Original Article

Effect of spontaneous breathing on ventilator-free days in critically ill patients—an analysis of patients in a large observational cohort

Aline Mela Dos Reis[1], Thais Dias Midega[1], Rodrigo Octavio Deliberato[1,2], Alistair EW Johnson[3], Lucas Bulgarelli[2,3], Thiago Domingos Correa[1], Leo Anthony Celi[3,4], Paolo Pelosi[5,6], Marcelo Gama de Abreu[7], Marcus J. Schultz[8,9,10], Ary Serpa Neto[1,8,11,12]; for the PROVE Network investigators*

[1]Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil; [2]Big Data Analytics Group, Hospital Israelita Albert Einstein, São Paulo, Brazil; [3]Laboratory for Computational Physiology, Institute for Medical Engineering & Science, MIT, Cambridge, MA, USA; [4]Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; [5]IRCCS San Martino Policlinico Hospital, Genoa, Italy; [6]Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy; [7]Pulmonary Engineering Group, Department of Anesthesiology and Intensive Care Medicine, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany; [8]Department of Intensive Care & 'Laboratory of Experimental Intensive Care and Anesthesiology' (L·E·I·C·A), Academic Medical Center, Amsterdam, The Netherlands; [9]Mahidol-Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [10]Nuffield Department of Medicine, University of Oxford, Oxford, UK; [11]Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia; [12]Data Analytics Research & Evaluation (DARE) Centre, Austin Hospital and University of Melbourne, Melbourne, Australia

Contributions: (I) Conception and design: AMD Reis, A Serpa Neto; (II) Administrative support: A Serpa Neto, LA Celi, M Gama de Abreu, P Pelosi, MJ Schultz; (III) Provision of study materials or patients: AMD Reis, RO Deliberato, AEW Johnson, L Bulgarelli, LA Celi; (IV) Collection and assembly of data: AMD Reis, RO Deliberato, AEW Johnson, L Bulgarelli, LA Celi; (V) Data analysis and interpretation: AMD Reis, TD Midega, A Serpa Neto; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ary Serpa Neto, MD, MSc, PhD. Australian and New Zealand Intensive Care Research Centre, Monash University, Level 3, 553 St. Kilda Rd., Melbourne, VIC 3004, Australia. Email: ary.serpaneto@monash.edu.

Background: Mechanical ventilation can injure lung tissue and respiratory muscles. The aim of the present study is to assess the effect of the amount of spontaneous breathing during mechanical ventilation on patient outcomes.

Methods: This is an analysis of the database of the 'Medical Information Mart for Intensive Care (MIMIC)'-III, considering intensive care units (ICUs) of the Beth Israel Deaconess Medical Center (BIDMC), Boston, MA. Adult patients who received invasive ventilation for at least 48 hours were included. Patients were categorized according to the amount of spontaneous breathing, i.e., ≥50% ('high spontaneous breathing') and <50% ('low spontaneous breathing') of time during first 48 hours of ventilation. The primary outcome was the number of ventilator-free days.

Results: In total, the analysis included 3,380 patients; 70.2% were classified as 'high spontaneous breathing', and 29.8% as 'low spontaneous breathing'. Patients in the 'high spontaneous breathing' group were older, had more comorbidities, and lower severity scores. In adjusted analysis, the amount of spontaneous breathing was not associated with the number of ventilator-free days [20.0 (0.0–24.2) *vs.* 19.0 (0.0–23.7) in high *vs.* low; absolute difference, 0.54 (95% CI, –0.10 to 1.19); P=0.101]. However, 'high spontaneous breathing' was associated with shorter duration of ventilation in survivors [6.5 (3.6 to 12.2) *vs.* 7.6 (4.1 to 13.9); absolute difference, –0.91 (95% CI, –1.80 to –0.02); P=0.046].

Conclusions: In patients surviving and receiving ventilation for at least 48 hours, the amount of spontaneous breathing during this period was not associated with an increased number of ventilator-free days.

Keywords: Mechanical ventilation; tidal volume; spontaneous breathing; acute respiratory distress syndrome

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(ARDS); positive end-expiratory pressure (PEEP); ventilator-induced lung injury

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Introduction

Mechanical ventilation has a strong potential to harm lung tissue and respiratory muscles. Prevention of lung injury translates to improved survival, shorter need for mechanical ventilation, and reduced length of stay in the intensive care unit (ICU) and hospital (1-3). One proven effective measure against ventilator-induced lung injury is the use of an adequately-sized, i.e., low tidal volume (V_T) (4-6). Maintaining respiratory muscle activity may prevent ventilator-induced diaphragm dysfunction (1,7).

There is a clear trend towards a preference for assisted over controlled modes of ventilation. Use of assisted ventilation which allows spontaneous breaths may not only reduce the risk of lung injury by additional recruitment of non-aerated areas, but also keeps a patient's diaphragm active (2,8,9). However, assisted ventilation may also result in high inspiratory efforts and a higher respiratory drive, which can potentially increase lung injury (10). Thus, it remains uncertain whether increased use of spontaneous breathing translates into clinical benefit. The results of a recent post-hoc analysis of a large observational study in acute respiratory distress syndrome (ARDS) patients suggests that spontaneous breathing in the first days of ventilation does not impact survival but hastens liberation from the ventilator (9).

To gain a better understanding of the effect of the amount of spontaneous breathing on outcome in critically ill patients who received mechanical ventilation for various reasons, the 'Medical Information Mart for Intensive Care (MIMIC)'-III was analyzed. The primary hypothesis tested was that the amount of spontaneous breathing is associated with an increased number of ventilator-free days at day 28 in patients surviving and receiving mechanical ventilation for at least 48 hours. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7901).

Methods

Study design and ethical concerns

This is a retrospective analysis of the MIMIC-III database that contains high-resolution clinical data from patients admitted to the ICUs of the Beth Israel Deaconess Medical Center (BIDMC), Boston, MA (11,12). The data in MIMIC-III has been previously de-identified, and the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review boards of the Massachusetts Institute of Technology (No. 0403000206) and Beth Israel Deaconess Medical Center (2001-P-001699/14). Due to the study's retrospective nature, the requirement for individual consent was waived.

Inclusion and exclusion criteria

Patients in the MIMIC-III version v1.4 database were selected for the current analysis if: (I) age ≥16 years; and (II) they received mechanical ventilation for at least 48 consecutive hours. Patients who received ventilation through a tracheostomy cannula at any time during the first 48 hours of ventilation. Only data of the first ICU admission of the first hospitalization were included. Patients transferred from other hospitals were considered only when mechanical ventilation started in the final hospital.

