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# Driving pressure is not predictive of ARDS outcome in chest trauma patients under mechanical ventilation

Matteo Arcelli

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Pour obtenir le titre de  
**DOCTEUR EN MEDECINE**

Présentée et soutenue publiquement  
Par  
**ARCELLI MATTEO**

LE 30/09/2021

TITRE :

Driving pressure is not predictive of ARDS outcome in chest trauma patients under  
mechanical ventilation

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JURY

**Président :** Monsieur le Professeur Xavier CAPDEVILA

**Assesseurs** (y compris directeur de thèse) :

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Madame le Docteur Audrey DE JONG

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# TABLE DES MATIÈRES

ABSTRACT.....	23
BACKGROUND.....	24
PATIENTS AND METHODS .....	25
Study Design and Setting .....	25
Inclusion criteria.....	25
Respiratory management of patients .....	26
Data collection.....	26
Study definition .....	27
Statistical Analysis .....	27
RESULTS .....	28
DISCUSSION .....	35
CONCLUSION .....	38
REFERENCES .....	40
APPENDICES .....	44
Annexe 1 .....	44
Annexe 2 .....	44
Annexe 3 .....	45
Annexe 4 .....	45
SERMENT D’HYPPOCRATE.....	46
RÉSUMÉ .....	47

# Driving pressure is not predictive of ARDS outcome in chest trauma patients under mechanical ventilation

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## ABSTRACT

**Background:** The relationship between the driving pressure of the respiratory system ( $\Delta P_{rs}$ ) under mechanical ventilation and worse outcome has never been studied specifically in chest trauma patients. The objective of the present study was to assess in cases of chest trauma the relationship between  $\Delta P_{rs}$  and severity of acute respiratory distress syndrome (ARDS) or death and length of stay.

**Methods:** A retrospective analysis of severe trauma patients (ISS >15) with chest injuries admitted to the Trauma Center from January 2010 to December 2018 was performed. Patients who received mechanical ventilation were included in our analysis. Mechanical ventilation parameters and  $\Delta P_{rs}$  were recorded during the stay in the intensive care unit. Association of  $\Delta P_{rs}$  and ARDS with mortality and outcomes was specifically studied at the onset of ARDS ( $\Delta P_{rs-ARDS}$ ) by receiver operator characteristic curve analysis, Kaplan-Meier curves and multivariate analysis.

**Results:** Among the 266 chest trauma patients studied, 194 (73%) developed ARDS.  $\Delta P_{rs}$  was significantly higher in the ARDS group versus in the no ARDS group ( $11.6 \pm 2.4$  cm H<sub>2</sub>O vs  $10.9 \pm 1.9$  cm H<sub>2</sub>O,  $p=0.04$ ). Among the patients with ARDS, no difference according to the duration of mechanical ventilation was found between the high  $\Delta P_{rs}$  group ( $\Delta P_{rs-ARDS} >14$  cm H<sub>2</sub>O) and the low  $\Delta P_{rs}$  group ( $\Delta P_{rs-ARDS} \leq 14$  cm H<sub>2</sub>O), ( $p=0.75$ ).  $\Delta P_{rs-ARDS}$  was not independently associated with the duration of mechanical ventilation (hazard ratio [HR], 1.006; 95% CI, 0.95–1.07;  $p=0.8$ ) or mortality (HR, 1.07; 95% CI, 0.9–1.28;  $p=0.45$ ).

**Conclusion:** A high  $\Delta P_{rs-ARDS}$  was not significantly associated with an increase in mechanical ventilation duration or mortality risk in ARDS patients with chest trauma in contrast with medical patients.

### Keywords:

Acute respiratory distress syndrome, Intensive care unit, Lung injury, Transpulmonary pressure, Ventilator-induced lung injury



## Background

Traumatic chest injuries are responsible for significant morbidity and are the cause of trauma-related death in 20%–25% of cases [1]. Following a trauma, patients affected by thoracic injuries are at risk of significant worsening of respiratory function, leading to mechanical ventilation need and acute respiratory distress syndrome (ARDS) in the most severe cases [2]. Causes of ARDS include direct injuries to the lungs and/or secondary mechanisms induced by the trauma setting (e.g. fat embolism, systemic inflammatory response and abdominal compartment syndrome). These physiopathological phenomena and the influence of harmful factors explain why many cases of ARDS occur more than 48 hours after admission [3]. In addition to these respiratory impairments related to trauma, lung injuries may also be aggravated by deleterious effects of mechanical ventilation, such as barotrauma or biotrauma [4, 5]. To prevent or minimize these expected complications, called ventilator-induced lung injury (VILI), current guidelines for lung-protective ventilation in patients with ARDS suggest the use of a low tidal volume ( $V_T$ ), higher levels of total positive end-expiratory pressure (PEEP) and limitation of the inspiratory plateau pressure of the respiratory system ( $P_{PLAT}$ ) under 30 cm H<sub>2</sub>O [6, 7]. Based on the same rationale, most experts strongly recommend this therapeutic approach in trauma patients [8]. However, this extrapolation of the medical setting is based on populations affected by ARDS from multiple origins. Post-traumatic ARDS represented only 8% to 13% of these cohorts [3]. Specific studies focusing on populations of trauma patients are lacking.

One of the major determinants of VILI is the driving pressure of the respiratory system ( $\Delta P_{rs}$ ), corresponding to the difference between  $P_{PLAT}$  and PEEP [9]. Many studies indeed demonstrated that  $\Delta P_{rs}$  in case of ARDS was associated with worst outcome [9,10].  $\Delta P_{rs}$  is a marker of alveolar collapse as well as lung strain and correlates well with lung stress [11].  $\Delta P_{rs}$

can be represented as the baby lung ventilation. Moreover, those findings remain to be confirmed in trauma patients.

The main goal of the present study was to assess in a population of severe trauma patients with chest injuries the relationship between  $\Delta P_{rs}$  observed at the onset of ARDS ( $\Delta P_{rs-ARDS}$ ) and outcomes.

## Methods

### Study design

The charts of severe trauma patients (Injury Severity Score [ISS] >15) admitted to Lapeyronie University Hospital (Level I Regional Trauma Center, Montpellier, France; Occitrauma network) over a 9-year period (January 2010 to December 2018) were reviewed retrospectively. We obtained approval from the local scientific and ethics committee of Montpellier University Hospital, Comité d'Organisation et de Gestion de l'Anesthésie Réanimation (COGAR), who stated that informed consent from the patient or next of kin was not required.

### Inclusion criteria

Consecutive trauma patients with chest trauma (Abbreviated Injury Scale [AIS]  $\geq 1$ ) who required invasive mechanical ventilation for a minimum of 48 hours were included in the present study [12]. Exclusion criteria were as follows: minors, immediate death, admission from another hospital, absence of initial computed tomography (CT) scan and incomplete medical records.

