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Spontaneous Breathing in Early Acute Respiratory Distress Syndrome: Insights From the Large Observational Study to UNderstand the Global Impact of Severe Acute Respiratory FailurE Study*

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***See also p. 297.**

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Members of the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) steering committee, national coordinators, and site investigators are listed in the **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/E146).

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Objectives: To describe the characteristics and outcomes of patients with acute respiratory distress syndrome with or without spontaneous breathing and to investigate whether the effects of spontaneous breathing on outcome depend on acute respiratory distress syndrome severity.

Design: Planned secondary analysis of a prospective, observational, multicentre cohort study.

Setting: International sample of 459 ICUs from 50 countries.

Patients: Patients with acute respiratory distress syndrome and at least 2 days of invasive mechanical ventilation and available data for the mode of mechanical ventilation and respiratory rate for the 2 first days.

Interventions: Analysis of patients with and without spontaneous breathing, defined by the mode of mechanical ventilation and by actual respiratory rate compared with set respiratory rate during the first 48 hours of mechanical ventilation.

Measurements and Main Results: Spontaneous breathing was present in 67% of patients with mild acute respiratory distress syndrome, 58% of patients with moderate acute respiratory distress syndrome, and 46% of patients with severe acute respiratory distress syndrome. Patients with spontaneous breathing were older and had lower acute respiratory distress syndrome severity, Sequential Organ Failure Assessment scores, ICU and hospital mortality, and were less likely to be diagnosed with acute respiratory distress syndrome by clinicians. In adjusted analysis, spontaneous breathing during the first 2 days was not associated with an effect on ICU or hospital mortality (33% vs 37%; odds ratio, 1.18 [0.92–1.51]; $p = 0.19$ and 37% vs 41%; odds ratio, 1.18 [0.93–1.50]; $p = 0.196$, respectively). Spontaneous breathing was associated with increased ventilator-free days (13 [0–22] vs 8 [0–20]; $p = 0.014$) and shorter duration of ICU stay (11 [6–20] vs 12 [7–22]; $p = 0.04$).

Conclusions: Spontaneous breathing is common in patients with acute respiratory distress syndrome during the first 48 hours of mechanical ventilation. Spontaneous breathing is not associated with worse outcomes and may hasten liberation from the ventilator and from ICU. Although these results support the use of spontaneous breathing in patients with acute respiratory distress syndrome independent of acute respiratory distress syndrome severity, the use of controlled ventilation indicates a bias toward use in patients with higher disease severity. In addition, because the lack of reliable data on inspiratory effort in our study, prospective studies incorporating the magnitude of inspiratory effort and adjusting for all potential severity confounders are required. (*Crit Care Med* 2019; 47:229–238)

Key Words: acute respiratory distress syndrome; controlled mechanical ventilation; spontaneous breathing; supported ventilation

In patients with acute respiratory distress syndrome (ARDS), lung protective mechanical ventilation (MV) is used to avoid ventilator-induced lung injury by limiting volume and pressure (1, 2). Patient spontaneous breathing (SB) activity may impede efforts to limit tidal volume (V_T) and suppressing SB with early neuromuscular blockade improves outcomes in patients with severe ARDS (3).

The use of partially supported breathing modes is increasing, but there is much uncertainty about its effects (4–6). SB has been shown to improve gas exchange, hemodynamics and nonpulmonary organ perfusion and function, is associated with reduced sedation, and may prevent disuse and loss of peripheral muscle and diaphragm function (7–10). Partially supported MV better resembles natural respiratory variability when compared with controlled MV (5, 11), improves lung mechanics and enhances tidal distribution to the dependent regions of the lung (12), reducing shunt and decreasing dead space (13). However, SB in MV may cause or worsen acute lung injury if ARDS is severe and spontaneous effort is vigorous (14, 15). SB contributes to the transpulmonary pressure (11) and may cause unsuspected overstretch of dependent lung during early inflation even when not increasing V_T (16).

The objective of this planned sub-study of the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) is to describe the characteristics and outcomes of patients with SB compared with patients with no SB during the first days of ARDS, and to investigate whether the effects of SB on outcome depend on the severity of ARDS.

PATIENTS AND METHODS

Study Design

Prospective, observational, international multicentre cohort study in 13,751 ventilated patients in 459 ICUs from 50 countries. The detailed study design and main results have been published previously (17). All participating ICUs obtained ethics committee approval, and either patient consent or ethics committee waiver of consent.

Data Collection

Data on arterial blood gases, mode and settings of ventilatory support, and Sequential Organ Failure Assessment (SOFA) score were collected on selected days during the ICU stay until day 28, ICU discharge, or death, whichever came first. Data on ventilatory settings were recorded simultaneously with arterial blood gas analysis. ICU and hospital survival were collected at the time of discharge and censored at 90 days after enrollment. We assessed clinician recognition of ARDS on day 1 of study entry, and when patients exited the study (17).

Patient Cohorts and Definitions

Patients receiving MV during the study period were enrolled. Exclusion criteria were age less than 16 years or inability to obtain informed consent if required. For the current study, we restricted analyses to the subset of patients with ARDS (18) on

day 1 or day 2 following the onset of acute hypoxemic respiratory failure (AHRF), who had at least 2 days of MV and available data for the mode of MV and respiratory rate (RR) for the 2 first days.

Patients were divided into two groups: patients with no SB activity (controlled, C group) and patients with SB activity (SB group). Patients were included in the C group if they received controlled mode ventilation with a set RR equal to the actual RR on both day 1 and 2 (actual RR = set RR); patients were included in the SB group if they received a mode of MV with no mandatory breaths (i.e., pressure support ventilation (PSV), proportional assist ventilation (PAV), continuous positive airway pressure (CPAP)) on day 1 and/or day 2 or if they received an assist control mode of ventilation and their actual RR was greater than the set RR on day 1 and/or day 2.

