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CLINICAL INVESTIGATION

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Association of Breathing Effort With Survival in Patients With Acute Respiratory Distress Syndrome

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OBJECTIVES: Invasive mechanical ventilation (IMV) is crucial for acute respiratory distress syndrome (ARDS) management, but mortality remains high. While spontaneous breathing is key to weaning, excessive respiratory effort may injure the lung and diaphragm. Most existing data on respiratory effort during IMV are based on brief periods of observation, potentially underestimating the burden of inappropriate efforts. This study aims to characterize the evolution of respiratory effort over time in ARDS patients and its relation to survival. We hypothesized that nonsurvivors would spend a greater proportion of time in the high-effort range during the active breathing phase compared with survivors.

DESIGN, SETTING, AND PATIENTS: In this prospective cohort study, we continuously recorded airway pressure, flow, esophageal, and gastric pressures in ARDS patients on mechanical ventilation during 7 days after the onset of spontaneous breathing. We analyzed physiologic respiratory effort variables, focusing on the proportion of time spent within defined effort ranges, and compared these data between ICU survivors and nonsurvivors. Statistical analysis was conducted using variance weighted methods to account for variability in the number of respiratory cycles analyzed per patient. This study is registered at ClinicalTrials.gov under identifier NCT06490523.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: A total of 1,485,405 respiratory cycles were analyzed from 26 ARDS patients (19 survivors, seven nonsurvivors). Nonsurvivors spent significantly more time in high effort (12% vs. 3%; $p = 0.006$). In contrast, survivors spent more time in the moderate-effort range (50% vs. 5%; $p < 0.001$). The time spend with high dynamic transpulmonary driving pressure (> 25 cm H_2O) was also significantly different between groups (32% survivors vs. 74% nonsurvivors; $p = 0.001$).

CONCLUSIONS: Patients who die of ARDS are more likely to be exposed to high respiratory effort for prolonged periods of time compared with survivors.

KEYWORDS: acute respiratory distress syndrome; esophageal pressure; mechanical ventilation; mortality; respiratory effort

The management of acute distress respiratory syndrome (ARDS) often includes invasive mechanical ventilation (IMV) as a life-sustaining therapy (1–3). Despite advancements in IMV management, mortality for ARDS patients requiring IMV remains high, ranging from 30% to 50% (1, 4–8). At the initial phase, mechanical ventilation is delivered without active respiratory muscle activity (passive mechanical ventilation) due to sedation and, sometimes, neuromuscular blockade (9). The initiation of spontaneous breathing is a critical step toward liberation from mechanical ventilation and offers

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KEY POINTS

Question: Does the proportion of time spent in high respiratory effort during the active breathing phase correlate with ICU survival in acute respiratory distress syndrome (ARDS) patients on invasive mechanical ventilation? This study analyzed continuous, high-density data collected over 7 days to characterize the evolution of respiratory effort and its association with patient outcomes.

Findings: In this prospective cohort study analyzing over 1.4 million respiratory cycles in 26 ARDS patients, nonsurvivors spent significantly more time in high respiratory effort (12% vs. 3%; p = 0.006) and had higher exposure to elevated dynamic transpulmonary driving pressures (> 25 cm H_2O) compared with survivors. Survivors exhibited more time in the moderate-effort range (50% vs. 5%; $p < 0.001$).

Meaning: In ARDS patients, prolonged exposure to high respiratory effort is associated with increased mortality, underscoring the critical role of optimizing respiratory effort to potentially improve clinical outcomes.

several advantages compared with passive mechanical ventilation (10–14). However, the patient's respiratory effort during IMV can also be associated with several mechanism of harm. Excessive respiratory effort has been hypothesized to cause patient self-inflicted lung injury (P-SILI) (10, 15–18) by significantly increasing the total pressure applied to the lungs. Excessive diaphragmatic contractions may lead to load-induced diaphragmatic injury (myotrauma) (19–21). Recent observational studies have linked these effects to longer durations of IMV, increased morbidity, and higher mortality (22, 23). Nevertheless, much of the existing data on respiratory effort during IMV has been gathered over short periods of time (24–26) (e.g., 5 min every day during 5 consecutive d). These short-term assessments may not accurately reflect the patient's respiratory effort over the entire course of mechanical ventilation. Consequently, there is a risk of underestimating the burden of sustained high respiratory effort and its potential harms.

To characterize in detail the evolution of respiratory effort over time, we conducted a prospective observational cohort study with continuous recordings of airway pressure (Paw), flow pressure, esophageal pressure (Pes), and gastric pressure (Pga) for up to 7 days after the onset of spontaneous breathing in ARDS patients on IMV. The aim of this study was to analyze the proportion of time spent within predefined respiratory effort ranges in relation to ICU survival. We hypothesized that nonsurvivors would spend more time in the high-effort during the active breathing phase compared with survivors.

MATERIALS AND METHODS

Design, Setting, and Study Population

This prospective physiologic cohort study (NCT06490523) was conducted in the medical ICU of Hospital del Mar, Barcelona, Spain. Over the course of 2 years (2020–2022), all patients 18 years old or older admitted to the ICU with acute respiratory distress syndrome (ARDS), as defined by the 2012 Berlin criteria (27), were screened for eligibility. Inclusion criteria required patients to be receiving IMV for ARDS, with a Pao_2/Fio_2 ratio less than or equal to 200 (moderate-to-severe ARDS) and a respiratory system compliance (Crs) less than or equal to 40 mL/cm H_2O at the time of intubation. Patients were excluded if they had chest drains, a contraindication to esophageal catheterization, or a concomitant acute exacerbation of obstructive airway disease. Ventilatory parameters and sedation were managed at the discretion of the treating team in accordance with unit protocols (**Online Data Supplement**, https://links.lww.com/CCM/H761, for further details).