## **Respiratory management of patients**

All patients included in the study were ventilated in our unit using a lung-protective mechanical ventilation protocol as defined in the literature: low tidal volume between 6 and 8 ml/kg of ideal body weight, limited  $P_{PLAT}$  and PEEP [13]. Ventilatory parameters were set to avoid intrinsic PEEP. Thoracic drainage was performed if necessary, with surgical dissection by an anterior approach for pneumothoraces (14 Fr) and axillary approach for haemothoraces (24 or 28 Fr). In specific settings such as severe bronchopleural fistulae, unilateral lung injuries, or refractory hypoxemia, an alternative to conventional mechanical ventilation may be used; for example, separated lung ventilation in the prone position, high-frequency percussive ventilation, or veno-venous extracorporeal membrane oxygenation in extreme cases.

## **Data collection**

The following data were extracted from the medical records: age, sex, mechanism, characteristics of injuries, mortality, duration of mechanical ventilation, length of stay in the intensive care unit (ICU) and hospital length of stay. In addition, ISS and AIS scores were obtained for each body region as well as the Simplified Acute Physiology Score (SAPS) II. Prone position, pH, partial pressure of carbon dioxide in arterial blood ( $PaCO_2$ ),  $PaO_2/FiO_2$ , lactate, haemoglobin, base deficit, respiratory rate,  $V_T$ , PEEP,  $P_{PLAT}$ , respiratory system compliance ( $Crs$ ), elastance of respiratory system ( $Ers$ ),  $\Delta Prs$  and  $PaO_2/FiO_2$  were recorded. Mechanical power (MP) was also computed as the product of  $\Delta Prs$  in Newtons ( $cm\ H_2O \times 0.098$ ), tidal volume and respiratory rate. It was expressed as J/min and was included in the analysis [14]. For the non ARDS group respiratory parameters were collected the day of admission following initial stabilisation. For the ARDS group these parameters were collected on the onset day of ARDS.

In addition, specific data on chest trauma were collected based on the CT scan on admission (size of pulmonary contusions, pneumothoraces, haemothoraces, rib fractures, flail chest and atelectasis) allowing the Thoracic Trauma Severity (TTS) score on admission to be determined on a scale ranging from 0 to 25 points [15, 16].

## **Study definitions**

ARDS was defined using the Berlin criteria consensus definition [17]: (1) timing: onset within 1 week of a known clinical insult or new or worsening respiratory symptoms; (2) chest imaging: bilateral opacities, not fully explained by effusions, lobar/lung collapse or nodules; (3) origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload. The ARDS diagnoses were retrospectively reviewed by two physicians (SR and MA). Patients were thus categorized into two groups according to the occurrence (ARDS group) or the absence of ARDS (no ARDS group). Timing was also considered: early ARDS (onset in the first 48 h after admission) and late ARDS (onset 48 h after admission). In the subgroup of ARDS patients,  $\Delta Prs_{-ARDS}$  was the  $\Delta Prs$  value that was observed at the onset of ARDS. The duration of mechanical ventilation, length of stay in the ICU and hospital length of stay for the ARDS group were extracted from medical records.

## **Statistical analysis**

The study population was first divided into two groups according to the occurrence of ARDS (ARDS and no ARDS groups) and compared. Quantitative variables were expressed as the mean (standard deviation [SD]) or median (interquartile range, 25%–75%) and compared using the Student t test or Wilcoxon-Mann-Whitney test as appropriate. Qualitative variables were expressed as number (%) and compared using the chi-squared test or Fisher test as appropriate. A descriptive analysis of the ARDS group focused on respiratory parameters was thus

performed. Box plots was used to expose these data. In the case of missing data, the number of missing values is clearly stated for each variable. An a priori threshold for  $\Delta$ Prs was defined based on previous results in the field ( $>14$  cmH<sub>2</sub>O) [9, 18]. Similarly, the threshold for MP was defined a priori as  $\geq 12$  J/min [14].

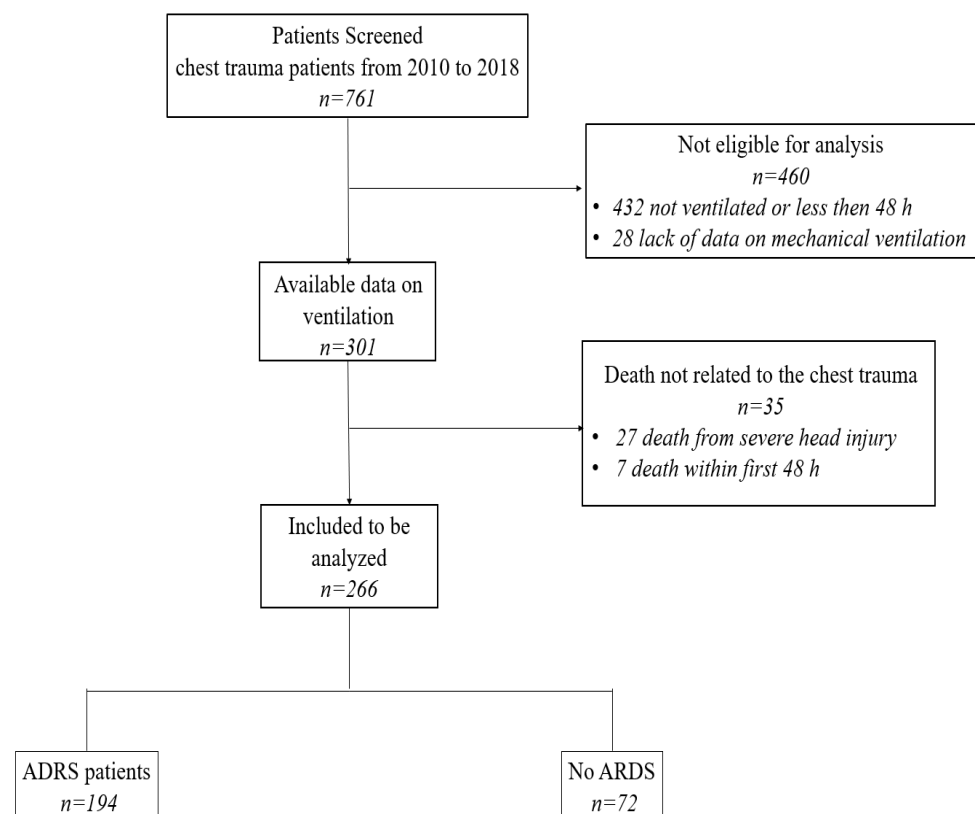
Thereafter, a specific analysis on predicting severity of ARDS using  $\Delta$ Prs and ROC curve analysis in the ARDS subgroup was performed. The area under the ROC curve (AUC) was expressed with the 95% confidence interval (CI). A survival analysis for weaning from mechanical ventilation was performed. Weaning from mechanical ventilation is censored by death before extubation. To draw Kaplan-Meier curves, the ARDS subgroup was divided according to the value of  $\Delta$ Prs or MP. The thresholds defined a priori for  $\Delta$ Prs and MP ( $>14$  cmH<sub>2</sub>O and  $\geq 12$  J/min respectively) were conserved in this part of the analysis. The log-rank test was used to compare these curves. False-positive and false-negative rates were determined.