Data extraction and preparation

The dataset was assessed for completeness and consistency; outliers, defined as observations that lied outside 1.5× interquartile range (IQR), were checked and substituted by the 5th or 95th percentile (13). Ventilatory variables were extracted as the highest and the lowest values per each time-frame of six hours during the first 48 hours of ventilation. These values were summarized as the mean for every 6-hour time window.

The ventilation modes were extracted per each time-frame of six hours during the first 48 hours of ventilation. The classification of the ventilation modes that was used for the longest time in each time-frame follows the categorization in previous studies (14,15), as follows:

- Modes mandating spontaneous breathing: in these modes spontaneous breathing is always required,

i.e., the ventilator will never provide a breath when the patient does not trigger the ventilator [e.g., 'continuous positive airway pressure' (CPAP), 'proportional assisted ventilation' (PAV) or 'pressure support ventilation' (PSV)]; and

- Modes allowing spontaneous breathing: spontaneous breathing is possible, but when the patient does not trigger the ventilator, only controlled breaths will be delivered [e.g., 'pressure-controlled ventilation' (PCV) or 'volume-controlled ventilation' (VCV)].

For details, see Tables S1,S2.

Definitions

For every 6 hours during the first 48 hours of ventilation, it was defined whether a patient was spontaneous breathing, as follows:

- A patient was considered not to have spontaneous breathing if set respiratory rate (RR) equaled the total RR, and
- A patient was considered to have spontaneous breathing if receiving a ventilation mode mandating spontaneous breathing, or if set RR was lower than the total RR.

Then each patient was classified as follows:

- Breathing spontaneously for equal or more than 50% of the time (high spontaneous breathing' patients), if the proportion of time with spontaneous breathing was ≥50% in the first 48 hours of ventilation; and
- Breathing spontaneous for less than 50% of the time ('low spontaneous breathing' patients), if the proportion of time with spontaneous breathing was <50% in the first 48 hours of ventilation.

Outcomes

The primary outcome was the number of ventilator-free days, defined as the number of days from successfully weaning to day 28; patients who died before weaning were deemed to have no ventilator-free days. Secondary outcomes included duration of ventilation in survivors, ICU-, hospital and 30-day mortality, and ICU- and hospital length of stay.

Power calculation

No formal sample size calculation was carried out, and all patients included in the current version of the dataset were eligible for inclusion.

Statistical analysis

Only complete case analysis was carried out and no assumption for missing data was done. All patients were followed until hospital discharge or death. Continuous variables are presented as medians with their interquartile ranges and categorical variables as total number and percentage. Proportions were compared using χ^2 or Fisher exact tests and continuous variables were compared using the *t* test or Wilcoxon rank sum test, as appropriate.

V_T size was collected as an absolute volume (mL) and then normalized for predicted body weight (mL/kg PBW). The PBW was calculated as equal to 50+0.91 (centimeters of height 152.4) in males, and 45.5+0.91 (centimeters of height 152.4) in females (16). Presence of the acute respiratory distress syndrome (ARDS) in the first 48 hours of ventilation was scored according to current definition for ARDS, the Berlin Definition, which means that all patients had to be reclassified when previous definitions or criteria were used (17).

All main analyses were performed using mixed-effect models to account for within-year clustering. Heterogeneity between years was determined by fitting a fixed interaction term between the variable of interest and year of admission as continuous variable, while overall effect of the comparison of 'high spontaneous breathing' with 'low spontaneous breathing' patients was reported with year of admission treat as a random effect.

In a first assessment, group assignment ('high spontaneous breathing' *vs.* 'low spontaneous breathing') was entered in a mixed-effect multivariable model adjusted for relevant covariates known to predict outcome (description in the Supplementary File). The variable of interest was forced in the models as it were the main focus of the study.

As the use and the effect of spontaneous breathing could vary according to baseline characteristics and severity of the patients, the following subgroups were assessed: (I) ARDS *vs.* non-ARDS in the first 48 h; (II) low tidal volume ventilation (LTVV) *vs.* non-LTVV, with LTTV defined as a median tidal volume ≤8 mL/kg PBW in the first 48 hours of ventilation; and (III) baseline PaO_2/FiO_2 ≤250 *vs.* PaO_2/FiO_2 >250. To determine if the relationship between group and the primary outcome differs between the subgroups, fixed interaction terms between treatment and subgroup were added in the adjusted models for the primary outcome described above. To further ascertain if the treatment-

subgroup interaction varied between the year of admission, a three-way fixed interaction between year, treatment and subgroup were also reported.

To address heterogeneity of treatment effect, the models described above were re-assessed in two groups using stricter definitions, as follows:

- exclusively breathing spontaneously ('always spontaneous breathing' patients), if the proportion of time with spontaneous breathing was 100% in the first 48 hours of ventilation; and
- never breathing spontaneous ('never spontaneous breathing' patients), if the proportion of time with spontaneous breathing was 0% in the first 48 hours of ventilation.

Statistical significance was considered to be at two-sided P<0.05. All analyses were performed with R v.3.6.0 (www.R-project.org).

Results

Patients

From 2001 until 2012, 3,380 patients were selected for the current analysis, 2,374 (70%) were classified as 'high spontaneous breathing' patients, and 1,006 (30%) as 'low spontaneous breathing' patients (Figure S1). Baseline characteristics are shown in *Table 1* and Table S3. 'High spontaneous breathing' patients were older, had more comorbidities, lower SOFA scores and less often needing vasopressors. Ventilation data are presented in *Table 2*, *Figure 1*, and Figure S2. In the first two days of ventilation, V_T was similar while PEEP, peak pressure and driving pressure were lower in 'high spontaneous breathing' patients.

The primary endpoint

Clinical outcomes are presented in *Table 3* and Table S4. Both in unadjusted and adjusted analysis, the number of ventilator-free days was not different between the two groups {20.0 (0.0 to 24.2) *vs.* 19.0 (0.0 to 23.7) in 'high spontaneous breathing' *vs.* 'low spontaneous breathing' patients, respectively; absolute difference, 0.19 [95% confidence interval (CI), –0.59 to 0.97]; P=0.635, and 20.0 (0.0 to 24.2) *vs.* 19.0 (0.0 to 23.7); absolute difference, 0.54 (95% CI, –0.10 to 1.19); P=0.101}.