Study Measurements and Signal Analysis

Following enrollment, a nasogastric catheter fitted with esophageal and gastric ballons (NutriVent; Sidam, Modena, Italy) was placed. Paw, flow, Pes, and Pga signals were recorded continuously for up to 7 days after the initiation of respiratory effort (or until extubation or death, if earlier) using a dedicated stand-alone signal acquisition system. Before signal acquisition, the correct inflation and placement of the balloons were always confirmed (28–31).

Clinical characteristics including age, sex, comorbidities, and severity of illness were collected at baseline. Ventilator settings, respiratory system

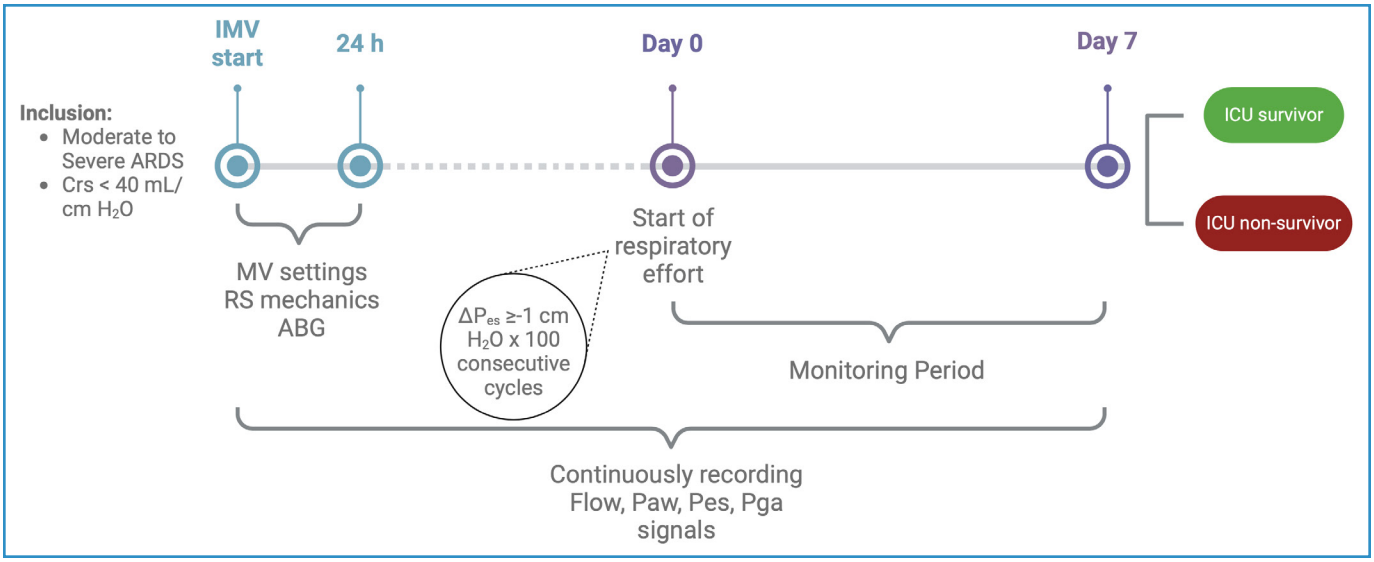

Figure 1. Study's flowchart. ABG = arterial blood gas, ARDS = acute respiratory distress syndrome, Crs = compliance of the respiratory system, IMV = invasive mechanical ventilation, MV = mechanical ventilation, Paw = airway pressure, Pes = esophageal pressure, Pga = gastric pressure, RS = respiratory system, ΔPes = esophageal pressure swing.

mechanics, and arterial blood gas analyses were recorded on the first day under IMV in passive conditions. Other characteristics were collected such as the use of prone position, extracorporeal life support, tracheostomy, duration of IMV, and ICU and hospital length of stay.

Analysis of Effort

Details on the signal acquisition and accuracy are provided in the Online Data Supplement (https://links.lww.com/CCM/H761). Continuous monitoring of patients commenced upon their connection to MV. The onset of the patient's respiratory effort was identified by the presence of inspiratory negative swings in the Pes signal (ΔPes ≤ −1 cm H_2O) over 100 consecutive respiratory cycles, irrespective of the applied ventilatory mode. Continuous recordings of Paw, flow, Pes, and Pga were captured for 7 days after that point or until extubation or death, whichever occurred first. Transdiaphragmatic pressure (Pdi) was computed by real-time digital subtraction of Pes from Pga. Muscular pressure (Pmus) was computed for each breath as the difference between the static recoil pressure of the chest wall and the swing in Pes under active conditions. The esophageal pressure–time product (PTPes) was derived as the time-based integral of Pmus (32–35). Signal samples were recorded at a frequency of 100 Hz. Recordings were analyzed offline using a dedicated software (Program for Advanced Analysis of Respiratory Mechanics intellectual property protected, Barcelona, Spain). **Figure 1** illustrates the study protocol.