To perform additional analyses and decrease heterogeneity in the SB group, we divided the SB group into a fully SB (SB-F) group and a partially SB (SB-P) group. Patients in the SB-F group had SB without any controlled or mandatory breaths (i.e., PSV, PAV, CPAP) on both day 1 and 2. All other patients with SB were included in the SB-P group.

For our primary analysis, we compared characteristics and outcomes of patients in the C group with patients in the SB group, stratified by ARDS severity based on the Pao_2/Fio_2 ratio. We performed additional analyses by comparing the C group with the SB-F group and with the SB-P group, by comparing survivors with nonsurvivors, and by propensity scoring matching analysis.

Statistical Analysis

For quantitative variables collected on day 1 and day 2, we calculated the mean value of the 2 days or used the available value if one of the two values was missing. Continuous variables are reported as mean ± SD or median (first–third quartiles) and categorical variables as count and proportion. Comparisons of proportions were made using chi-square or Fisher exact tests. Continuous variables were compared using Student *t* test or Wilcoxon rank-sum test when two groups were compared, and corresponding paired tests for matched patients, as appropriate. Comparing continuous variables for three groups, we used analysis of variance or Kruskal-Wallis tests. Tukey range tests were used to compare all possible pairs of means within the three groups.

We performed bivariate analyses to identify factors potentially associated with hospital mortality, assuming that patients discharged alive from hospital before 90 days were alive on day 90. Covariates found to be associated with hospital mortality in the bivariate analysis with a *p* value of less than or equal to 0.20 were entered in stepwise (forward and backward) multivariable logistic regression analyses with significance alpha levels less than or equal to 0.05 for retention. MV (C or SB) was forced in the model as it was the main focus of this study. In addition, the Pao_2/Fio_2 ratio was included in the model to assess whether the effects of SB on outcome depend on ARDS severity. Results are shown as odds ratios (ORs) with 95% CI and as beta coefficient with SE.

As a sensitivity analysis, we used a propensity approach to control for observed confounding factors that might influence MV group or hospital mortality. We estimated the propensity score of having no SB in the first 2 days of ARDS using a logistic regression model including potential predictors (detailed in **eTables 4-8**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147). Missing data were imputed with chained equation, where missing variables for each patient were averaged across 30 completed datasets. Patients from the C group were matched with patients from the SB group, using a 1:1 matching procedure without replacement and caliper width of 0.2, as recommended (19). Similarly, patients from the C group were matched with patients from the SB-F group to overcome heterogeneity in the SB group. Balances in confounders before and after matching were checked using standardized mean differences. No assumptions were made for missing data apart for the propensity score, and we followed the Strengthening the Reporting of Observational Studies in Epidemiology recommendations (20). Statistical analysis was performed with R (Version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria). All *p* values were two-sided, and values less than 0.05 were deemed significant.

RESULTS

Prevalence of SB Activity

Of 12,906 patients screened for the LUNG SAFE study, 2,813 patients fulfilled ARDS criteria within 2 days of AHRF onset (**Fig. 1**). Of these, 1,756 patients had at least 2 days of MV and available data for the mode of MV and RR for the 2 first days. Seven-hundred forty patients had no SB during the first 2 days (C group, 42%) and 1,016 patients had SB (SB group, 58%), with 180 patients without any controlled or mandatory breaths on both day 1 and 2 (SB-F group, 10%). The distribution of ventilatory modes on day 1 and 2 in patients in the SB-P group is shown in **eFigure 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/E147).

Stratified by ARDS severity, SB was present in 67% of patients (344/515) with mild ARDS, 58% of patients (488/844) with moderate ARDS, and 46% of patients (184/397) with severe ARDS.

Demographic and Clinical Characteristics

Patients in the SB group were older and had significantly lower ARDS severity, SOFA scores and nonpulmonary SOFA scores (**Table 1**). There were no differences in comorbidities or admission type between groups. Risk factors for ARDS were similar, except for nonpulmonary sepsis, which was higher in the SB group. SB was associated with more ICU beds and with a lower physician-to-bed, but a higher nurse-to-bed ratio. Clinician recognition of ARDS at any time during the study, but not at baseline, was lower in the SB group.

After stratification by Pao_2/Fio_2 ratio less than 150, or greater than or equal to 150, age and body weight were similar in both groups (Table 1). Patients in the SB group had lower SOFA and nonpulmonary SOFA scores in both strata, indicating that they were less sick. Patients in the SB group with $Pao_2/$