Secondary endpoints

In unadjusted analysis, 'high spontaneous breathing' patients had a shorter duration of ventilation and a shorter ICU length of stay. In the adjusted analysis, only duration of ventilation remained lower in 'high spontaneous breathing' patients.

Subgroup analyses

Results of the subgroup analyses are present in Figure S3. There was no interaction among any of the subgroups and 'high spontaneous breathing' patients.

Additional analysis

Of all patients available, 1,809 (53.5%) were classified as 'always spontaneous breathing' patients, and 755 (22.3%) as 'never spontaneous breathing' patients. Baseline characteristics, vital signs and laboratory tests, and ventilation data in 'always spontaneous breathing' patients and 'never spontaneous breathing' patients are shown in Tables S5-S7, and Figures S4,S5.

In unadjusted analysis, ICU length of stay was different between 'always spontaneous breathing' patients and 'never spontaneous breathing' patients (Table S8). In the adjusted analysis, ventilator-free days was higher in 'always spontaneous breathing' patients (Table S9).

Discussion

The results of this retrospective analysis of the database of a large cohort of mechanically ventilated ICU patients surviving and receiving ventilation for at least 48 hours can be summarized as follows: (I) many patients breath spontaneously for more than 50% of the time within the first 48 hours of invasive ventilation; (II) the proportion of spontaneous breathing in the first 48 hours is not associated with the number of ventilator-free days when one compares high *vs.* low spontaneous breathing; (III) but this proportion is associated with a shorter duration of ventilation among survivors. In addition, (IV) 'always spontaneous breathing' is associated with more ventilator-free days.

The main strength of this analysis is the comprehensive and high-resolution data capture throughout the hospital course of a large group of well-defined and characterized ICU patients. By excluding patients who were breathing through a tracheostomy in the first 48 hours, we avoided the inclusion of patients receiving long-term mechanical ventilation prior to the hospitalization, and those expecting to receive long-term mechanical ventilation (e.g., patients

Table 1 Baseline characteristics of the included patients according to the groups

	High spontaneous breathing (n=2,374)	Low spontaneous breathing (n=1,006)	P value
Age, years	66.6 [52.9–77.8]	61.7 [47.3–74.6]	<0.001
Male gender	1,306 (55.0)	594 (59.0)	0.034
Weight, kg	78.2 [66.0–94.6]	81.0 [67.8–97.8]	0.001
Height, cm	170 [163–178]	173 [163–178]	0.009
Body mass index, kg/m^2	27.4 [23.9–32.3]	28.3 [24.2–33.2]	0.015
Predicted body weight, kg	63.9 [54.7–73.1]	66.2 [56.9–73.1]	0.008
Admission type			0.334
Surgical elective	172 (7.2)	78 (7.8)	
Surgical urgency	100 (4.2)	32 (3.2)	
Clinical	2,102 (88.5)	896 (89.1)	
Source of admission			0.032
Emergency room	1,173 (49.4)	520 (51.7)	
Office or operating room	244 (10.3)	104 (10.3)	
Ward or step-down unit	326 (13.7)	162 (16.1)	
Transferred from other hospital	611 (25.7)	217 (21.6)	
Other	20 (0.9)	3 (0.3)	
Initial diagnosis			<0.001
Sepsis (including pneumonia)	519 (21.9)	177 (17.6)	
Cardiovascular disease	504 (21.2)	279 (27.7)	
Other respiratory condition	369 (15.5)	133 (13.2)	
Neurological condition	453 (19.1)	199 (19.8)	
Renal condition	31 (1.3)	6 (0.6)	
Other	498 (21.0)	212 (21.1)	
COPD	137 (5.8)	53 (5.3)	0.618
Smoking	1,130 (48.2)	475 (48.6)	0.147
Elixhauser comorbidity score	6 [2–12]	5 [0–11]	0.004
Support in the first 24 hours			
Vasopressor	1,104 (46.5)	586 (58.3)	<0.001
Renal replacement therapy	123 (5.2)	45 (4.5)	0.436
Limitation of support	584 (26.3)	201 (21.3)	0.003
Severity of illness			
SAPS II	42 [33–53]	43 [32–55]	0.869
OASIS	38 [33–44]	37 [32–43]	<0.001
SOFA	6 [4–9]	7 [4–9]	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

	High spontaneous breathing (n=2,374)	Low spontaneous breathing (n=1,006)	P value
Vital signs			
SAS	3.0 [2.8–3.4]	3.0 [2.3–3.3]	<0.001
Heart rate, bpm	92 [80–104]	92 [80–103]	0.753
Mean arterial pressure, mmHg	80 [73–89]	81 [73–90]	0.257
SpO_2, %	96 [94–98]	96 [94–98]	0.021
Temperature, ℃	37.1 [36.6–37.7]	37.0 [36.4–37.4]	<0.001
Laboratory tests			
pH	7.38 [7.33–7.42]	7.36 [7.31–7.40]	<0.001
PaO_2/FiO_2	258 [185–361]	264 [186–367]	0.517
SpO_2/FiO_2	176 [140–209]	163 [137–197]	<0.001
$PaCO_2$, mmHg	39 [35–44]	40 [36–45]	0.003

Data are median [quartile 25%–quartile 75%] or No. (%). BMI, body mass index; PBW, predicted body weight; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; SAPS, Simplified Acute Physiology Score; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment; bpm, beats per minute.

with neurological or neuromuscular disease). Also, the analysis leverages the availability of time–stamped vital signs, laboratory test results, and ventilatory parameters. This is the first clinical study addressing spontaneous breathing during mechanical ventilation in critically ill patients with this level of resolution and granularity of the data. Instead of defining the type of ventilation according to one single assessment per day, as in the majority of the studies (9), in the present investigation, this was assessed for every 6 hour-time windows, increasing the power of the study and avoiding surveillance bias. Also, the 48-hour time-interval inclusion criterion guaranteed that all patients were exposed to mechanical ventilation for a sufficient period of time. Finally, all results considered the effect of time using mixed-effect models with year of admission in the ICU as random effect. Indeed, this is important since distinct ventilation practices were applied over time.

The finding of this investigation mirror, at least in part, the analysis of the LUNG SAFE study (9) that showed spontaneous breathing to be associated with shorter duration of mechanical ventilation and ICU length stay in patients with ARDS. Our findings are also in agreement with results from studies of airway pressure release ventilation (APRV), a ventilation mode that allows spontaneous breathing, on patients with ARDS (3). Indeed, use of APRV was associated with shorter duration of ventilation and ICU length of stay. However, bias may have been introduced in these analyses, since spontaneous breathing was used more often in less sick patients.