Statistical Analysis

The primary objective of the study was to analyze the proportion of time spent in high respiratory effort for Pmus, PTPes, ΔPes, and tidal change in Pdi (ΔPdi) during the first 7 days following the initiation of spontaneous breathing, stratified by ICU survival status. The predefined high-effort range for each physiologic respiratory effort variable was: Pmus greater than 15 cm H_2O, ΔPes less than −10 cm H_2O, PTPes greater than 150 cm H_2O/s/min, ΔPdi greater than 12 cm H_2O, based on previous literature (36–39). Effort outside the high-effort range was categorized as moderate if it remained within predefined ranges: Pmus 5–15 cm H_2O, ΔPes −5 to −10 cm H_2O, PTPes 50–150 cm H_2O/s/min, and ΔPdi 3–12 cm H_2O. Effort was further categorized as low if it fell below the lower limit, or absent/very low effort if the patient returned to a passive state or merely triggered the breath without any substantial effort.

The secondary objective was to analyze the median values of Pmus, PTPes, ΔPes, and ΔPdi over the observation period according to survival status.

Patients were classified as survivors or nonsurvivors based on vital status at ICU discharge. Categorical variables were expressed as frequencies and percentages, while continuous variables were described in terms of median and interquartile range (IQR, 25–75th percentile). Differences between groups were analyzed using Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous data. Associations between variables were analyzed using a mixed-effects model. Additionally, a post hoc sensitivity analysis was performed excluding patients with mild ARDS at 24 hours to assess the potential impact of baseline oxygenation differences. This analysis is presented in the Online Data Supplement (https://links.lww.com/CCM/H761).

As the number of cycles analyzed for each patient varied (**Fig. E1**, https://links.lww.com/CCM/H761), the analysis of all variables during the monitoring phase was weighted according to each patient's representation within the total sample as follows: number of patient's respiratory cycles with effort analyzed divided by the total number of all patients' respiratory cycles with effort analyzed. All statistical tests were considered significant at a p value of less than or equal to 0.05.

Statistical analyses were performed using the "Stats" package of the "SciPy" module in Python 3.11 (Python Software Foundation, Wilmington, DE) with PyCharm 2023.2.1 (JetBrains s.r.o., Prague, Czech Republic), R Version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria), and the Statistical Package for the Social Sciences, version 18 (SPSS, IBM Corp., Chicago, IL).

The study is reported in conformance with the Strengthening the Reporting of Observational studies in Epidemiology recommendations (40).

Ethical Considerations

Informed consent was obtained from substitute decision-makers before enrollment. The Institutional Review Board (IRB) at Parc de Salut Mar/Hospital del Mar approved the study protocol "Advanced Monitoring of Respiratory Effort during Mechanical Ventilation in Acute Respiratory Distress Syndrome" in September 7, 2020 (IRB code: 2021/9742), and the study was conducted in accordance with the amended Declaration of Helsinki in its latest version.

RESULTS

Study Population

Between December 2020 and November 2022, 142 patients were screened for eligibility, of whom 31 were enrolled in the study (**Fig. E2**, https://links.lww.com/CCM/H761). Five patients were excluded from the analysis because of poor-quality of recordings, leaving 26 patients for the final analysis, comprising 19 ICU survivors and seven ICU nonsurvivors. A total of 1,485,405 respiratory cycles following the initiation of respiratory effort were analyzed. The number of cycles analyzed per patient did not differ significantly between groups (mean of 54,069 cycles per patient in ICU survivors vs. 65,442 cycles per patient in ICU nonsurvivors; $p = 0.651$).

The clinical characteristics of study groups at baseline are presented in **Table 1**. Although no significant differences were observed in demographics, comorbidities, or severity at admission between the two groups, nonsurvivors tended to exhibit more severely impaired lung mechanics and oxygenation (Table 1).

Assisted Spontaneous Ventilation Period

Throughout the entire duration of mechanical ventilation, survivors and nonsurvivors began to resume spontaneous breathing after a median of 9 days (IQR, 4–21 d) for survivors vs. 11 days (IQR, 1–24 d) for nonsurvivors ($p = 0.975$). Both groups spend most of their total ventilation time in spontaneous breathing, with survivors and nonsurvivors spending a median of 75% and 89%, respectively, of the total duration compared with passive ventilation ($p = 0.821$) (**Fig. E3**, https://links.lww.com/CCM/H761). **Table 2** presents the respiratory characteristics at the time of spontaneous breathing resumption (day 0). No differences were observed in mechanical ventilation parameters, respiratory mechanics, or gas exchange. However, F_{IO_2} was set higher for nonsurvivors compared with survivors (median [IQR], 0.50 [0.40–0.50] vs. 0.40 [0.35–0.40]; $p = 0.041$).