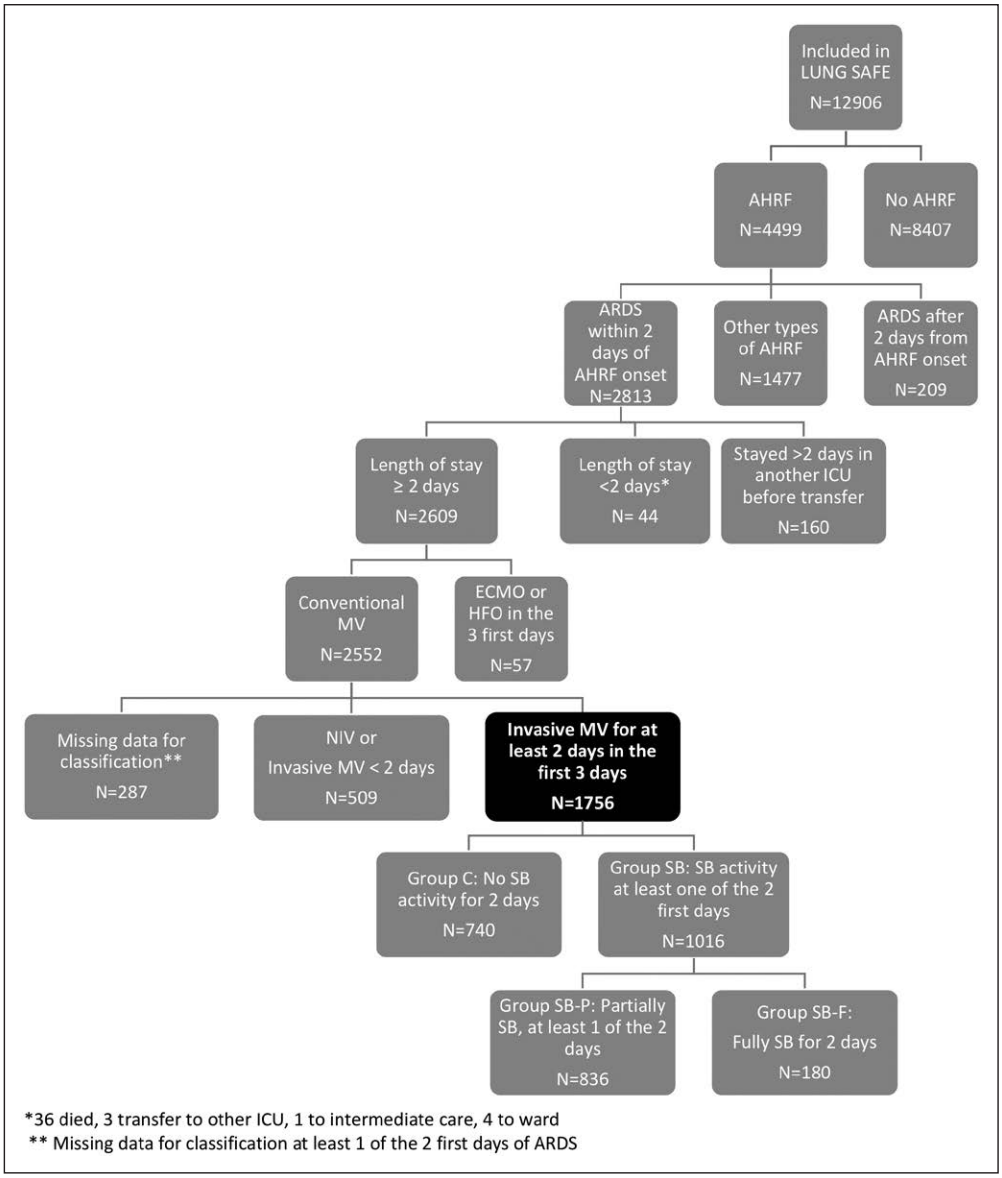

Figure 1. Flowchart of the study population. AHRF = acute hypoxemic respiratory failure, ARDS = acute respiratory distress syndrome, ECMO = extracorporeal membrane oxygenation, HFO = high-frequency oscillation ventilation, LUNG SAFE = Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE, MV = mechanical ventilation, NIV = noninvasive ventilation, SB = spontaneous breathing, SB-F = fully SB, SB-P = partially SB. Group C represent controlled group.

F_{IO_2} ratio greater than or equal to 150 were less likely to be diagnosed with ARDS by the clinician compared with patients in the C group. SB patients in both strata were less likely to have received sedation and lung recruitment maneuvers in the first 48 hours.

The demographic and clinical characteristics of the C and SB groups, stratified to ARDS severity mild, moderate, and severe are shown in **eTable 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/E147).

Ventilation and Physiologic Variables

Mean V_T were higher in patients with SB (7.9 ± 1.7 vs 7.5 ± 1.5 mL/kg predicted body weight (PBW); $p < 0.001$) (**Table 2**). In the SB group, 60% of patients received a V_T of 8 mL/kg of PBW or less; this was 68% in the C group ($p < 0.001$) (**Fig. 2*A***). Plateau pressures, peak inspiratory pressures, and levels of positive end-expiratory pressure (PEEP) were significantly lower in the SB group (Table 2; and **Fig. 2**, ***B*** and ***C***). Among the 683 patients with available data both for plateau pressure and V_T, 69% in the SB group and 65% in the C group ($p = 0.354$) fell within the limits for protective ventilation (defined as plateau pressure ≤ 30 cm H_2O and V_T ≤ 8 mL/kg PBW) (**Fig. 3**). Despite lower levels of standardized minute ventilation in the SB group, Pa_{CO_2} levels were lower and pH higher. The differences in V_T, PEEP, peak pressures, Pa_{CO_2} levels, and pH remained significant after stratification by Pa_{O_2}/F_{IO_2} ratio (Table 2).

Ventilation and physiologic variables of the C and SB groups stratified to ARDS severity mild, moderate, and severe are shown in eTable 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/E147).

Clinical Outcomes in Unadjusted Analyses

The SB group had significantly shorter duration of MV, higher number of ventilator-free days (VFDs), and shorter stay in the ICU than the C group. ICU and hospital mortality were lowest in the SB group (Table 2). When stratified by Pa_{O_2}/F_{IO_2} ratio, patients in the SB group had more VFD and lower ICU mortality in both strata. ICU length of stay (LOS) was shorter only in the SB group when Pa_{O_2}/F_{IO_2} ratio less than 150. There were no differences in rates of life-sustaining therapies limitation decisions between the groups. Clinical outcomes, stratified by ARDS severity mild, moderate, and severe is shown in eTable 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/E147).

Additional and Adjusted Analyses

Patients in the SB-F group had lower SOFA scores, lower ARDS severity and were less likely to be diagnosed with ARDS both on day 1 and at any time than patients in the SB-P or the C

TABLE 1. Characteristics of Patients With Acute Respiratory Distress Syndrome With Spontaneous Breathing Activity (Spontaneous Breathing Group) and Without Spontaneous Breathing Activity (C group), Stratified by Pao_2/Fio_2 Ratio