In previous observational studies, bias may have been introduced in the analysis from confounding by indication, since spontaneous breathing is usually used more often in less sick patients. In addition, the classification of patients was based on one single observation point per each ventilation day (9). Of note, confounding by indication may not have been fully addressed by our analysis despite adjustment. But categorizing patients according to presence of spontaneous breathing at eight time–frames in the first 48 hours, surveillance bias was mitigated, at least more than in previous studies.

The potential benefits of the use of spontaneous breathing in patients receiving mechanical ventilation should be interpreted with caution. First, ventilator dyssynchronies are common, and its occurrence could increase with spontaneous breathing, and are associated with worse outcomes (18,19). Also, previous studies in ARDS patients suggest that the effect of spontaneous breathing depends on the etiology and severity, with risk of harm proportional to ARDS severity (9,20,21). An appropriate assessment of respiratory drive and inspiratory efforts is important when assessing the potential benefits of spontaneous breathing, and should be encouraged at

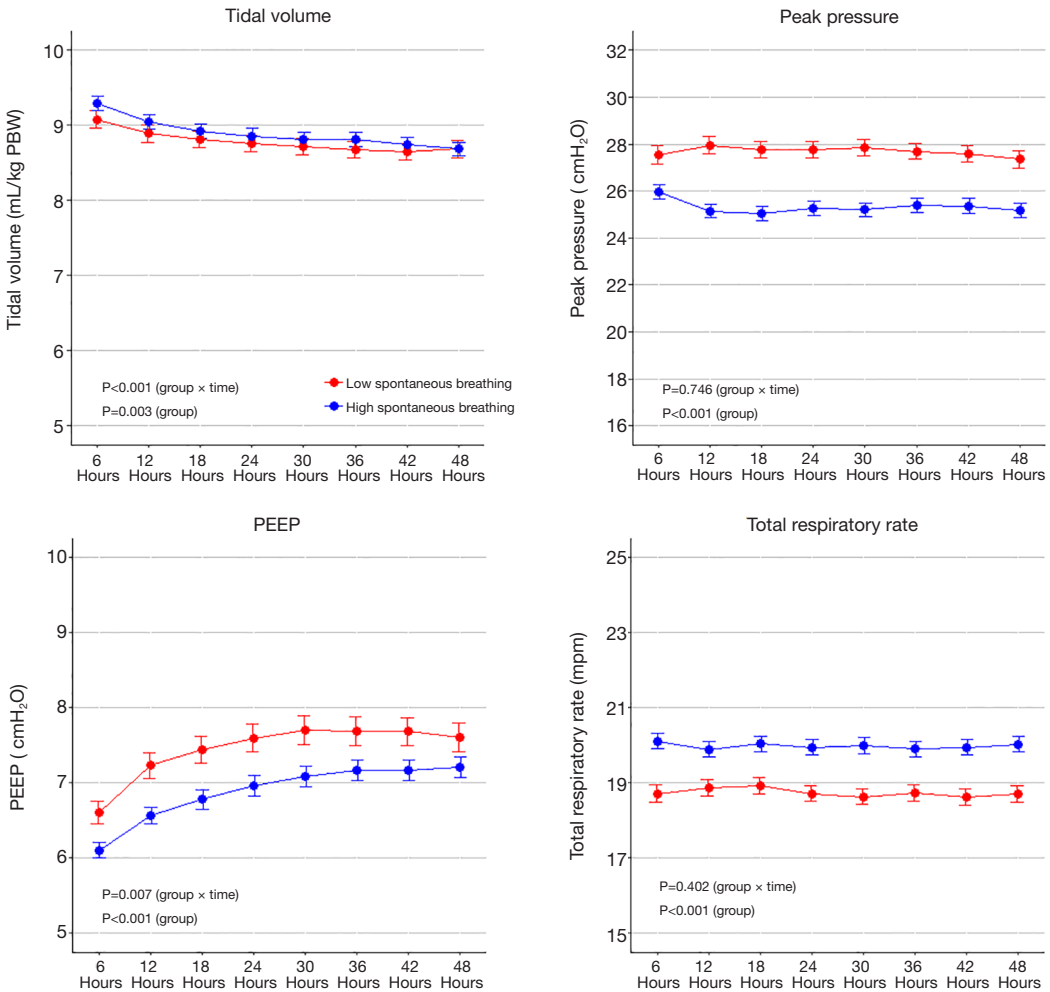

Figure 1 Measurements of ventilatory parameters every 6 hours for the first 48 hours of ventilation. Circles and bars are mean and 95% confidence interval. Mixed-effect longitudinal models with random intercept for patients and with group, time and the interaction of group × time as fixed effects. P values for the group reflect the overall test for difference between groups across the 48 hours while P values for the group × time interaction evaluate if change over time differed by group.

bedside (10). Measurements like airway occluding pressures, esophageal manometry, diaphragm electrical activity and even occlusion holds during PSV, are optimal to determine if harm arises from the spontaneous breaths (22-25). It is important to emphasize that in the present study the presence of inspiratory effort was not assessed and the presence of spontaneous activity was based in the mode of ventilation and respiratory rate. However, to the date this is a widely used approach to detect spontaneous breathing in observational studies (9,26,27).

In the present analysis, the V_T size was similar in patients with 'high spontaneous breathing' and those with 'low spontaneous breathing'. However, plateau and peak pressure, and PEEP were significantly lower in the group with 'high spontaneous breathing'. It is important to note that patients in the 'high spontaneous breathing' were more often ventilated with PSV, thus, the lower peak pressure can be due to the ventilatory mode and not only due to other respiratory factors, like the severity of the disease. The finding of a similar V_T size between the two groups is important, since a large V_T during spontaneous breathing may indicate a high inspiratory effort potentially increasing lung injury (9). However, in the presence of lower airway pressures, as in this analysis, even a larger V_T size may be acceptable when there are no other signs of increased inspiratory efforts, since it may just represent a more