Respiratory Variables During Assisted Breathing (Weighted Analysis)

Respiratory variables during the active breathing phase for survivors and nonsurvivors are presented in **Table 3**. Nonsurvivors exhibited a higher respiratory rate (median [IQR], 29 breaths/min [26–31 breaths/min] vs. 25 breaths/min [24–26 breaths/min]; $p = 0.000$) and a shorter

TABLE 1.
Demographics, Baseline Characteristics, and Respiratory Characteristics 24 Hours After Invasive Mechanical Ventilation Initiation

Analyzed Variables	ICU Survivors (*n* = 19)	ICU Nonsurvivors (*n* = 7)	*p*
Demographics			
Gender (female)	7 (37)	2 (29)	0.694
Age (yr)	58 (49–65)	64 (57–68)	0.169
Height (cm)	165 (160–171)	163 (162–168)	0.910
Weight (kg)	82 (70–92)	93 (79–110)	0.209
Body mass index (kg/m^2)	29 (27–32)	35 (29–44)	0.209
Comorbidities			
Steroid use or immunosuppression	9 (47)	5 (71)	0.275
Chronic kidney disease	1 (5)	1 (14)	0.444
Chronic heart disease	1 (5)	2 (29)	0.099
Chronic lung disease	7 (37)	2 (29)	0.694
Severity at admission			
Acute Physiology and Chronic Health Evaluation II score	16 (13–20)	17 (15–19)	0.427
Ventilator parameters			
Tidal volume for predicted body weight (mL/kg)	6.0 (5.3–6.7)	6.2 (5.0–7.5)	0.611
Respiratory rate (breaths/min)	28 (26–30)	28 (25–30)	0.651
Minute ventilation (min/L)	9.9 (9.0–10.6)	9.6 (9.5–11.5)	0.427
Plateau pressure (cm H_2O)	29 (26–30)	32 (30–32)	**0.041**
Positive end-expiratory pressure (cm H_2O)	18 (13–18)	16 (14–18)	0.534
F_{IO_2} (L)	0.70 (0.50–0.80)	0.60 (0.60–1.00)	0.572
Lung mechanics			
Driving pressure (cm H_2O)	11 (10–14)	14 (11–18)	0.135
Respiratory system compliance (mL/cm H_2O)	33 (27–41)	27 (19–34)	0.094
Transpulmonary end-expiratory pressure (cm H_2O)	2.5 (–0.2 to 5.7)	2.9 (–0.4 to 5.8)	0.775
Ventilatory ratio	2.0 (1.7–2.4)	2.0 (1.4–2.1)	0.306
Arterial blood gas			
pH (mm Hg)	7.32 (7.29–7.39)	7.32 (7.22–7.38)	0.692
Pa_{O_2} (mm Hg)	91 (73–117)	90 (75–160)	0.778
Pa_{CO_2} (mm Hg)	48 (40–58)	42 (36–46)	0.083
Bicarbonate (mEq/L)	25 (21–28)	22 (21–23)	0.094
Pa_{O_2}/F_{IO_2} ratio	156 (91–222)	124 (83–162)	0.254
Acute respiratory distress syndrome severity			0.302
Mild	5 (26)	0 (0)	
Moderate	9 (48)	4 (57)	
Severe	5 (26)	3 (43)	

All data are expressed as *n* (%) or median (interquartile range). Boldface value indicates statistically significant differences.

TABLE 2.
Respiratory Variables at the Onset of Spontaneous Breathing (Day 0)

Analyzed Variables	ICU Survivors ($n = 19$)	ICU Nonsurvivors ($n = 7$)	p
Ventilator variables			
Tidal volume for predicted body weight (cm H_2O)	7.0 (5.5–7.6)	6.6 (5.6–7.4)	0.710
Respiratory rate (breaths/min)	25 (23–30)	27 (24–31)	0.380
Pressure support (cm H_2O)	14 (10–18)	16 (14–20)	0.452
Positive end-expiratory pressure (cm H_2O)	12 (9–16)	12 (10–15)	0.866
Lung mechanics			
Dynamic transpulmonary driving pressure (cm H_2O)	15 (11–19)	20 (15–23)	0.094
End-expiratory transpulmonary pressure (cm H_2O)	3.5 (1.5–4.1)	4.2 (0.5–6.4)	0.742
Dynamic lung compliance (mL/cm H_2O)	24.6 (14.6–29.3)	18.4 (18.4–22.0)	0.134
Dynamic airway resistance (cm H_2O/s/L)	12.7 (8.2–14.5)	12.7 (10.4–18.0)	0.988
Gas exchange			
F_{IO_2}	0.40 (0.35–0.40)	0.50 (0.40–0.50)	**0.041**
Pa_{O_2}/F_{IO_2} (cm H_2O)	202 (174–237)	173 (164–203)	0.152
Pa_{CO_2} (cm H_2O)	46 (38–52)	50 (44–58)	0.497

All data are expressed as median (interquartile range). Boldface value indicates statistically significant differences.

respiratory cycle duration (median [IQR], 2.1 s [1.9–2.4 s] vs. 2.4 s [2.3–2.5 s]; $p = 0.003$). Additionally, they had higher dynamic transpulmonary driving pressure (ΔPLdyn; median [IQR], 21 cm H_2O [14–35 cm H_2O] vs. 19 cm H_2O [13–22 cm H_2O]; $p = 0.027$) and higher end-expiratory transpulmonary pressure (median [IQR], 2 cm H_2O [–0.2 to 4.4 cm H_2O] vs. –0.6 cm H_2O [–1.2 to 2.0 cm H_2O]; $p = 0.001$). While nonsurvivors had a higher median pressure support requirement (median [IQR], 14 cm H_2O [6–14 cm H_2O] vs. 9 cm H_2O [8–13 cm H_2O]), this difference was not statistically significant ($p = 0.401$). Similarly, no significative differences were observed in specific dynamic pulmonary compliance (median [IQR], 25 cm H_2O/s/min [16–29 cm H_2O/s/min] for survivors vs. 18 cm H_2O/s/min [18–24 cm H_2O/s/min] for nonsurvivors; $p = 0.119$) or airway resistance (median [IQR], 8.5 mL/cm H_2O [6.6–12.2 mL/cm H_2O] for survivors vs. 10 mL/cm H_2O [0.8–12.7 mL/cm H_2O] for nonsurvivors; $p = 0.126$) between groups. The nonweighted analysis is included in **Table E1** (https://links.lww.com/CCM/H761).