	Pao_2:Fio_2 ratio ≥ 150, *n* = 908		Pao_2:Fio_2 ratio < 150, *n* = 848		ARDS, All, *n* = 1,756		
Characteristics	Patients With SB Activity (SB Group), *n* = 584	Patients With No SB Activity (C Group), *n* = 324	Patients With SB Activity (SB Group), *n* = 432	Patients With No SB Activity (C Group), *n* = 416	Patients With SB Activity (SB Group), *n* = 1016	Patients With No SB Activity (C Group), *n* = 740	*p*
Age, yr, mean (SD)	62.6 ± 16.7	60.4 ± 17.3	59.8 ± 16.7	59.4 ± 16.9	61.4 (16.8)	59.8 (17.1)	0.048
Males, *n* (%)	357 (61.1)	201 (62.0)	285 (66.0)	262 (63.0)	642 (63.2)	463 (62.6)	0.829
Height, cm, mean (SD)	167.8 ± 10.1	168.3 ± 9.7	168.0 ± 10.0	168.8 ± 9.8	167.9 ± 10.0	168.6 ± 9.8	0.170
Weight, kg, mean (SD)	75.4 ± 19.8	77.7 ± 20.0	78.0 ± 32.8	80.7 ± 22.2	76.6 (26.2)	79.4 (21.3)	0.015
SOFA score day 1, mean (SD)	9.0 ± 3.7	10.0 ± 3.6[a]	10.4 ± 3.7	11.1 ± 4.2[a]	9.8 (3.8)	10.6 (4.0)	< 0.001
Nonpulmonary SOFA score day 1, mean (SD)	6.4 ± 3.8	7.3 ± 3.7[a]	6.7 ± 3.7	7.3 ± 4.1[a]	6.6 (3.7)	7.3 (4.0)	< 0.001
Chronic disease, *n* (%)							
Diabetes	130 (22.3)	82 (25.3)	93 (21.5)	97 (23.3)	223 (21.9)	179 (24.2)	0.296
Chronic obstructive pulmonary disease	121 (20.7)	61 (18.8)	88 (20.4)	98 (23.6)	209 (20.6)	159 (21.5)	0.685
Chronic renal failure	64 (11.0)	35 (10.8)	34 (7.9)	32 (7.7)	98 (9.6)	67 (9.1)	0.736
Neoplasm or immunosuppression	119 (20.4)	59 (18.2)	99 (22.9)	79 (19.0)	218 (21.5)	138 (18.6)	0.166
Chronic heart failure	52 (8.9)	30 (9.3)	43 (10.0)	39 (9.4)	95 (9.4)	69 (9.3)	1.000
Chronic liver failure	26 (4.5)	12 (3.7)	19 (4.4)	20 (4.8)	45 (4.4)	32 (4.3)	1.000
Home ventilation	13 (2.2)	3 (0.9)	7 (1.6)	5 (1.2)	20 (2.0)	8 (1.1)	0.203
Admission type, *n* (%)							0.115
Medical	408 (69.9)	221 (68.2)	337 (78.0)	337 (81.0)	745 (73.3)	558 (75.4)	
Surgical (postoperative elective)	45 (7.7)	19 (5.9)	22 (5.1)	18 (4.3)	67 (6.6)	37 (5.0)	
Surgical	108 (18.5)	62 (19.1%)	59 (13.7)	44 (10.6)	167 (16.4)	106 (14.3)	
Trauma	23 (3.9)	22 (6.8%)	14 (3.2)	17 (4.1)	37 (3.6)	39 (5.3)	
Risk factor for ARDS, *n* (%)							
Pneumonia	315 (53.9)	165 (50.9)	277 (64.1)	263 (63.2)	592 (58.3)	428 (57.8)	0.857
Nonpulmonary sepsis	125 (21.4)	56 (17.3)	70 (16.2)	55 (13.2)	195 (19.2)	111 (15.0)	0.022
Aspiration	88 (15.1)	67 (20.7)[a]	74 (17.1)	71 (17.1)	162 (15.9)	138 (18.6)	0.139
Trauma	30 (5.1)	25 (7.7)	25 (5.8)	19 (4.6)	55 (5.4)	44 (5.9)	0.632
Inhalation	15 (2.6)	9 (2.8)	11 (2.5)	14 (3.4)	26 (2.6)	23 (3.1)	0.493
Pancreatitis	12 (2.1)	8 (2.5)	12 (2.8)	10 (2.4)	24 (2.4)	18 (2.4)	0.919
Burns	1 (0.2)	1 (0.3%)	4 (0.9)	0 (0.0)	5 (0.5)	1 (0.1)	0.238
Pulmonary vasculitis	4 (0.7)	6 (1.9)	4 (0.9)	8 (1.9)	8 (0.8)	14 (1.9)	0.046
Noncardiogenic shock	49 (8.4)	31 (9.6)	32 (7.4)	29 (7.0)	81 (8.0)	60 (8.1)	0.989
Overdose	13 (2.2)	7 (2.2)	8 (1.9)	10 (2.4)	21 (2.1)	17 (2.3)	0.742
Transfusion-related acute lung injury	26 (4.5)	15 (4.6)	15 (3.5)	23 (5.5)	41 (4.0)	38 (5.1)	0.276
Number of ICU beds, median (IQR)	18.0 (12.0–26.0)	16.0 (10.0–24.0)[a]	16.0 (10.0–25.0)	16.0 (10.0–22.8)	18.0 (12.0–26.0)	16.0 (10.0–23.0)	0.003
Number of patients/staff physician, median (IQR)	6.0 (2.7–10.6)	4.5 (2.6–8.5)[a]	5.0 (2.8–11.0)	3.8 (2.4–8.0)[a]	5.4 (2.8–11.0)	4.0 (2.5–8.1)	< 0.001

(*Continued*)

TABLE 1. (*Continued*). Characteristics of Patients With Acute Respiratory Distress Syndrome With Spontaneous Breathing Activity (Spontaneous Breathing Group) and Without Spontaneous Breathing Activity (C group), Stratified by Pao_2/Fio_2 Ratio