Finally, the relationship between  $\Delta$ Prs or MP and different outcomes (duration of mechanical ventilation, occurrence of death, length of stay in the hospital and in the ICU) were assessed using a multivariate Cox regression analysis. In this analysis, the occurrence of ventilator-associated pneumonia was particularly considered as a confounding factor with the duration of mechanical ventilation. The statistical analysis was performed by CD and KB from the Clinical Research and Epidemiology Unit of Montpellier University Hospital using SAS statistical software (version 9.4; SAS Institute; Cary, NC). Statistical significance was set at a bilateral alpha risk  $<0.05$ .

## Results

Among the 1669 patients admitted with chest trauma to our trauma ICU during the study period, 761 (46%) met the inclusion criteria. Of these, 460 (60%) were not eligible for analysis due to duration of mechanical ventilation less than 48 h in 432 cases and a lack of data in 28 cases. Finally, 301 patients were included in the study. Of these, 35 patients (11%) were

excluded from our analysis due to early death (traumatic brain injury or early haemorrhagic shock). The 266 remaining patients were thus included in our analysis. The flowchart of the study is presented in **Fig. 1**. Among the study population, 204 patients were male (77%), the mean age was 43.0 ( $\pm$ 19.3) years, and the mean ISS was 32 ( $\pm$ 10). One-hundred and fifty patients (56%) were classified as AIS  $\geq$ 3 thoracic trauma, 84 (31%) were AIS  $\geq$ 3 abdominal trauma and 135 (51%) were AIS  $\geq$ 3 traumatic brain injury. The mean TTS score was 9.5 ( $\pm$ 4.9). The mortality rate was 6%; 15 patients died during the hospital stay. The mean PaO<sub>2</sub>/FiO<sub>2</sub> ratio on admission was 317 ( $\pm$ 173). A total of 194 patients (73%) experienced ARDS in the first week after admission; 52% early ARDS and 48% late ARDS (**Appendix. 1**). The mean duration of mechanical ventilation was 16.3 ( $\pm$ 13.9) days. The main demographic characteristics of the patients are presented in **Table 1**.



**Figure 1.** Flowchart of the study

**Table 1** Baseline characteristics

Variable		Total population N=266	ARDS		p
			No n=72	Yes n=194	
Sex, n (%)	Men	204 (76.69)	50 (69.44)	154 (79.38)	0.09
Age (years)		43.60 ( $\pm$ 19.28)	34.92 ( $\pm$ 16.56)	46.82 ( $\pm$ 19.27)	<0.01
BMI (kg/m <sup>2</sup> )		25.04 ( $\pm$ 4.60)	23.69 ( $\pm$ 4.88)	25.54 ( $\pm$ 4.40)	<0.01
SAPS II		39.87 ( $\pm$ 15.61)	35.40 ( $\pm$ 12.13)	41.53 ( $\pm$ 16.44)	0.01
ISS		31.70 ( $\pm$ 9.95)	31.36 ( $\pm$ 9.39)	31.83 ( $\pm$ 10.17)	0.81
TTS		9.49 ( $\pm$ 4.86)	5.73 ( $\pm$ 3.29)	10.88 ( $\pm$ 4.62)	<0.01
Thoracic trauma, n (%)					0.03
	Mild (AIS 1 or 2)	116 (43.61)	41 (56.94)	75 (38.66)	
	Moderate (AIS 3 or 4)	133 (50.00)	28 (38.89)	105 (54.12)	
	Severe (AIS 5 or 6)	17 (6.39)	3 (4.17)	14 (7.22)	
Pneumothoraces, n (%)					0.05
	No	129 (48.50)	34 (47.22)	95 (48.97)	
	Mild (AIS 1 or 2)	58 (21.80)	23 (31.94)	35 (18.04)	
	Moderate (AIS 3 or 4)	30 (11.28)	7 (9.72)	23 (11.86)	
	Severe (AIS 5 or 6)	49 (18.42)	8 (11.11)	41 (21.13)	
Hemothoraces, n (%)					0.09
	No	177 (66.54)	56 (77.78)	121 (62.37)	
	Mild (AIS 1 or 2)	28 (10.53)	5 (6.94)	23 (11.86)	
	Moderate (AIS 3 or 4)	36 (13.53)	8 (11.11)	28 (14.43)	
	Severe (AIS 5 or 6)	25 (9.40)	3 (4.17)	22 (11.34)	
Traumatic brain injury, n (%)					0.70
	No	106 (39.85)	28 (38.89)	78 (40.21)	
	Mild (AIS 1 or 2)	25 (9.40)	9 (12.50)	16 (8.25)	
	Moderate (AIS 3 or 4)	112 (42.11)	28 (38.89)	84 (43.30)	
	Severe (AIS 5 or 6)	23 (8.65)	7 (9.72)	16 (8.25)	
Abdominal trauma, n (%)					0.30
	No	130 (48.87)	31 (43.06)	99 (51.03)	
	Mild (AIS 1 or 2)	52 (19.55)	12 (16.67)	40 (20.62)	
	Moderate (AIS 3 or 4)	68 (25.56)	24 (33.33)	44 (22.68)	
	Severe (AIS 5 or 6)	16 (6.02)	5 (6.94)	11 (5.67)	
Hemoperitoneum, n (%)					0.08

	No	186 (69.92)	43 (59.72)	143 (73.71)	
	Mild (AIS 1 or 2)	37 (13.91)	16 (22.22)	21 (10.82)	
	Moderate (AIS 3 or 4)	24 (9.02)	8 (11.11)	16 (8.25)	
	Severe (AIS 5 or 6)	19 (7.14)	5 (6.94)	14 (7.22)	
pH at entry		7.34 ( $\pm$ 0.09)	7.37 ( $\pm$ 0.08)	7.34 ( $\pm$ 0.09)	0.01
Base deficit at entry		5.72 ( $\pm$ 3.59)	5.64 ( $\pm$ 3.89)	5.75 ( $\pm$ 3.48)	0.43
Lactates at entry		3.58 ( $\pm$ 2.59)	3.58 ( $\pm$ 2.40)	3.59 ( $\pm$ 2.66)	0.94
Haemoglobin at entry		11.54 ( $\pm$ 2.64)	11.33 ( $\pm$ 2.84)	11.62 ( $\pm$ 2.56)	0.47

Data are expressed as mean  $\pm$ SD, or as number of patients (percentage) as appropriate

BMI, body mass index; SAPS II, Simplified Acute Physiology Score 2; ISS, Injury Severity Score; TTS, Thoracic Trauma Severity score; AIS, Abbreviated Injury Score

$\Delta$ Prs was significantly higher in the ARDS group than in the no ARDS group; 11.8 ( $\pm$ 2.9) cm H<sub>2</sub>O vs 12 ( $\pm$ 2.03) cm H<sub>2</sub>O ( $p=0.04$ ). P<sub>PLAT</sub> and MP showed the same behaviour; 18 ( $\pm$ 3) cm H<sub>2</sub>O vs 16 ( $\pm$ 2) cm H<sub>2</sub>O, ( $p<0.001$ ) and 11.5 ( $\pm$ 3.6) J/min vs 9.6 ( $\pm$ 3.0) J/min ( $p<0.001$ ), respectively. The characteristics of the ventilatory parameters and outcomes of the patients are presented in **Table 2**.