Table 2 Ventilatory characteristics of the patients included

	High spontaneous breathing (n=2,374)	Low spontaneous breathing (n=1,006)	Absolute difference*** (95% confidence interval)	P value
Percentage of spontaneous breathing	100 [100–100]	0 [0–0]	83.88 (82.71 to 85.07)	< 0.001
First day of ventilation				
Ventilator mode				
Assisted controlled	1,308 (38.7)	553 (16.4)		<0.001
Pressure-regulated volume control	608 (18.0)	315 (9.3)		
Pressure support ventilation	149 (4.4)	0 (0.0)		
Synchronized intermittent mandatory ventilation	298 (8.8)	133 (3.9)		
Other	11 (0.3)	5 (0.1)		
Tidal volume, mL/kg PBW	8.8 [7.8–10.0]	8.8 [7.9–10.0]	0.03 (–0.11 to 0.17)	0.685
PEEP, cmH_2O	5 [5–7]	6 [5–9]	–0.58 (–0.76 to –0.41)	<0.001
Peak pressure, cmH_2O	25 [21–29]	28 [24–32]	–2.85 (–3.25 to –2.44)	<0.001
Driving pressure, cmH_2O*	14 [11–17]	15 [12–17]	–0.71 (–0.99 to –0.43)	<0.001
Number of patients with P_{plat} available	2,293 (96.5)	1,002 (99.6)	–	–
Respiratory rate, mpm	20 [18–23]	19 [17–21]	1.55 (1.17 to 1.93)	<0.001
Mechanical power, J/min**	23.5 [17.8–30.8]	23.9 [18.4–31.2]	–0.33 (–1.16 to 0.51)	0.443
Minute ventilation, L/min	12.0 [10.1–14.2]	11.1 [9.6–12.9]	0.89 (0.62 to 1.17)	<0.001
FiO_2, %	55 [45–70]	60 [50–70]	–1.87 (–2.73 to –1.02)	<0.001
Second day of ventilation				
Ventilator mode				
Assisted controlled	1,175 (34.8)	550 (16.3)		<0.001
Pressure-regulated volume control	558 (16.5)	318 (9.4)		
Pressure support ventilation	338 (10.0)	5 (0.1)		
Synchronized intermittent mandatory ventilation	270 (8.0)	131 (3.9)		
Other	33 (1.0)	2 (0.0)		
Tidal volume, mL/kg PBW	8.6 [7.6–9.7]	8.6 [7.6–9.6]	0.01 (–0.12 to 0.15)	0.869
PEEP, cmH_2O	5 [5–9]	6 [5–10]	–0.75 (–0.97 to –0.52)	<0.001
Peak pressure, cmH_2O	25 [20–29]	28 [23–32]	–2.81 (–3.23 to –2.40)	<0.001
Driving pressure, cmH_2O*	13 [11–16]	14 [11–16]	–0.50 (–0.78 to –0.23)	<0.001
Number of patients with P_{plat} available	2,330 (98.1)	1,005 (99.9)	–	–
Respiratory rate, mpm	20 [17–23]	18 [16–21]	1.58 (1.25 to 1.92)	<0.001
Mechanical power, J/min**	21.2 [15.9–28.0]	21 [16.3–27.6]	0.13 (–0.52 to 0.79)	0.693
Minute ventilation, L/min	11.2 [9.4–13.4]	10.2 [8.6–12.2]	1.00 (0.78 to 1.22)	<0.001
FiO_2, %	45 [40–50]	45 [40–55]	–0.89 (–1.67 to –0.12)	0.025

Data are median [quartile 25%–quartile 75%]. *calculated when plateau pressure is available and as plateau pressure – PEEP; ** calculated when plateau pressure is available and as: 0.098× tidal volume × respiratory rate × (peak pressure – driving pressure/2); ***mean difference from a univariable mixed-effect linear model with year as random effect. PEEP, positive end-expiratory pressure; FiO_2, inspired fraction of oxygen.

Table 3 Adjusted analyses for the primary and secondary outcomes

	High spontaneous breathing (n=2,374)	Low spontaneous breathing (n=1,006)	Absolute difference*,** (95% confidence interval)	P value
Ventilator-free days at day 28	20.0 (0.0–24.2)	19.0 (0.00–23.7)	0.54 (–0.10 to 1.19)[a]	0.101
Duration of ventilation in survivors, days	6.5 (3.6–12.2)	7.6 (4.1–13.9)	–0.91 (–1.80 to –0.02)[a]	0.046
ICU length of stay, days	9.5 (5.8–15.7)	10.0 (6.0–17.1)	–0.67 (–1.49 to 0.15)[a]	0.110
Hospital length of stay, days	15.4 (9.6–24.2)	15.8 (9.3–25.3)	–0.26 (–1.47 to 0.95)[a]	0.672
ICU mortality	598 (25.2)	246 (24.5)	–0.43 (–3.09 to 2.23)[b]	0.751
Hospital mortality	712 (30.0)	281 (27.9)	–0.17 (–2.85 to 2.49)[b]	0.903
30-day mortality	696 (29.3)	280 (27.8)	–0.38 (–3.10 to 2.33)[b]	0.786

Data are median (quartile 25%–quartile 75%) or No. (%). *absolute difference from a multivariable mixed = effect linear model with year as random effect and adjusted for: age, gender, weight, initial diagnosis, Elixhauser comorbidity score, use of vasopressor in the first day, limitation of support, SAPS II, OASIS, SOFA at day 1, heart rate at day 1 and 2, mean arterial pressure at day 1 and 2, and SpO_2/FiO_2 at day 1 and 2. **continuous variables were standardized before inclusion to improve convergence. [a]effect estimate is mean difference; [b]effect estimate is risk ratio. ICU, intensive care unit.

compliant respiratory system (28).

Limitations

The observational retrospective nature of the study should be considered when interpreting the findings. Residual confounding is always a concern despite appropriate modeling and sensitivity analyses. The data was extracted from a single–center which may limit generalizability. Only patients who survived and received invasive ventilation for at least 48 hours were included, aiming to select more severely ill patients and also those who had been exposed to the primary exposure of interest for a sufficient period of time. However, the results cannot be applied to patients who were extubated or died within 48 hours of ICU admission. Total RR was compared with set RR to determine whether patients had spontaneous breathing. Nevertheless, it cannot be ascertained that patients whose total and set rate did not have spontaneous breathing. Also, the exposure assessed was dependent on the patient clinical condition over time, and this should be considered when interpreting the results. In addition, since the dataset used in this study is for clinical purposes and the present analysis is a secondary analysis of these data, we cannot guarantee that plateau pressure and other ventilatory variables were collected under standard conditions. Finally, the observation that patients with no spontaneous breathing were sicker may reflect a systematic bias toward the use of controlled ventilation in patients with higher severity.