	Pao_2:Fio_2 ratio ≥ 150, *n* = 908		Pao_2:Fio_2 ratio < 150, *n* = 848		ARDS, All, *n* = 1,756		
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Number of patients/nurse, median (IQR)	1.4 (1.0–2.0)	1.5 (1.0–2.1)	1.3 (1.0–2.0)	1.6 (1.0–2.2)[a]	1.4 (1.0–2.0)	1.5 (1.0–2.2)	0.019
Clinician recognition of ARDS, *n* (%)							
On first day of ARDS	161 (27.6)	101 (31.2)	160 (37.0)	162 (38.9)	321 (31.6)	263 (35.5)	0.093
At any time	317 (54.3)	200 (61.7)[a]	305 (70.6)	318 (76.4)	622 (61.2)	518 (70.0)	< 0.001
Treatment adjuncts in first 48 hr, *n* (%)							
Sedation	439 (75.2)	287 (88.6)[a]	348 (80.6)	390 (93.8)[a]	787 (77.5)	677 (91.5)	< 0.001
Neuromuscular blockade	41 (7.0)	43 (13.3)[a]	51 (11.8)	144 (34.6)[a]	92 (9.1)	187 (25.3)	< 0.001
Prone positioning	8 (1.4)	10 (3.1)	16 (3.7)	48 (11.5)[a]	24 (2.4)	58 (7.8)	< 0.001
Lung recruitment manoeuvres	62 (10.6)	53 (16.4)[a]	91 (21.1)	113 (27.2)[a]	153 (15.1)	166 (22.4)	< 0.001
Tracheostomy at any time	83 (14.2)	45 (13.9)	54 (12.5)	51 (12.3)	137 (13.5)	96 (13.0)	0.810

ARDS = acute respiratory distress syndrome, IQR = interquartile range, SB = spontaneous breathing, SOFA = Sequential Organ Failure Assessment.
[a]$p < 0.05$ C group vs SB group.

group (**eTable 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147). Both ICU and hospital mortality were lowest in the SB-F group. Of patients in the SB-F group, 22% changed to either being in the SB-P or in the C group. Patients who changed had a higher hospital mortality rate compared with patients who continued to be in the SB-F group (53% vs 32%; $p = 0.032$), but with similar rates of clinician recognition of ARDS (58% vs 49%; $p = 0.460$).

Characteristics of survivors compared with nonsurvivors are shown in **eTable 3** (Supplemental Digital Content 2, http://links.lww.com/CCM/E147). Vt was not different between survivors and nonsurvivors in all patients with ARDS, and when stratified by ARDS severity (**eFig. 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147). The following factors were associated with increased mortality: older age, lower body weight, type of admission, active neoplasm, chronic liver failure, higher SOFA scores, and ARDS severity. Potentially modifiable factors included higher peak inspiratory and plateau pressures and increased RR. In a multivariable logistic regression model, after adjusting for covariates significantly associated with outcome, SB was not independently associated with ICU mortality (OR, 1.17; 95% CI, 0.92–1.49; $p = 0.208$) or hospital mortality (OR, 1.13; 95% CI, 0.92–1.50; $p = 0.298$) (**eTables 4** and **5**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147). When limiting the multivariable logistic regression analysis to patients with Pao_2/Fio_2 ratio less than 150 or greater than or equal to 150, SB was not independently associated with hospital mortality (**eTables 6** and **7**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147). The Pao_2/Fio_2 ratio did not independently affect the outcomes of SB on hospital mortality (interaction term Pao_2/Fio_2 ratio × no SB: beta coefficient –0.003; se 0.018; $p = 0.865$) (**eTable 8**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147).

For sensitivity analysis by propensity score matching, we matched 555 of 740 patients (75%) in the C group with 555 of 1,016 patients (55%) in the SB group (**eTable 9**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147). Missing data are shown in **eTable 10** (Supplemental Digital Content 2, http://links.lww.com/CCM/E147). The two groups were well matched on demographic characteristics, comorbidities, and SOFA (eTable 9 and **eFig. 3**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147). After matching there was no significant difference in ICU and hospital mortality rates, but the SB group had more VFD (13 [0–22] vs 8 [0–20]; $p = 0.014$) and shorter ICU LOS (11 [6–20] vs 12 [7–22]; $p = 0.04$). When adjusting the model by removing variables potentially related to the ventilatory mode (peak inspiratory pressure, RR, minute ventilation, Vt, Pco_2), we matched 668 patients. This modification did not change the results (**eTable 11** and **eFig. 4**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147).

For sensitivity analysis by propensity score matching, we also matched 89 of 740 patients (12%) in the C group with 89 of 180 patients (49%) in the SB-F group. (**eTable 12**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147). The two groups were well matched on demographic characteristics, comorbidities, and SOFA (eTable 12 and **eFig. 5**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147). After matching there was no significant difference in any of the outcomes. When

TABLE 2. Ventilation, Physiologic, and Outcome Variables of Patients With Acute Respiratory Distress Syndrome With Spontaneous Breathing Activity (Spontaneous Breathing Group) and Without Spontaneous Breathing Activity (C group), Stratified by Pao_2/FIO_2 Ratio