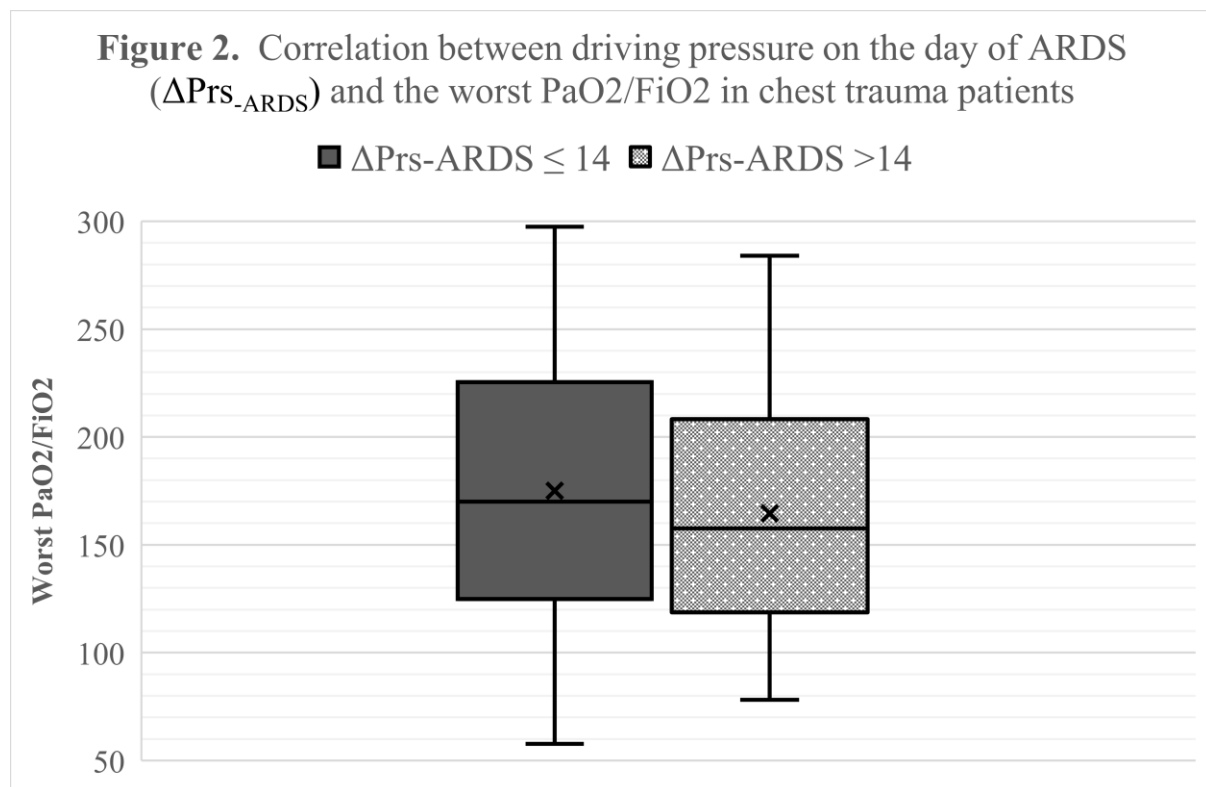
**Table 2** Respiratory characteristics and outcome

Variable		Total population N=266	ARDS		p
			No n=72	Yes n=194	
PAO <sub>2</sub> /FiO <sub>2</sub> at entry		317.03 (±173.30)	494.54 (±166.90)	251.14 (±121.95)	< 0.01
Worst PaO <sub>2</sub> /FiO <sub>2</sub>		232.49 (±120.65)	397.13 (±75.90)	171.39 (±63.26)	< 0.01
ARDS severity, n (%)					
	Mild	64 (24.06)		64 (32.99)	
	Moderate	100 (37.59)		100 (51.55)	
	Severe	30 (11.28)		30 (15.46)	
Early ARDS, n (%)					
	<48 h	101 (37.97)		101 (52.06)	
	≥48 h	93 (34.96)		93 (47.94)	
Day of occurrence of ARDS		2.22 (±2.41)		2.22 (±2.41)	
Driving pressure (ΔPrs; cm H <sub>2</sub> O)		11.58 (±2.70)	10.96 (±2.03)	11.81 (±2.89)	0.04
Driving pressure, n (%)					0.27
	<14 cm H <sub>2</sub> O	230 (86.47)	65 (90.28)	165 (85.05)	
	>14 cm H <sub>2</sub> O	36 (13.53)	7 (9.72)	29 (14.95)	
Mean Driving pressure over the first 5 days (cm H <sub>2</sub> O)		11.47 (±2.24)	10.93 (±1.84)	11.68 (±2.34)	0.02
Plateau pressure (P <sub>PLAT</sub> ; cm H <sub>2</sub> O)		17.26 (±3.09)	16.23 (±2.31)	17.64 (±3.26)	< 0.01
Static compliance (C <sub>rs</sub> ; cm H <sub>2</sub> O)		47.53 (±11.45)	47.69 (±8.42)	47.47 (±12.40)	0.53
Mechanical power (MP; cm H <sub>2</sub> O)		11.00 (±3.50)	9.60 (±2.98)	11.52 (±3.55)	< 0.01
VAP, n (%)					< 0.01
	No	110 (41.35)	47 (65.28)	63 (32.47)	
	Yes	156 (58.65)	25 (34.72)	131 (67.53)	
Death (, n (%))					0.08
	No	251 (94.36)	71 (98.61)	180 (92.78)	
	Yes	15 (5.64)	1 (1.39)	14 (7.22)	
Length Duration of mechanical ventilation (days)		16.32 (±13.89)	12.30 (±12.34)	17.81 (±14.16)	< 0.01
28 Free days free of ventilation		13.05 (±9.95)	16.78 (±9.36)	11.67 (±9.83)	< 0.01
Length of stay in ICU (days)		26.32 (±20.43)	20.72 (±18.02)	28.40 (±20.92)	< 0.01
Length of hospital stay (days)		36.22 (±28.57)	30.47 (±19.08)	38.37 (±31.15)	0.03

Data are expressed as mean±SD, or as number of patients (percentage) as appropriate. VAP, ventilator-acquired pneumonia

The results of the descriptive analysis are shown in **Fig. 2** for the subgroup analysis of the ARDS group. The AUC of the ROC curve for ΔPrs-ARDS in predicting the severity of ARDS was 0.59 (95% CI, 0.48–0.71; *p*=0.06) for moderate and severe ARDS (**Appendix. 2**), and 0.60 (95% CI, 0.58–0.61; *p*=0.04) for severe ARDS. A ΔPrs-ARDS value >14 cm H<sub>2</sub>O had a sensitivity of 20.8% (95% CI, 13.8%–27.7%), a specificity of 88.9% (95% CI, 81.1%–96.6%), a predictive positive value of 79.4 (95% CI, 65.8%–93%) and a negative predictive value of

35.2 (95% CI, 27.8%–42.6 %) for predicting severe ARDS.