Muscular, Esophageal, and Transdiaphragmatic Pressures Time Ranges

No significant differences were found in the median values of respiratory effort variables between the two groups during the monitoring period (Table 3).

Figure 2 focuses on the first 7 days after the resumption of spontaneous breathing and shows the distribution of various effort ranges for Pmus and ΔPes in survivors and nonsurvivors. ΔPdi and PTPes are presented in **Figure E15** (https://links.lww.com/CCM/H761). Nonsurvivors consistently spent a greater proportion of time in high-effort range across all variables compared with survivors (median daily proportion of time in the high-effort range of Pmus, 12% vs. 3%; $p = 0.006$). In contrast, survivors spent significantly more time within the moderate-effort range for all four analyzed respiratory effort variables (median daily proportion of time in the moderate-effort range of Pmus, 50% vs. 5%; $p < 0.001$). Except for day 6, survivors also spent more time with absent or very low effort (median daily proportion of time in the absent/very low effort range of Pmus, 46% vs. 30%; $p = 0.742$). The average distribution of the 7-day period and the nonweighted analyses are available in **Figures E4** and **E16** (https://links.lww.com/CCM/H761), respectively.

Dynamic Transpulmonary Driving Pressure Over Time

The daily distribution of the ΔPLdyn for survivors and nonsurvivors is shown in **Figure 3**. The median daily proportion of time in the high range of ΔPLdyn (> 25 cm

TABLE 3.
Respiratory Variables From the Onset of Spontaneous Breathing (Weighted Analysis)

Analyzed Variables	ICU Survivors ($n = 19$)	ICU Nonsurvivors ($n = 7$)	p
Time from orotracheal intubation to spontaneous breathing detection (d)	9 (4–21)	11 (1–24)	0.975
Ventilator variables			
Tidal volume for predicted body weight (cm H_2O)	7.0 (5.5–7.2)	7.2 (5.2–8.0)	0.921
Respiratory rate (breaths/min)	25 (24–26)	29 (26–31)	**0.000**
Pressure support (cm H_2O)	9 (8–13)	14 (6–14)	0.401
Positive end-expiratory pressure (cm H_2O)	7 (6–13)	10 (5–17)	0.855
Spontaneous respiratory cycle			
Total cycle duration (s)	2.4 (2.3–2.5)	2.1 (1.9–2.4)	**0.003**
Mechanical inspiration duration (s)	0.8 (0.7–0.9)	0.8 (0.6–0.8)	**0.010**
Patient's inspiration duration (s)	0.8 (0.6–1.0)	0.9 (0.6–1.1)	0.929
Lung mechanics			
Dynamic transpulmonary driving pressure (cm H_2O)	19 (13–22)	21 (14–35)	**0.027**
End-expiratory transpulmonary pressure (cm H_2O)	−0.6 (−1.2 to 2.0)	2.0 (−0.2 to 4.4)	**0.001**
Dynamic lung compliance (mL/cm H_2O)	25 (16–29)	18 (18–24)	0.119
Dynamic airway resistance (cm H_2O/s/L)	8.5 (6.6–12.2)	10.0 (0.8–12.7)	0.126
Respiratory effort			
ΔPes (cm H_2O)	8 (4–9)	7 (5–29)	0.262
Respiratory muscle pressure (cm H_2O)	11 (7–12)	10 (8–33)	0.337
Tidal change in transdiaphragmatic pressure (cm H_2O)	9 (3–9)	7 (3–29)	0.146
PTPes per min (cm H_2O/s/min)	126 (50–176)	42 (34–306)	0.798
PTPes per cycle (cm H_2O/s)	5.1 (2.3–7.9)	1.5 (0.9–11.9)	0.814
Inspiratory volume/ΔPes (mL/cm H_2O)	56 (42–93)	67 (22–69)	0.146

PTPes = esophageal pressure–time product, ΔPes = tidal change in esophageal pressure.
All data are expressed as median (interquartile range). Boldface values indicate statistically significant differences.

H_2O), was 32% for survivors vs. 74% for nonsurvivors, $p = 0.001$. Higher ΔPLdyn was correlated with higher Pmus ($p < 0.0001$) and Pmus accounted for 87% of the within-subjects variance in ΔPLdyn (conditional $R^2 = 0.872$) (**Fig. E5**, https://links.lww.com/CCM/H761). The nonweighted analyses are included in **Figure E6** (https://links.lww.com/CCM/H761).

Clinical Management and Outcomes

Differences in clinical management and outcome variables between survivors and nonsurvivors are summarized in **Table E2** (https://links.lww.com/CCM/H761). Prone position was more frequently used in nonsurvivors. Only one patient in the survivor group required extracorporeal oxygenation support (14%; $p = 0.093$), while two patients (11%) in the survivor group and one (14%) in the nonsurvivor group required extracorporeal CO_2 removal. Tracheostomy was performed in 11 (58%) survivors and 5 (71%) nonsurvivors ($p = 0.529$) (Table E2, https://links.lww.com/CCM/H761).