Conclusions

In conclusion, in this analysis of a large ICU dataset of high resolution, in critically ill patients surviving and receiving ventilation for at least 48 hours, the amount of spontaneous breathing during this period was not associated with an increased number of ventilator-free days at day 28. This finding was not different for the various subgroups However, the amount of spontaneous breathing was associated with duration of mechanical ventilation among survivors, and the number of ventilator-free days at day 28 was higher in 'always spontaneous breathing' patients compared to 'never spontaneous breathing' patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (No. 0403000206) and individual consent for this retrospective analysis was waived.

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Additional methods

Characteristics of the study dataset

The data were prospectively collected and stored in two different databases. The Medical Information Mart for Intensive Care III database (MIMIC-III v1.4), is a freely accessible and conveniently-sized database that contains high resolution information from hospital monitoring systems (including laboratory data, medication, and hospital administrative data) and bedside monitoring systems (vital signs, caregivers notes, radiology reports). This database is hosted by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology (MIT) and contains data for over 50,000 de-identified patient admissions to ICUs at the BIDMC from 2001 to 2012. We used the MIMIC Code Repository to define many concepts in MIMIC-III.

Ethical approval

The Institutional Review Board of the Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (No. 0403000206) approved use of the MIMIC database.

Statistical analyses

Relevant covariates known to predict outcome were entered into the multivariable model if a p value less than 0.1 was found in the univariable model and when the percentage of missing was less than 10%. In the adjusted models for the comparison of the groups (high *vs.* low spontaneous breathing and always *vs.* never spontaneous breathing), relevant covariates known to predict outcome were included, not considering variables with more than 10% of missing. In addition, ventilatory variables were not included in the model, since they are closely related to the types of ventilation studied and could mediate the relationship between them and outcomes. At the end, the following variables were considered: age, gender, weight, initial diagnosis, Elixhauser comorbidity score, use of vasopressor in the first day, limitation of support, SAPS II, OASIS, SOFA at day 1, heart rate at day 1 and 2, mean arterial pressure at day 1 and 2, and SpO_2/FiO_2 at day 1 and 2. All continuous variables were standardized before inclusion in the models to improve convergence. The use of neuromuscular blocking agents was not considered in the models due to its highly correlation with the variable of interest (spontaneous breathing).

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Table S1 Classification of ventilation modes in the MIMIC-III dataset

Original Classification	Re–classification	Mode Mandating Spontaneous Breathing
APRV	Airway Pressure Release Ventilation (APRV)	No
APRV/Biphasic+ApnVol	Airway Pressure Release Ventilation (APRV)	No
Assist Control	Assist Control	No
CMV	Continuous Mandatory Ventilation	No
CMV/ASSIST	Continuous Mandatory Ventilation	No
CMV/ASSIST/AutoFlow	Pressure Regulated Volume Control (PRVC)	No
CMV/AutoFlow	Pressure Regulated Volume Control (PRVC)	No
CPAP	Continuous Positive Airway Pressure (CPAP)	Yes
CPAP/PPS	Proportional Assist Ventilation (PAV)	Yes
CPAP/PSV	Pressure Support Ventilation (PSV)	Yes
CPAP/PSV+Apn TCPL	Pressure Support Ventilation (PSV)	Yes
CPAP/PSV+ApnPres	Pressure Support Ventilation (PSV)	Yes
CPAP/PSV+ApnVol	Pressure Support Ventilation (PSV)	Yes
CPAP+PS	Pressure Support Ventilation (PSV)	Yes
MMV	Mandatory Minute Ventilation (MMV)	No
MMV/AutoFlow	Mandatory Minute Ventilation (MMV)	No
MMV/PSV	Mandatory Minute Ventilation–PSV (MMV–PSV)	No
MMV/PSV/AutoFlow	Mandatory Minute Ventilation–PSV (MMV–PSV)	No
Other/Remarks	Other	No
PCV+	Pressure Control	No
PCV+/PSV	Pressure Control	No
PCV+Assist	Pressure Control	No
PRES/AC	Pressure Control	No
Pressure Control	Pressure Control	No
Pressure Support	Pressure Support Ventilation (PSV)	Yes
PRVC/AC	Pressure Regulated Volume Control (PRVC)	No
PSV/SBT	Pressure Support Ventilation (PSV)	Yes
SIMV	Synchronized Intermittent Mandatory Ventilation (SIMV)	No
SIMV/AutoFlow	Synchronized Intermittent Mandatory Ventilation (SIMV)	No
SIMV/PSV	Synchronized Intermittent Mandatory Ventilation (SIMV)	No
SIMV/PSV/AutoFlow	Synchronized Intermittent Mandatory Ventilation (SIMV)	No
SIMV+PS	Synchronized Intermittent Mandatory Ventilation (SIMV)	No
Standby	Other	No
SYNCHRON MASTER	Synchronized Intermittent Mandatory Ventilation (SIMV)	No
SYNCHRON SLAVE	Synchronized Intermittent Mandatory Ventilation (SIMV)	No
TCPCV	Pressure Control	No
VOL/AC	Volume Control	No

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Table S2 Example of how patients were categorized in the present study in the MIMIC–III when using an assist control mode

ID	Moment	Set Lowest RR	Total Lowest RR	Set Highest RR	Total Highest RR	SA	Percentage of SB
01	1	10	10	23	23	No	
01	2	9	9	25	25	No	
01	3	10	12	29	31	Yes	
01	4	13	13	25	28	Excluded	$\frac{N_M\ SB}{N_O} \therefore \left(\frac{3}{6}\right) \times 100 = 50\%$
01	5	12	14	22	25	Yes	
01	6	12	14	24	24	Excluded	
01	7	12	15	23	24	Yes	
01	8	10	10	21	21	No	
02	1	10	10	22	23	Excluded	
02	2	14	14	25	25	No	
02	3	17	17	28	28	No	
02	4	9	9	25	25	No	
02	5	11	11	24	24	No	$\frac{N_M\ SB}{N_O} \therefore \left(\frac{0}{7}\right) \times 100 = 00\%$
02	6	10	10	26	26	No	
02	7	11	11	29	29	No	
02	8	12	12	30	30	No	

ID: unique identificator; RR: respiratory rate; SB: spontaneous breathing; N_M SB: number of moments with spontaneous breathing; N_O: number of observations available.

