 CONCLUSION

In selected brain-injured patients with ARDS, prone positioning achieved the expected improvement in oxygenation without an evident signal of excess neurological intolerance compared with patients managed without proning. Among eight proned patients with evaluable TCD documentation, one developed a pathological pattern suggestive of possible intracranial hypertension and required osmotherapy followed by external ventricular drainage. In settings where invasive ICP monitoring is not routinely available, serial TCD may provide a pragmatic non-invasive adjunct for patient selection and cerebral hemodynamic surveillance. However, the small sample size, retrospective single-center design, incomplete TCD data and major potential for selection bias preclude any causal conclusion regarding the effect of prone positioning on ICP or neurological outcome. These findings should be considered a reassuring safety signal that warrants prospective validation rather than evidence of neurological safety.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare that they have no competing interests.

Statement of ethical approval

The requirement for individual informed consent was waived owing to the retrospective, observational design. The study was conducted in accordance with the Declaration of Helsinki.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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