Survivors had a median hospital stay of 62 days (IQR, 32–88 d; $p = 0.107$) (Table E2, https://links.lww.com/CCM/H761). All ICU survivors were discharged from the hospital. An extended statistical analysis is available in the Online Data Supplement (https://links.lww.com/CCM/H761).

DISCUSSION

The main findings of this study are: 1) Median values of effort variables remained within normal ranges and did not differ significantly between groups; 2) However, nonsurvivors spent a significantly greater proportion of time within the high-effort range (including Pmus, PTPes, ΔPes, and ΔPdi) during the first 7 days of spontaneous breathing compared with survivors; and 3) The median daily proportion of time with a high dynamic transpulmonary pressure (ΔPLdyn > 25 cm H_2O) was also significantly higher in nonsurvivors.

This study suggests that prolonged exposure to high respiratory effort may be associated with ICU mortality in ARDS patients. However, given the observational nature of the study, these findings should be interpreted with caution. While this study does not establish a causal relationship, our findings emphasize the potential relevance of continuously monitoring respiratory effort in the clinical setting.

Despite the prolonged period before resuming spontaneous breathing (median [IQR], 9 d [4–21 d] for survivors vs. 11 d [1–24 d] for nonsurvivors; p = 0.975), both survivors and nonsurvivors were substantially exposed to spontaneous breathing during most of their time on mechanical ventilation. Survivors spend a median of 75%, and nonsurvivors 89%, of the total mechanical ventilation period in spontaneous breathing. Furthermore, in terms of ventilation settings, respiratory mechanics, and gas exchange, both groups were comparable at onset of spontaneous breathing.

A possible explanation for this association is the concept of P-SILI, a hypothesis that has been discussed in both experimental and clinical literature (18, 41, 42). However, the role of prolonged high respiratory effort in this context remains to be fully elucidated. According to this hypothesis, patients may exacerbate lung damage through various mechanisms, including increased respiratory effort. Prolonged exposure to high respiratory effort may increase transpulmonary pressure and lung stress, potentially contributing to lung injury over time. However, the exact clinical impact of sustained high effort remains uncertain.

While we observed a slightly higher median dynamic transpulmonary pressure in nonsurvivors, the clinical relevance of this 2 cm H_2O difference is likely limited. However, nonsurvivors spent a significantly greater proportion of time with a high dynamic transpulmonary pressure (ΔPLdyn > 25 cm H_2O) compared with survivors. Additionally, the mixed-effects model demonstrated a very strong correlation between ΔPLdyn and Pmus, indicating that respiratory muscles activity is a major contributor to elevated ΔPLdyn.

It is particularly notable, that nonsurvivors spend significantly more time in high effort than survivors, despite having normal median values of effort variables. This difference is evident from day 1 of monitoring (i.e., first day of transition to spontaneous breathing) and is sustained throughout the 7-day period. Respiratory effort may be greater in nonsurvivors because they may also have elevated lung elastance/impaired lung mechanics or more severe organ failure/s, leading to a more pronounced increase in respiratory effort in response to elevated oxygen demands during situations such as hygiene activities, pain, or anxiety. This heightened effort might be necessary to achieve adequate inspiratory tidal volume but could also contribute to lung injury. Alternately, these patients may have derangements in the control of breathing resulting in poorly controlled respiratory drive (43). This lack of control could lead to erratic respiratory effort, akin to a car speeding uncontrollably down a road. In this scenario, patients may oscillate between periods of respiratory distress (high effort), which prompts an intervention such as increased sedation, leading to a subsequent state of minimal or absent effort. Consequently, this results in normal median values of respiratory effort variables, yet an abnormal distribution of effort over time. Therefore, even if a patient has an average respiratory effort within the normal range, they may still spend extended periods exerting high or very low efforts.

An important consideration in interpreting our findings is the severity of illness at inclusion. Unlike studies classifying ARDS solely by oxygenation, our selection criteria also required low C_{RS} (≤ 40 mL/cm H_2O), a known marker of greater disease severity and worse outcomes (44, 45). This likely contributed to the prolonged mechanical ventilation and hospital stay in our cohort, independent of respiratory effort alone. Furthermore, while the initial trigger of ARDS may resolve, some patients remain with profoundly impaired lung mechanics, which can significantly impact their ability to sustain spontaneous breathing and successfully wean from mechanical ventilation.