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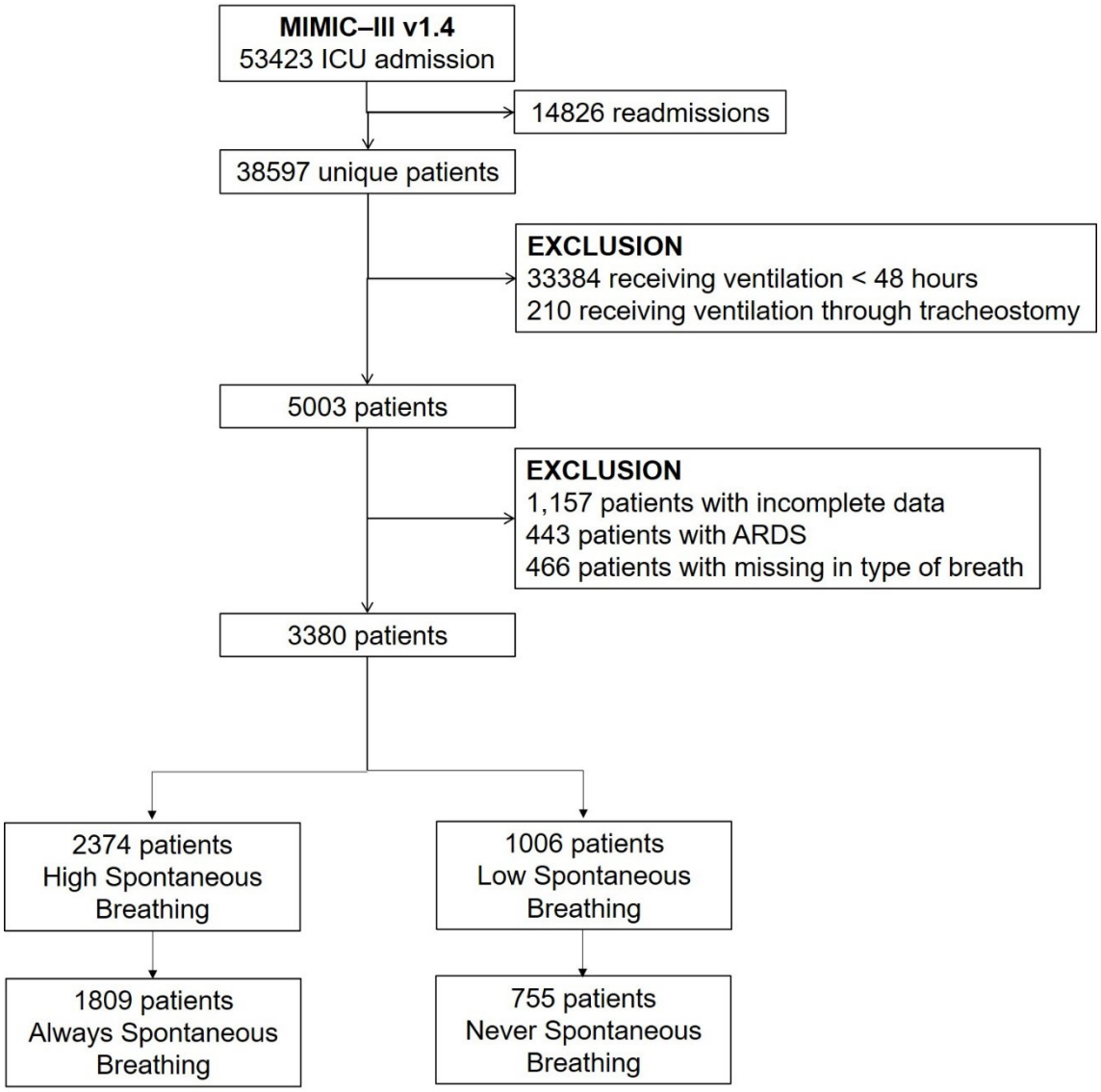

Figure S1 Flowchart of the study in the MIMIC-III dataset.

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Table S3 Vital signs and laboratory tests

	High Spontaneous Breathing (n=2374)	Low Spontaneous Breathing (n=1006)	Absolute Difference* (95% Confidence Interval)	P value
First day of ventilation				
SAS	3.0 (2.8–3.4)	3.0 (2.3–3.3)	0.26 (0.19 to 0.33)	< 0.001
Heart rate, bpm	92 (80–104)	92 (80–103)	0.18 (-0.96 to 1.33)	0.753
Mean arterial pressure, mmHg	80 (73–89)	81 (73–90)	-0.55 (-1.49 to 0.40)	0.257
SpO_2, %	96 (94–98)	96 (94–98)	0.31 (0.05 to 0.57)	0.021
Temperature, ºC	37.1 (36.6–37.7)	37.0 (36.4–37.4)	0.19 (0.14 to 0.25)	< 0.001
pH	7.38 (7.33–7.42)	7.36 (7.31–7.40)	0.02 (0.01 to 0.03)	< 0.001
PaO_2/FiO_2	258 (185–361)	264 (186–367)	-2.94 (-11.84 to 5.98)	0.517
SpO_2/FiO_2	176 (140–209)	163 (137–197)	6.81 (3.97 to 9.65)	< 0.001
$PaCO_2$, mmHg	39 (35–44)	40 (36–45)	-1.01 (-1.67 to -0.35)	0.003
Second day of ventilation				
SAS	3.1 (3.0–3.7)	3.0 (2.5–3.3)	0.31 (0.24 to 0.38)	< 0.001
Heart rate, bpm	90 (79–102)	89 (78–100)	1.45 (0.35 to 2.56)	0.010
Mean arterial pressure, mmHg	81 (73–90)	80 (73–90)	0.08 (-0.75 to 0.90)	0.856
SpO_2, %	97 (95–98)	97 (95–98)	-0.05 (-0.27 to 0.17)	0.648
Temperature, ºC	37.3 (36.8–37.8)	37.2 (36.7–37.7)	0.10 (0.06 to 0.15)	< 0.001
pH	7.40 (7.36–7.43)	7.41 (7.36–7.44)	-0.01 (-0.01 to 0.00)	0.019
PaO_2/FiO_2	247 (187–324)	243 (186–321)	1.62 (-5.19 to 8.46)	0.643
SpO_2/FiO_2	213 (184–244)	207 (176–244)	3.30 (0.17 to 6.44)	0.039
$PaCO_2$, mmHg	39 (34–44)	38 (34–42)	0.81 (0.19 to 1.42)	0.010

Data are median (quartile 25% - quartile 75%). SpO_2: pulse oximetry; SAS: sedation agitation scale. *mean difference from a univariable mixed-effect linear model with year as random effect.