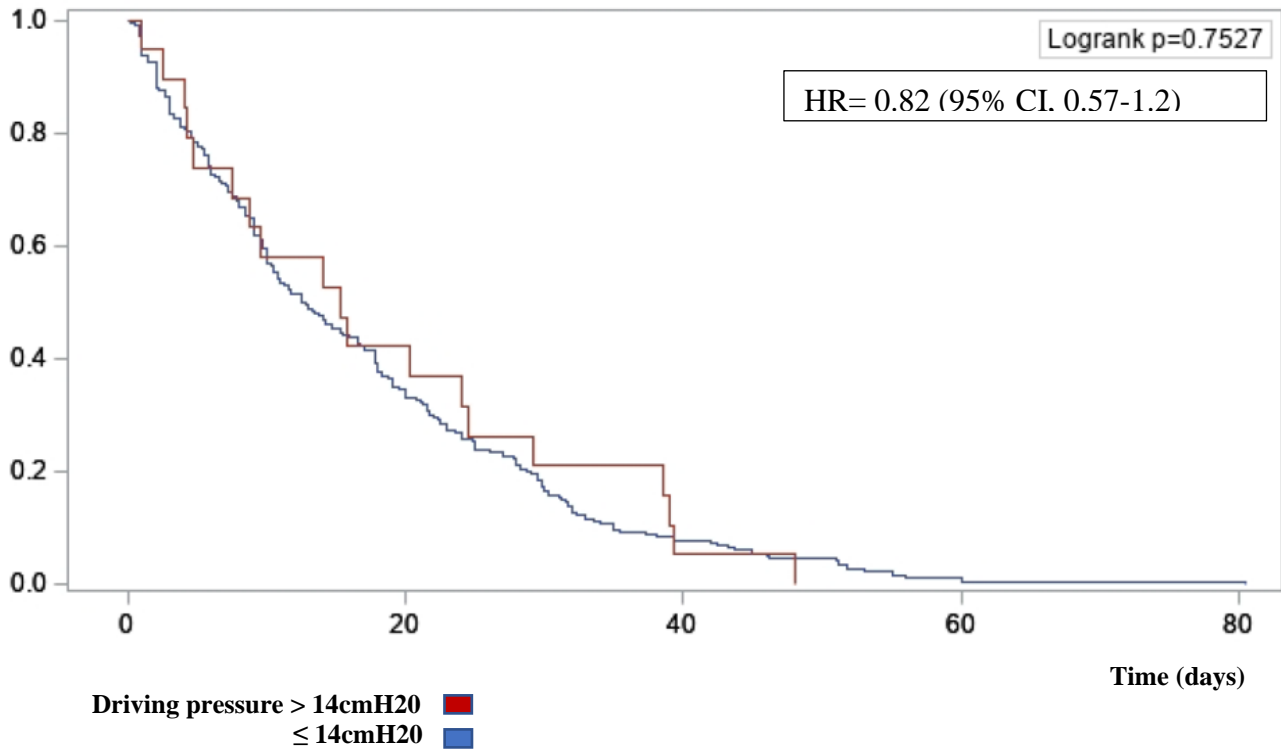


In the survival analysis using the a priori  $\Delta P_{rs-ARDS}$  threshold  $>14$  cm H<sub>2</sub>O, the duration of mechanical ventilation did not differ between the high and the low driving pressure groups HR= 0.82 (95% CI, 0.57-1.2),  $p=0.3$  **Fig. 3**. This was also observed for ICU length of stay ( $p=0,78$ ) and hospital length of stay ( $p=0.75$ ). Kaplan-Meier curves using MP are presented in (**Appendix. 3**). In the multivariate analysis,  $\Delta P_{rs-ARDS}$  was not found to be independently associated with the duration of mechanical ventilation (hazard ratio [HR], 1.01; 95% CI, 0.95–1.07;  $p=0.8$ ) or mortality (HR, 1.07; 95% CI, 0.9–1.28;  $p=0.45$ ) **Table 3**. When considering  $\Delta P_{rs-ARDS}$  in two groups ( $\leq 14$  cm H<sub>2</sub>O and  $>14$  cm H<sub>2</sub>O) no association was found for mortality or duration of mechanical ventilation **Table 3**. Similarly, no other respiratory parameters, such as  $P_{PLAT}$  (HR, 0.98; 95% CI, 0.93–1.02;  $p=0.33$ ), Crs (HR, 0.98; 95% CI 0.98–1.00;  $p=0.12$ ) and MP (HR, 0.98; 95% CI, 0.94–1.02;  $p=0.22$ ), were found to be independently associated with duration of mechanical ventilation or mortality (**Appendix. 4**).

**Table 3** Multivariate cox regression analysis results on duration of ventilation ( $\Delta P_{rs}$  as a continuous variable) and  $\Delta P_{rs-ARDS}$  according to the group (superior or inferior to 14 cm H<sub>2</sub>O) outcome

Variable	Modality	Hazard ratio	95% confidence interval	<i>p</i>
<b>Duration of ventilation</b>				
Age (years)	+1 year	0.99	0.99-1.00	<0.04
SAPS II	+1 point	0.97	0.96-0.99	<0.0001
ISS	+1 point	0.99	0.97-1.01	0.25
Chest injury				
Reference	AIS <2			
	$\geq 2$ AIS $\leq 4$	0.95	0.7-1.29	0.75
	AIS >4	0.51	0.26-0.97	0.04
Head injury				
Reference	No injury			
	AIS <2	0.91	0.56-1.48	0.7
	$\geq 2$ AIS $\leq 4$	0.84	0.6-1.18	0.31
	AIS >4	0.45	0.25-0.81	0.007
$\Delta P_{rs-ARDS}$	+1 cm H <sub>2</sub> O	1.01	0.95-1.08	0.84
<b>Group outcome<sup>a</sup></b>				
Mortality	$\Delta P_{rs-ARDS} > 14$ cm H <sub>2</sub> O	1.42	0.44-4.54	0.56
Ventilation duration	$\Delta P_{rs-ARDS} > 14$ cm H <sub>2</sub> O	0.9	0.61-1.33	0.59

<sup>a</sup>Cox model for mortality was adjusted on SAPS II and arterial pH. Cox model for ventilation duration was adjusted on age, SAPS II, ISS, AIS thorax, AIS skull, haemoperitoneum, driving pressure in trauma ICU and ventilator-associated pneumonia



**Figure 3.** Kaplan-Meier curves for time to weaning from mechanical ventilation according to driving pressure

## Discussion

This is the first study to assess the association of  $\Delta Prs$  with outcomes in a specific population of chest trauma patients. The main finding is that the  $\Delta Prs$  value at the onset of ARDS was not associated with the duration of mechanical ventilation, mortality risk or ICU length of stay either in survival analysis or multivariate analysis. Our analysis demonstrates therefore that  $\Delta Prs$  is an unreliable predictor of outcomes in this specific population.