	Pao_2:FIO_2 ratio ≥ 150, *n* = 908		Pao_2:FIO_2 ratio < 150, *n* = 848		Acute Respiratory Distress Syndrome, All, *n* = 1,756		
Variables	Patients With SB Activity (SB Group)	Patients With No SB Activity (C Group)	Patients With SB Activity (SB Group)	Patients With No SB Activity (C Group)	Patients With SB Activity (SB Group)	Patients With No SB Activity (C Group)	*p*
FIO_2, median (IQR)	0.4 (0.4–0.5)	0.5 (0.4–0.6)[a]	0.6 (0.6–0.8)	0.7 (0.6–0.8)[a]	0.5 (0.4–0.7)	0.6 (0.5–0.8)	< 0.001
Respiratory rate (actual), mean (SD)	20.2 ± 5.3	19.2 ± 4.9[a]	22.1 ± 5.5	21.4 ± 5.4	21.0 (5.5)	20.4 (5.3)	0.024
Tidal volume, mL/kg predicted body weight, mean (SD)	7.9 ± 1.8	7.6 ± 1.5[a]	7.8 ± 1.7	7.5 ± 1.5[a]	7.9 (1.7)	7.5 (1.5)	< 0.001
Minute ventilation, L/min, mean (SD)	9.86 ± 3.43	9.79 ± 3.28	11.60 ± 4.02	11.96 ± 4.94	10.59 (3.79)	11.01 (4.43)	0.038
Positive end-expiratory pressure, cm H_2O, mean (SD)	7.4 ± 2.6	8.0 ± 2.7[a]	8.8 ± 2.8	9.5 ± 3.3[a]	8.0 (2.7)	8.9 (3.1)	< 0.001
Peak pressure, cm H_2O, mean (SD)	23.4 ± 6.8	28.0 ± 8.0[a]	25.9 ± 6.8	30.9 ± 6.8[a]	24.5 (6.9)	29.6 (7.5)	< 0.001
Plateau pressure, cm H_2O[b], mean (SD)	20.9 ± 5.3	22.2 ± 5.0[a]	24.0 ± 5.8	24.8 ± 5.8	22.2 (5.7)	23.8 (5.7)	< 0.001
Compliance, mL/cm H_2O[c], mean (SD)	37.8 ± 15.0	36.1 ± 14.5	33.5 ± 14.1	33.4 ± 14.0	36.0 (14.8)	34.5 (14.3)	0.161
Peripheral oxygen saturation, median (IQR)	97.0 (95.5–98.5)	97.0 (95.9–98.5)	95.0 (92.5–97.0)	95.0 (93.0–97.0)	96.5 (94.5–98.0)	96.0 (94.0–98.0)	0.307
$PaCO_2$, mm Hg, mean (SD)	38.0 ± 10.9	40.1 ± 12.9[a]	41.1 ± 13.1	44.1 ± 16.4[a]	39.3 (11.9)	42.4 (15.0)	< 0.001
pH, mean (SD)	7.37 ± 0.08	7.34 ± 0.09[a]	7.35 ± 0.10	7.31 ± 0.11[a]	7.36 (0.09)	7.32 (0.10)	< 0.001
Duration of mechanical ventilation, median (IQR), d	8.0 (4.0–14.0)	9.0 (5.0–14.8)	8.0 (4.0–15.0)	11.0 (6.0–19.0)[a]	8.0 (4.0–14.0)	10.0 (5.0–17.0)	< 0.001
Invasive ventilation free-days to day 28, median (IQR), d	16.0 (0.0–23.0)	10.5 (0.0–21.0)[a]	12.0 (0.0–21.0)	0.0 (0.0–18.0)[a]	15.0 (0.0–22.0)	5.5 (0.0–19.0)	< 0.001
ICU length of stay, median (IQR), d	11.0 (6.0–19.0)	11.0 (6.0–20.0)	11.0 (6.0–19.0)	13.0 (7.0–23.0)[a]	11.0 (6.0–19.0)	12.0 (7.0–22.0)	0.012
Hospital length of stay, median (IQR), d	19.0 (10.0–35.0)	17.0 (9.0–35.0)	17.0 (8.0–30.0)	20.0 (10.0–34.0)	18.0 (9.0–33.0)	19.0 (9.0–35.0)	0.414
ICU mortality, *n* (%)	168 (28.8)	115 (35.5)[a]	149 (34.5)	173 (41.6)[a]	317 (31.2)	288 (38.9)	0.001
Hospital mortality, *n* (%)	206 (35.5)	135 (41.7)	171 (39.6)	184 (44.7)	377 (37.3)	319 (43.3)	0.012
Treatment limitations, *n* (%)	130 (22.3)	89 (27.5)	111 (25.7)	98 (23.6)	241 (23.7)	187 (25.3)	0.455

IQR = interquartile range, SB = spontaneous breathing.

[a]$p < 0.05$ C group vs SB group.

[b]Data for plateau pressure was available for 431 patients in the SB group and 402 in the C group.

[c]Data for compliance was available for 429 patients in the SB group and 400 in the C group.

adjusting the model by removing variables potentially related to the ventilatory mode (peak inspiratory pressure, RR, minute ventilation, VT, PCO_2), we matched 166 patients. This modification did not change the results (**eTable 13** and **eFig. 6**, Supplemental Digital Content 2, http://links.lww.com/CCM/E147).

DISCUSSION

In this LUNG SAFE ancillary study, we examined the current practice and outcomes of SB in ARDS. Patients with SB were older and less sick, had lower ventilatory pressures with higher pH and lower $PaCO_2$, despite similar standardized minute ventilation and independent of ARDS severity. VT was higher in SB patients, but the absolute difference was small and unlikely to be clinically meaningful. After adjustment for covariates and propensity matching which included measures of severity of disease, there was no difference in hospital mortality between the groups, but patients with SB had more VFDs and shorter ICU LOS. Patients with SB had less exposure to sedation than