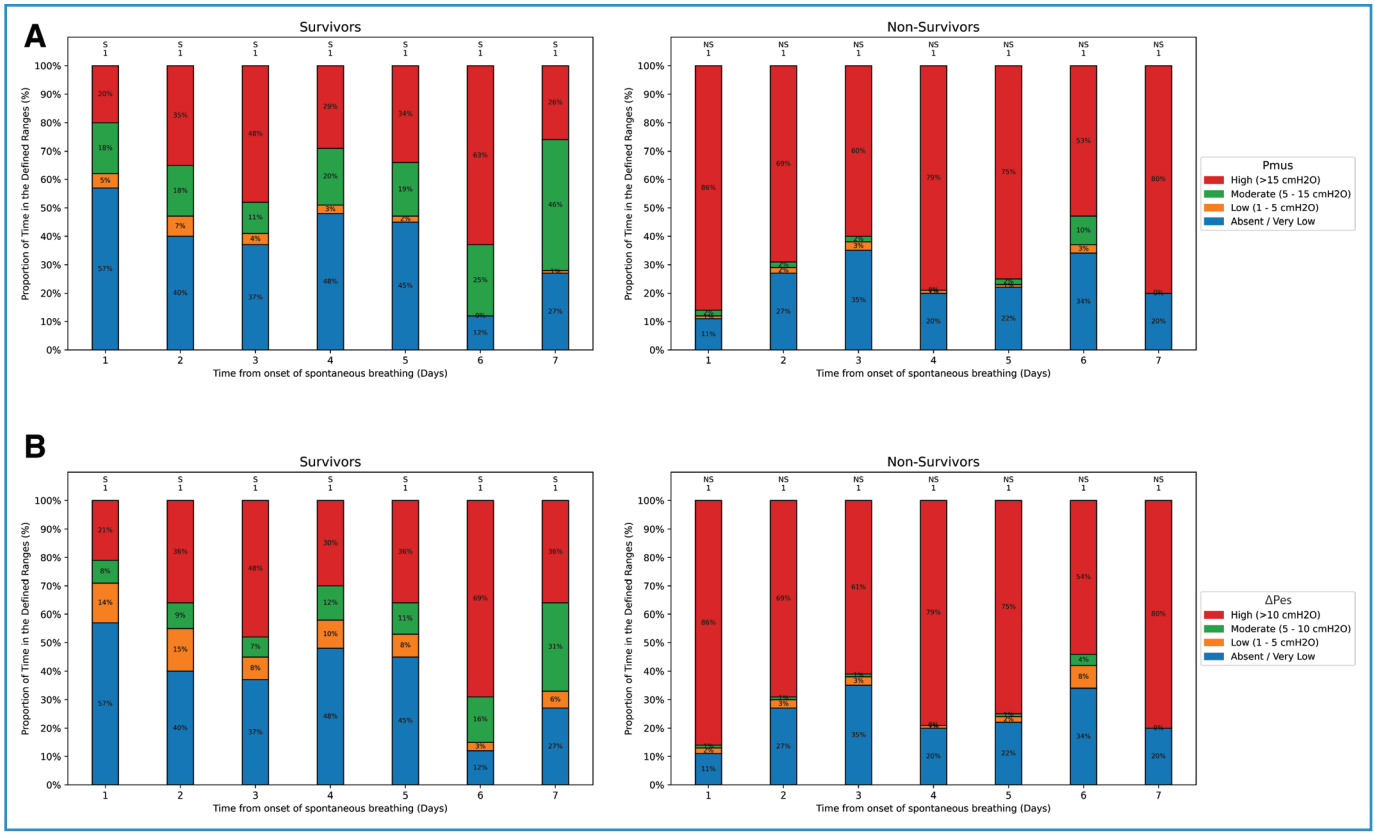

Figure 2. Time distribution of muscular and esophageal pressures during 7 d following the onset of spontaneous breathing (weighted analysis). *Stacked bars charts* representing the percentage of time spent on the different respiratory effort ranges—high (*red*), moderate (*green*), low (*yellow*), and absent/very low (*blue*)—for respiratory muscular pressure (Pmus) and esophageal pressure swing (ΔPes) during the 7 d following the onset of spontaneous breathing. The **left** show data for survivors (S), and the **right** for nonsurvivors (NS). The *numbers* above *each stack bar* indicate the number of patients monitored each day, considering deaths or extubations within each group. **A**, Pmus. **B**, ΔPes. *$p \leq 0.05$ vs. NS. **$p \leq 0.01$ vs. NS. ***$p \leq 0.001$ vs. NS.