Nowadays,  $\Delta Prs$ , usually called the driving pressure, is used universally in clinical practice to reflect lung strain and correlates well with the mechanical stress generated by  $V_T$  on the ventilated lung [11].  $\Delta Prs$  also means respiratory system compliance for a given  $V_T$ . Thus, a high  $\Delta Prs$  may indicate impairment of respiratory system compliance by a decrease in the

functional size of the lung. This phenomenon, called baby lung within context of ARDS, is related to alveolar collapse.

Many studies have demonstrated that  $\Delta P_{rs}$  is associated with mortality in patients with ARDS [9, 10, 18]. However, these previous studies focused on ARDS in medical settings. The morbid association between  $\Delta P_{rs}$  and mortality may nevertheless be altered in different clinical situations. Thus, De Jong et al [18] have reported that in obese patients with ARDS,  $\Delta P_{rs}$  was not associated with mortality. Similarly, our data suggest the absence of a relationship between  $\Delta P_{rs}$  and outcomes in the case of patients with ARDS related to trauma. One of the main pathophysiological explanations for this difference observed between the medical and trauma contexts could be significant modifications of chest wall compliance related to traumatic injuries. Traumatic parietal dehiscence increases chest wall compliance, which may lead to an increase in  $\Delta P_{rs}$  [19]. Thus,  $\Delta P_{rs}$  reflects both chest wall and lung compliance and it may be directly modified by strong variation in chest wall compliance in cases of severe chest trauma.  $\Delta P_{rs} = \Delta P_{cw} + \Delta P_l$ ,  $\Delta P_{cw}$  being the chest wall driving pressure and  $\Delta P_l$  being the transpulmonary driving pressure.,  $\Delta P_l$  would offer a better reflection of actual lung compliance and alveolar collapse [20]. Similarly, to obese patients, in chest trauma patients, much of the pressure provided by the ventilator will be used to distend the chest wall rather than the lung. Hence, there may not be an increase in transpulmonary pressure with accompanying lung overdistension. The only way to monitor the  $\Delta P_l$  of real interest from bench to bedside is to measure oesophageal pressure which is an estimation of pleural pressure and allows to determine  $\Delta P_{cw}$ . Thus, physicians may quickly differentiate a high  $\Delta P_{rs}$  due to an increase in  $\Delta P_{cw}$ , without a real lung injury, or inversely a high  $\Delta P_{rs}$  with a normal  $\Delta P_{cw}$ , a sign of lung pathology.

ARDS related to chest trauma represents a low percentage of case of ARDS and has its own specific properties. Its incidence is estimated to be between 10% and 30% of critically ill

trauma patients, mainly depending on the severity of the trauma in injured patients. Surprisingly, trauma-related ARDS is known to be twice less likely to lead to death than medical ARDS [21]. Our cohort presents similar results with a low mortality rate in the ARDS group (7%). Traumatic ARDS is characterized by a typical immunological profile different from ARDS in a medical setting. The early phase following trauma is thus characterized by an important and uncontrolled inflammatory response in the lung tissues. The importance of this inflammatory response depends on the intensity of the initial trauma but also on the genetic profile of the patient. A previous work by Xiao et al. [22] in a severe trauma population showed that the early leukocyte genomic response was simultaneously associated with increased expression of genes involved in the systemic inflammatory, innate immune, and compensatory anti-inflammatory responses, as well as in the suppression of genes involved in adaptive immunity. All these modifications induce a massive release of damage-associated molecular pattern molecules from injured tissues [23]. Massive release of epithelial biomarkers such as sRAGE, for example, is responsible for dysfunction of the capillary-alveolar barrier, increase in inflammation, and oxidative stress favouring fibrosis in cases of ARDS [24, 25]. These specific characteristics explain the specificities of ARDS after chest trauma, its lower lethality rate, and maybe the absence of association between  $\Delta$ Prs and outcomes in the trauma context.

The present study has some limitations. First, its design was monocentric with a retrospective analysis, which limits extrapolation of the results. However, the data were collected prospectively with the ICU software, and the management of patients with ARDS was standardized according to international recommendations. Only a few data are missing regarding the driving pressure (28 of 329; 8%) in trauma patients under mechanical ventilation. Second, no threshold analysis was performed according to the  $\Delta$ Prs. Patients who died from traumatic brain injury or from haemorrhagic shock in first 48 h after admission were excluded from our study. Consequently, only 15 non-survivors are present in our final analysis. This

may lead to a lack of power and threshold analysis is impossible. However, previous work also used a threshold of 14 cm H<sub>2</sub>O for  $\Delta$ Prs [9, 18]. Third, patients in our cohort were severely injured with a mean ISS of 32, and about 25% of the cohort also had abdominal injuries. Increase in abdominal pressure may also be involved in the change in chest wall compliance and create an analysis bias. It is therefore impossible to exclusively attribute our results only to chest injuries. However, multiple traumas are a frequent situation, which makes our study close to real life.

## Conclusion

The results of the present study demonstrate that driving pressure in a specific population of chest trauma patients was a poor predictor for ARDS severity and had no correlation with worse outcomes. Changes in chest compliance due to traumatic injuries could explain this unexpected observation. Therefore, our results suggest that the use of transpulmonary pressure would be relevant in chest trauma patients to directly monitor injured lungs and guide an optimal mechanical ventilation strategy. Further studies will be necessary to prove the positive impact of transpulmonary pressure on chest trauma management.

## Declarations

### **Ethics approval and consent to participate**

We obtained approval from the local scientific and ethics committee of Montpellier University Hospital, Comité d'Organisation et de Gestion de l'Anesthésie Réanimation (COGAR), who stated that informed consent from the patient or next of kin was not required.

## **Consent for publication**

Informed consent from the patient or next of kin was not required.

## **Availability of data and materials**

All data are extracted from medical record.

## **Competing interests**

The authors declare no competing interests.

## **Funding**

Support was provided solely from institutional and departmental resources.

## **Authors' contributions**

S.R., M.A, and K.B collected clinical data for this study; S.R., M.A, and K.B collected pharmaceutical and blood requirements. J.C, S.R, A. DJ, C.D prepared the draft of the study and conducted the statistical analysis. S.R. and M.A. wrote the article, which was revised by S.J, T.L, A.DJ and X.C.