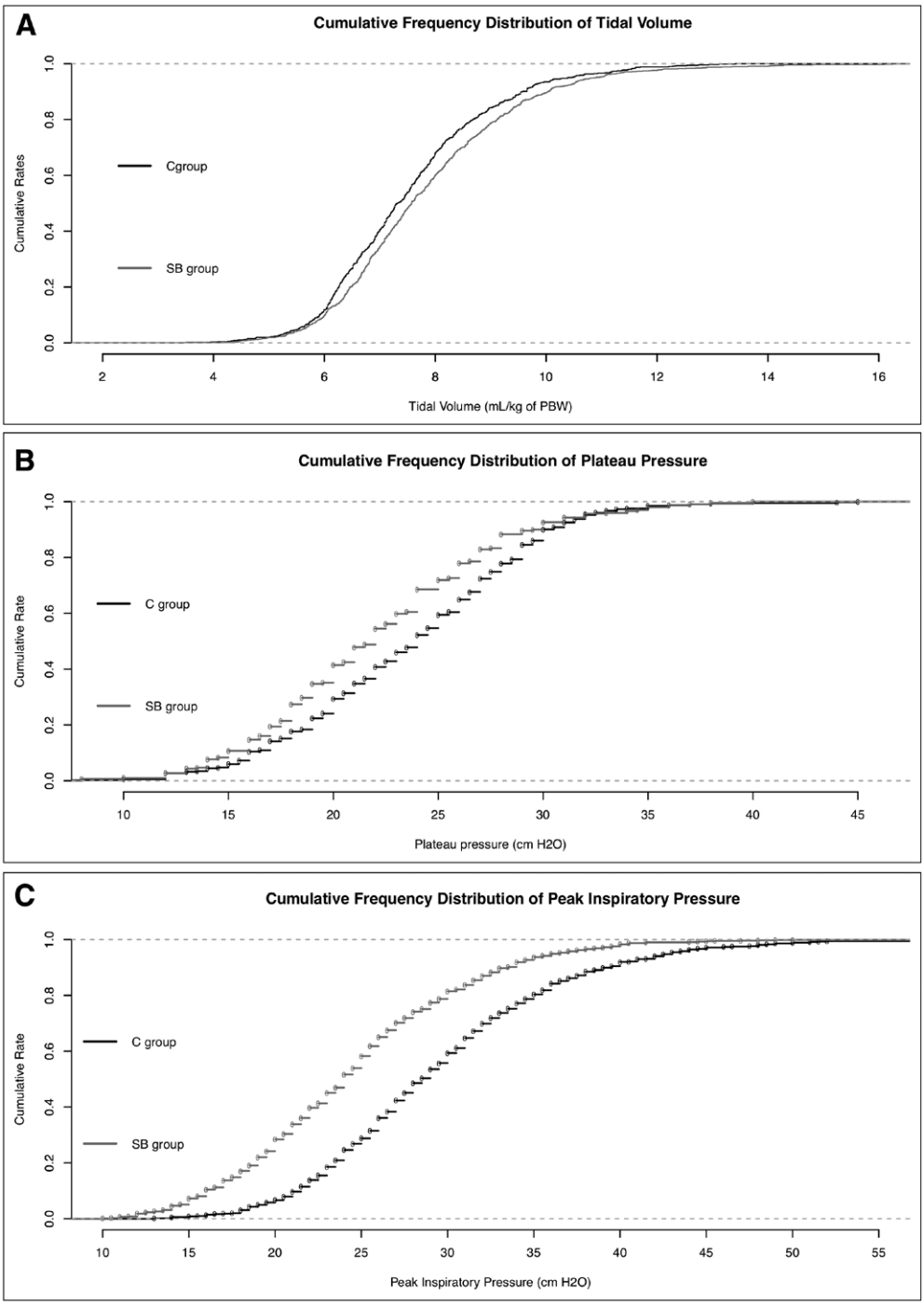

Figure 2. A, Cumulative frequency distribution of the mean tidal volume of day 1 and 2. **B**, Cumulative frequency distribution of the mean plateau pressure of day 1 and 2. **C**, Cumulative frequency distribution of the mean peak inspiratory pressure of day 1 and 2. PBW = predicted body weight, SB = spontaneous breathing. C group represent patients with no SB activity and SB group represent patients with SB activity.

patients on controlled MV, which could be a factor contributing to the difference in VFDs and ICU LOS.

These findings need to be interpreted with caution. We did not assess the potential for patient-ventilator asynchrony. Asynchronies are common, occur in all modes of MV and are associated with worse outcome (21, 22). The SB group was heterogeneous and included different MV modes. Different modes that allow SB may have different effects on lung aeration (23). When limiting the analysis to patients who had only spontaneous (SB-F) versus only controlled (C) breathing on the first 2 days after ARDS onset, there was also no difference in hospital mortality between the groups. The size estimate and direction of the effect of SB-F compared with C on VFD and ICU LOS appeared similar to the main analysis but was no longer statistically significant, most likely because of the reduced power in the smaller sample size.

Patients without SB constituted a more severe group of patients, which could explain why clinicians initiate controlled ventilation. This statement is supported by our finding that patients on controlled ventilation were more likely to be diagnosed with ARDS by the clinician. Consistent with our findings in patients managed with NIV (24), patients who "failed" SB-F and were switched to SB-P or controlled ventilation at any time after the first 2 days, had a higher mortality.

Previous studies have suggested that the effects of SB during MV in ARDS may depend on ARDS etiology and severity, with possible beneficial effects in mild to moderate ARDS and harmful effects in severe ARDS (25–27). We did not find an association between ARDS severity, or etiology, and outcomes in patients with or without SB.

We did not find a significant effect of V_T on mortality. We believe this analysis is confounded by the absence of good indicators for inspiratory effort in SB patients in this study. Large V_T during SB in ARDS patients may indicate a high inspiratory effort or less severe ARDS with a more compliant respiratory system. Our results indicate that the level of inspiratory effort in patients on MV cannot be reliably predicted from either the ventilatory mode, V_T, or RR. However, from our data, it seems