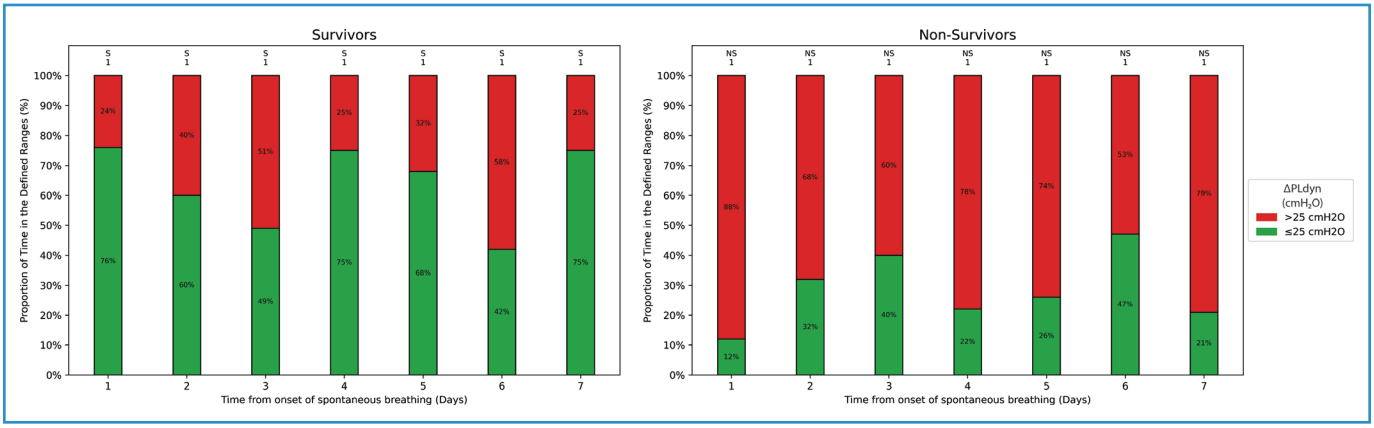

Figure 3. Time distribution of dynamic transpulmonary driving pressure (ΔPLdyn) during the 7 d following the onset of spontaneous breathing (weighted analysis). *Stacked bars charts* representing the percentage of time spent on two different thresholds of dynamic transpulmonary pressure: greater than 25 cm H_2O (*red*) and less than or equal to 25 cm H_2O (*green*)—during the 7 d following the onset of spontaneous breathing. The **left** shows data for survivors (S), and the **right** for nonsurvivors (NS). The *numbers* above *each stack bar* indicate the number of patients monitored each day, considering deaths or extubations within each group. Nonsignificative differences were found between groups per day.

In our cohort, all patients met moderate-to-severe ARDS criteria, but those with persistently low compliance likely faced greater difficulty in transitioning to spontaneous breathing, regardless of improvements in oxygenation. To further explore this, we conducted a post hoc analysis excluding patients with mild ARDS at 24 hours. This analysis, presented in the Online Data Supplement (Table E5 and Figs. E13 and E14, https://links.lww.com/CCM/H761), confirmed similar trends to the main cohort, supporting the consistency of the observed physiologic signal across different baseline oxygenation profiles.

To our knowledge, this is the first study to analyze such a large number of ventilatory cycles with such high data density during the initial phase of spontaneous breathing in ARDS patients on IMV. This extensive dataset has allowed us to continuously assess patient's respiratory mechanics in real time, providing a detailed and dynamic understanding of their condition throughout the monitoring period. In contrast, previous studies have often relied on infrequent measurements, typically taken once daily over short periods (24–26), which may not accurately capture the patient's respiratory state throughout the day, as our results suggest.

This work is subject to several limitations. First, while our study provides a high-density characterization of respiratory effort over multiple days, we did not perform a detailed trajectory analysis or cluster analysis due to sample size limitations. Investigating whether increasing effort over time correlates with worse outcomes, or whether specific effort-response patterns exist among subgroups, would require a larger dataset with more robust statistical modeling. Future studies should explore these approaches to further refine our understanding of ventilatory effort phenotypes and their clinical implications.

Second, this is a single-center study, which limits its generalizability. For example, the study population experienced a prolonged period of diaphragm inactivity (median [IQR], 9 d [4–21 d] for survivors vs. 11 d [1–24 d] for nonsurvivors; $p = 0.975$, until continuous respiratory effort was detected). During this time, patients either did not exert any respiratory effort, or efforts were less than −1 cm H_2O of Pes or lasted fewer than 100 consecutive respiratory cycles. While this represents a limitation, it is important to note that patients with moderate to severe ARDS often require extended periods of sedation and/or paralytics to prevent further lung injury (1).

Third, the compared groups showed differences in static mechanics on the first day of mechanical ventilation (plateau pressure, driving pressure, Crs). These differences were minimal, and most did not reach statistical significance (driving pressure and Crs). Notably, driving pressure remained below the threshold associated with higher mortality (46).

Fourth, the appropriate limits for the respiratory effort variables are not well defined. The ranges used in this study are based on the physiology of healthy subjects (36–39). In patients with lung injury, these limits are likely to vary according to their respiratory system mechanical characteristics at the onset of assisted ventilation. Further studies are needed to establish these limits for critically ill patients and determine if they are associated with lung elastance and functional residual capacity.

Fifth, data on sedation and the use of neuromuscular blocking agents (NMBAs) were not collected in this study. Sedation was managed according to protocol and at the discretion of the treating team, and its detailed analysis was beyond the scope of this observational study. The association between respiratory effort, sedation and NMBA is complex, influenced by multiple confounders, and warrants further investigation with more granular data.

Finally, despite achieving very precise monitoring of ventilatory mechanics during the first 7 days of assisted ventilation, data beyond this period were not analyzed. Additionally, although we obtained a highly variable data density between patients, it does not cover the entirety of the evaluated period. Further studies with more extended and detailed monitoring could complement and enhance these findings.

CONCLUSIONS

Patients who die of ARDS tend to experience prolonged exposure to high respiratory effort compared with survivors. Clinical trials are warranted to evaluate whether strategies aimed at limiting the duration of high respiratory effort can improve outcomes in ARDS.

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Drs. Parrilla-Gómez and Castellví-Font conceived and designed the study. Drs. Parrilla-Gómez, Castellví-Font, Parrilla-Gómez, Festa, Martín-López, and Marco contributed to the study's methodological framework. Dr. Parrilla-Gómez, Dr. Castellví-Font, Dr. Antolín Terreros, Ms. Mestre Somoza, Ms. Blanes Bravo, Ms. Pratsobrerroca de la Rubia, and Mr. Boutonnet were responsible for patient recruitment and data acquisition. Drs. Parrilla-Gómez, Castellví-Font, Parrilla-Gómez, Festa, Martín-López, and Marco curated and analyzed the data. Drs. Parrilla-Gómez and Castellví-Font wrote the initial draft of the article. All authors critically reviewed and edited the article for important intellectual content. Drs. Brochard, Goligher, and Masclans provided oversight and made significant intellectual contributions, particularly in data interpretation. All authors approved the final version of the article.

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