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**Fig. 1** Flowchart of the study

**Fig. 2** Correlation between  $\Delta P_{rs-ARDS}$  and the worst  $PaO_2/FiO_2$  in ARDS patients.

**Fig. 3** Kaplan-Meier curves for time to weaning from mechanical ventilation according to driving pressure level

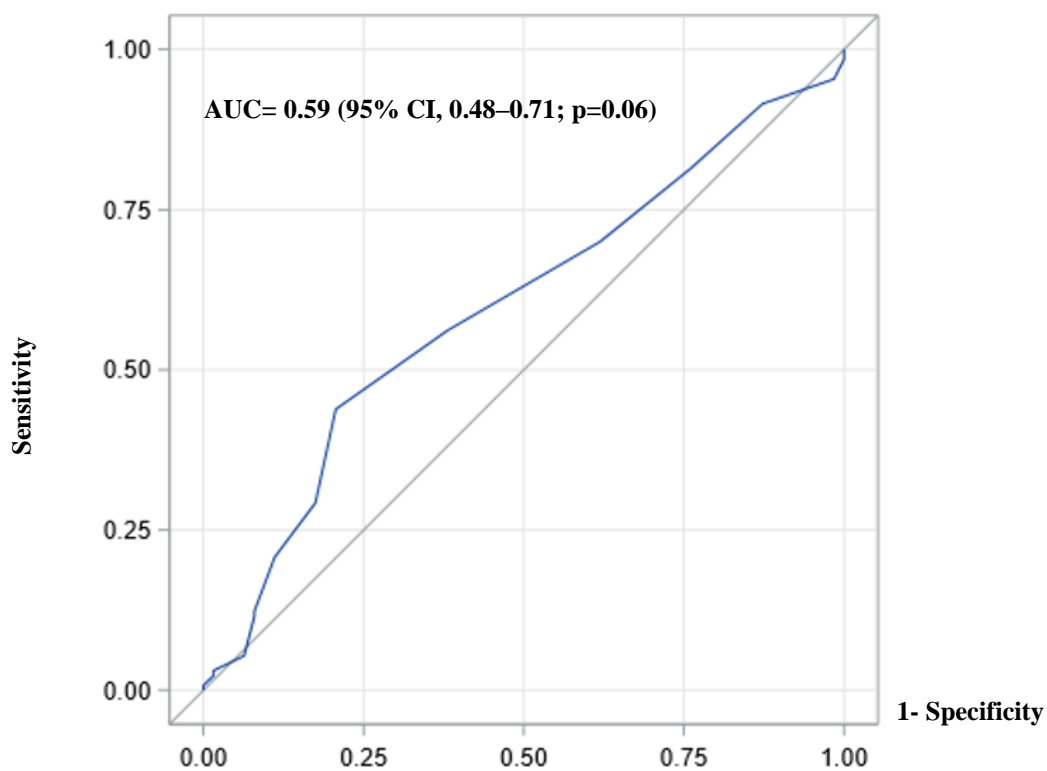
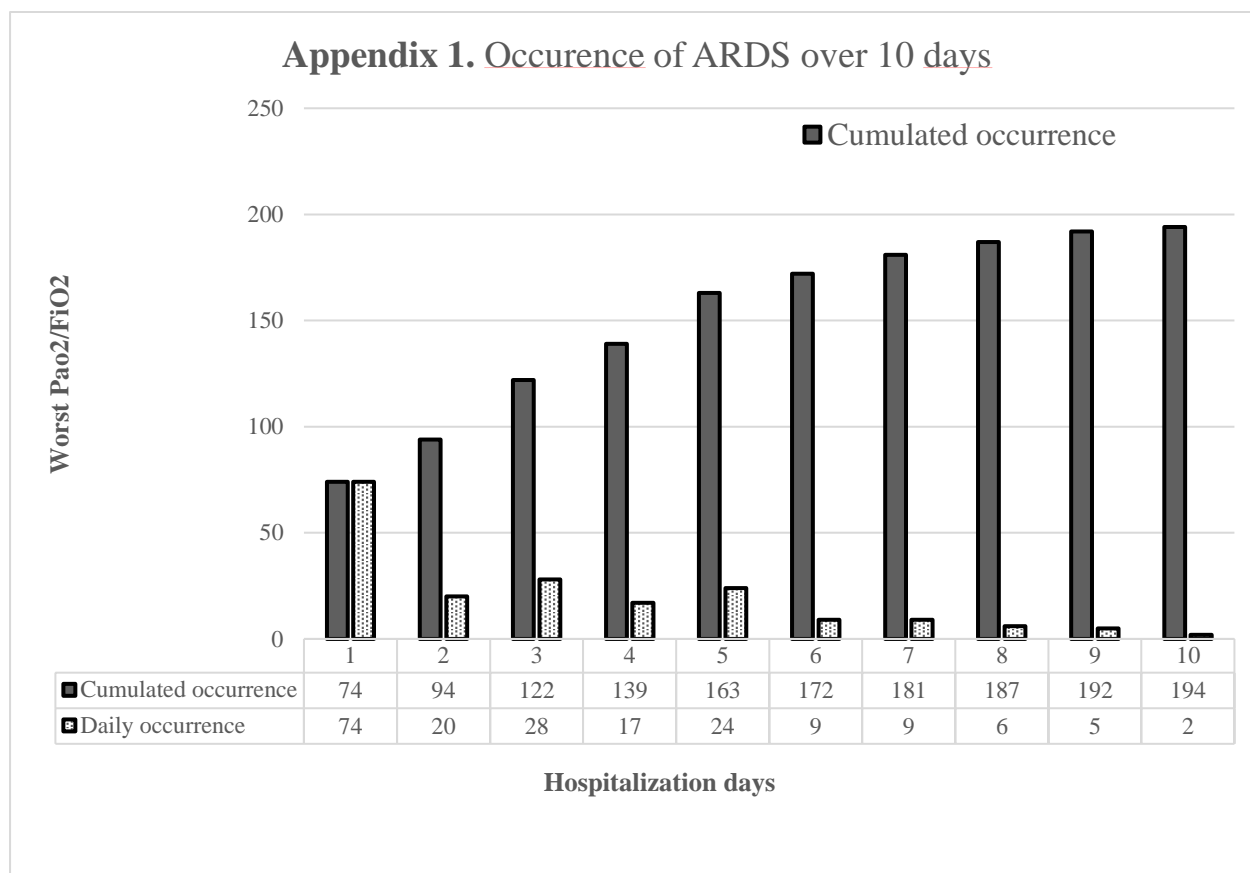
**Appendix. 1** Occurrence of ARDS over 10 days