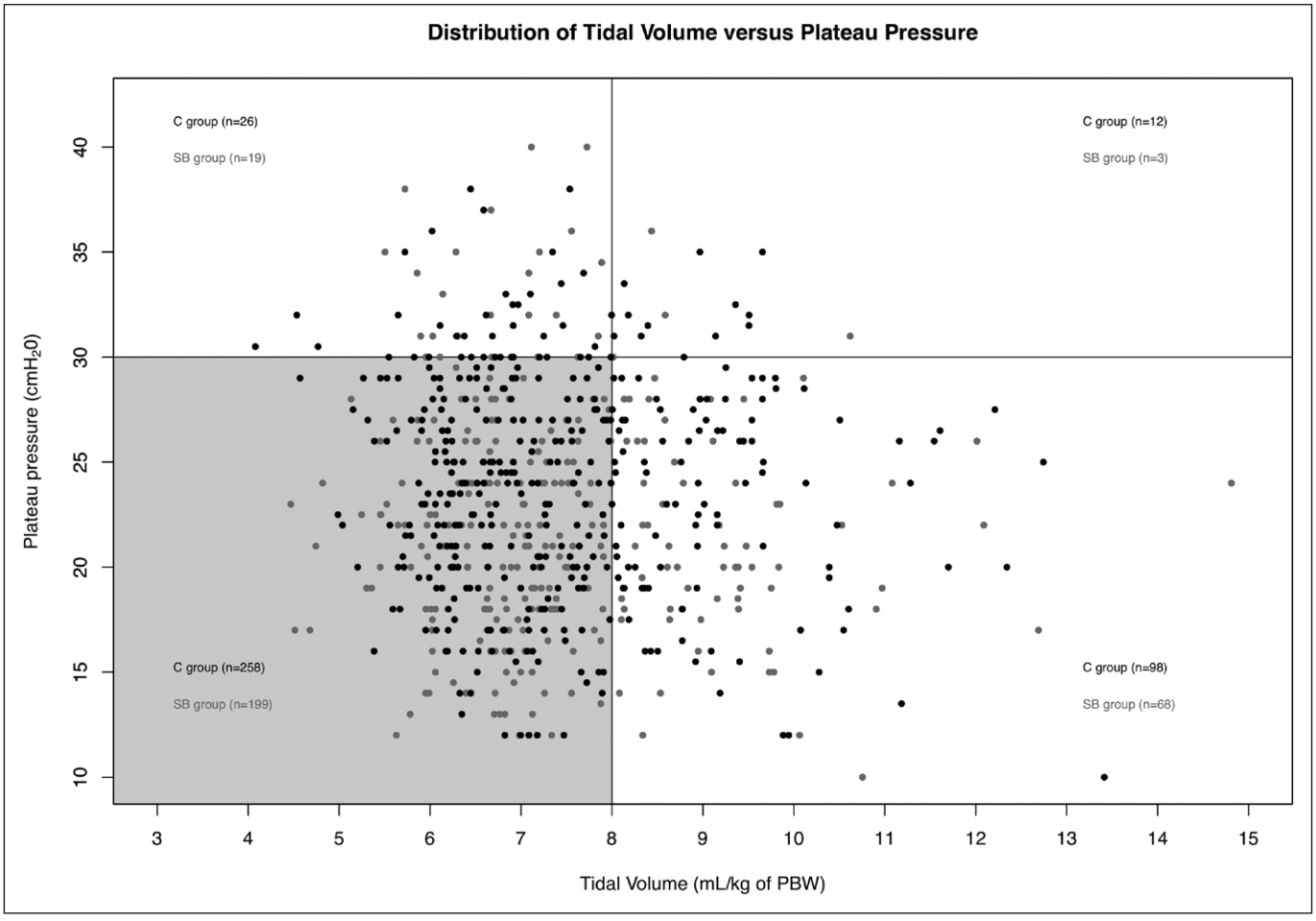

Figure 3. Distribution of tidal volume versus plateau pressure (means of day 1 and 2) for each patient for which these data are available. The limits for protective ventilation are defined as plateau pressure less than or equal to 30 cm H_2O and tidal volume of less than or equal to 8 mL/kg of predicted body weight (PBW). SB = spontaneous breathing. C group represent patients with no SB activity and SB group represent patients with SB activity.

that large inspiratory efforts with SB are either infrequent or not "excessive" (at population level) when clinicians are free to choose the ventilator settings in their clinical practice.

Reliable assessment of respiratory drive and inspiratory breathing effort is key toward understanding the balance between harm and benefit of SB (28). In an experimental model of ARDS, high transpulmonary pressure generated by strong SB effort worsened lung injury even when plateau pressures were limited to less than 30 cm H_2O (29). Other data also suggest that SB patients with high respiratory drive may develop a form of patient self-inflicted lung injury (30). The increase in transmural pulmonary vascular pressure swings caused by inspiratory effort may worsen vascular leakage. Other mechanisms that could contribute to harm caused by SB include the occurrence of occult breath stacking (31) and reverse triggering when large spontaneous diaphragmatic contractions can be triggered by the ventilator in heavily sedated, nonparalyzed patients (32).

Our study has several limitations. Data were collected once per day, and we did not collect hours of duration of MV modes. In addition to the set ventilatory mode, we compared actual RR with set RR to determine whether patients had SB. However, we cannot be certain that patients whose actual rate equals the set rate do not have SB. Limiting our analysis of patients in the C group to those who received neuromuscular blockade on the first 2 days showed similar results (data not shown). Further, the presence of triggering in an AC or partially assisted mode does not provide insight into the magnitude of inspiratory effort. The use of V_T as a surrogate marker for lung distension and inspiratory effort has limitations as discussed earlier.

Finally, because of the observational nature of the study, there are unmeasured confounders. In our belief, the observation that patients with no SB were sicker and had worse unadjusted outcomes may reflect a systematic clinicians' bias toward the use of controlled ventilation in patients with higher ARDS severity. It remains unclear whether these sicker patients would have benefited from the maintenance of SB. This treatment indication bias cannot be properly addressed apart from a randomized clinical study.

We believe further research using better markers of respiratory drive and effort is needed to address the question whether SB during MV is beneficial or harmful in patients with ARDS. Several techniques have been proposed, including airway occlusion pressure (P0.1), esophageal manometry, diaphragm electrical activity, or diaphragm ultrasound (33, 34). An adequately powered prospective randomized clinical trial should be conducted to compare controlled MV with PSV in patients

with ARDS, stratified by severity and adjusting for all potential severity confounders.

In conclusion, in a large cohort of patients with ARDS, SB during MV on the first 2 days was apparent in more than half of patients and was associated with increased VFDs and shorter ICU stay in adjusted analysis, without an effect on hospital mortality. Although these results support the use of SB in patients with ARDS independent of ARDS severity, the use of controlled ventilation indicates a bias toward use in patients with higher disease severity, and further analysis of our nonrandomized cohort is not able to address the potential intrinsic benefits or harms of SB during MV of ARDS patients.

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