**Appendix. 2** ROC curve for predicting moderate and severe ARDS using driving pressure.

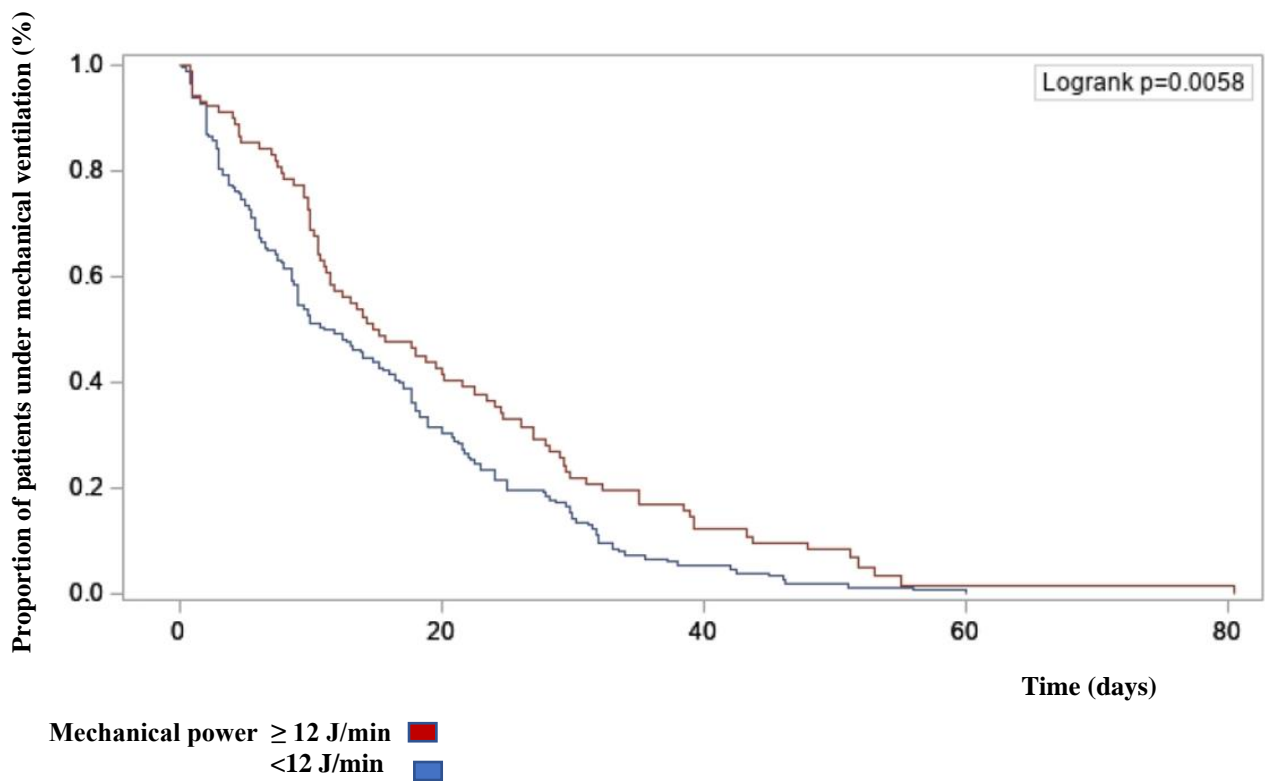
**Appendix. 3** Kaplan-Meier curves for time to weaning from mechanical ventilation according to mechanical power level

**Appendix. 4** Multivariate cox regression analysis results using plateau pressure or compliance or mechanical power as a predictive variable instead of driving pressure

## Annexes



**Appendix 2.** Roc curve for predicting moderate and severe ARDS using driving pressure



**Appendix 3.** Kaplan-Meier curves for time to weaning from mechanical ventilation according to mechanical power level

Variable <sup>a</sup>	Modality	Hazard ratio	95% confidence interval	<i>p</i>
Plateau pressure	+1 cm H <sub>2</sub> O	0.98	0.93-1.02	0.33
Plateau pressure	<25 cm H <sub>2</sub> O	0.84	0.36-1.92	0.67
Compliance	+1 ml/cm H <sub>2</sub> O	0.99	0.98-1.00	0.12
Compliance	>31 ml/cm H <sub>2</sub> O	1.16	0.67-2.01	0.6
Mechanical power	+1 J/min	0.98	0.94-1.02	0.22
Mechanical power	<12 J/min	0.92	0.68-1.23	0.57

Cox models for each variable were adjusted on age, SAPS II, ISS, AIS thorax, AIS skull, haemoperitoneum, driving pressure in trauma ICU and ventilator-associated pneumonia

**Appendix 4.** Multivariate cox regression analysis results using plateau pressure or compliance or mechanical power as a predictive variable instead of driving pressure

## SERMENT

- *En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Être suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.*
- *Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.*
- *Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*
- *Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*
- *Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.*

## Résumé

**Introduction :** La relation entre la pression motrice du système respiratoire ( $\Delta Prs$ ) sous ventilation mécanique et la survie n'a jamais été étudiée spécifiquement chez les patients ayant subi un traumatisme thoracique. L'objectif de cette étude était d'évaluer en cas de traumatisme thoracique la relation entre la  $\Delta Prs$  et la sévérité du syndrome de détresse respiratoire aiguë (SDRA) ainsi que le décès et la durée du séjour.

**Matériel et méthodes :** Une analyse rétrospective des patients traumatisés sévères (ISS >15) avec des traumatismes thoraciques admis au centre régional de traumatologie de janvier 2010 à décembre 2018 a été réalisée. Les patients ayant reçu une ventilation mécanique ont été inclus dans notre analyse. Les paramètres de ventilation mécanique et la  $\Delta Prs$  ont été enregistrés pendant le séjour en réanimation. L'association de la  $\Delta Prs$  et de la survie a été spécifiquement étudiée au début du SDRA ( $\Delta Prs$ -ARDS) par analyse de courbe ROC, courbes de Kaplan-Meier ainsi qu'une analyse multivariée.

**Résultats :** Parmi les 266 patients ayant subi un traumatisme thoracique, 194 (73 %) ont développé un SDRA. La  $\Delta Prs$  était significativement plus élevée dans le groupe SDRA par rapport au groupe sans SDRA ( $11,6 \pm 2,4$  cm H<sub>2</sub>O vs  $10,9 \pm 1,9$  cm H<sub>2</sub>O,  $p = 0,04$ ). Parmi les patients avec SDRA, aucune différence dans la durée de ventilation mécanique n'a été retrouvée entre le groupe  $\Delta Prs$ -ARDS >14 cm H<sub>2</sub>O et le groupe ( $\Delta Prs$ -ARDS  $\leq 14$  cm H<sub>2</sub>O) ( $p=0,75$  bas).  $\Delta Prs$ -ARDS n'était pas associé de manière indépendante à la durée de ventilation mécanique (rapport de risque [HR], 1,006 ; IC à 95 %, 0,95-1,07 ;  $p = 0,8$ ) ou à la mortalité (HR, 1,07 ; IC à 95 %, 0,9 à 1,28 ;  $p = 0,45$ ).

**Conclusion :** Une  $\Delta Prs$ -ARDS élevée n'était significativement pas associée à une augmentation de la durée de la ventilation mécanique ou du risque de mortalité chez les patients atteints de SDRA avec traumatisme thoracique, contrairement aux patients médicaux.

### Mots clés:

Syndrome de détresse respiratoire aiguë, Unité de soins intensifs, Lésion pulmonaire, Pression transpulmonaire, Lésion pulmonaire induite par la ventilation