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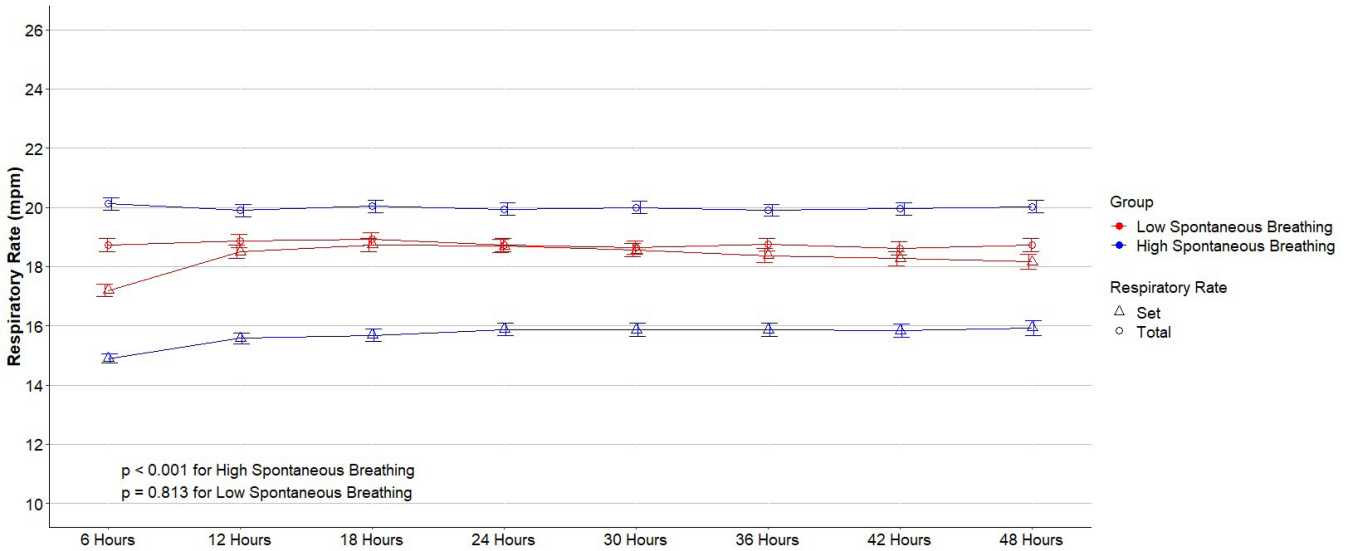

Figure S2 Comparison of set and total respiratory rate among groups. Symbols and bars are mean and 95% confidence interval. Mixed-effect longitudinal models with random intercept for patients and year of admission, and with group, time and the interaction of group x time as fixed effects. P values reported are for the group and reflect the overall test for difference between groups across the 48 hours.

Table S4 Unadjusted analyses for the primary and secondary outcomes

	High Spontaneous Breathing (n=2374)	Low Spontaneous Breathing (n=1006)	Absolute Difference* (95% Confidence Interval)	P value
Ventilator–free days at day 28	20.0 (0.0–24.2)	19.0 (0.00–23.7)	0.19 (-0.59 to 0.97)[a]	0.635
Duration of ventilation in survivors, days	6.5 (3.6–12.2)	7.6 (4.1–13.9)	-1.03 (-1.90 to -0.15)[a]	0.021
ICU length of stay, days	9.5 (5.8–15.7)	10.0 (6.0–17.1)	-0.80 (-1.57 to -0.02)[a]	0.043
Hospital length of stay, days	15.4 (9.6–24.2)	15.8 (9.3–25.3)	-0.81 (-1.97 to 0.35)[a]	0.170
ICU mortality	598 (25.2)	246 (24.5)	0.74 (-2.46 to 3.93)[b]	0.651
Hospital mortality	712 (30.0)	281 (27.9)	2.06 (-1.30 to 5.42)[b]	0.230
30–day mortality	696 (29.3)	280 (27.8)	1.48 (-1.86 to 4.83)[b]	0.384

Data are median (quartile 25% - quartile 75%) or N (percentage). ICU: intensive care unit; *absolute difference from a univariable mixed-effect linear model with year as random effect; [a]effect estimate is mean difference; [b]effect estimate is risk ratio.

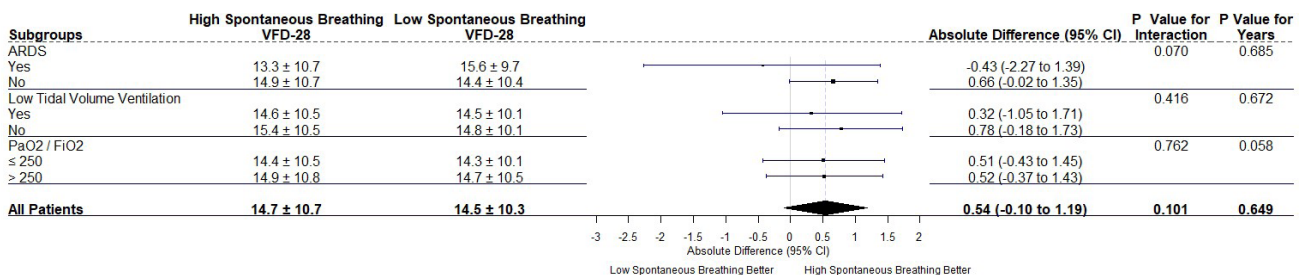

Figure S3 Subgroup analyses.

Table S5 Baseline characteristics of the included patients according to more strict groups

	Always Spontaneous Breathing (n=1809)	Never Spontaneous Breathing (n=755)	P value
Age, years	67.5 (54.0–78.3)	61.8 (47.3–74.9)	< 0.001
Male gender	977 (54.0)	454 (60.1)	0.005
Weight, kg	77.0 (65.5–92.8)	81.1 (68.3–98.6)	< 0.001
Height, cm	170 (164–177)	173 (163–178)	0.001
Body mass index, kg/m^2	27.3 (23.8–32.2)	28.3 (24.2–33.2)	0.011
Predicted body weight, kg	63.9 (54.7–73.1)	66.2 (56.9–73.1)	0.001
Admission type			0.032
Surgical elective	136 (7.5)	61 (8.1)	
Surgical urgency	89 (4.9)	20 (2.6)	
Clinical	1584 (87.6)	674 (89.3)	
Source of admission			0.024
Emergency room	881 (48.7)	383 (50.7)	
Office or operating room	195 (10.8)	81 (10.7)	
Ward or step-down unit	235 (13.0)	125 (16.6)	
Transferred from other hospital	482 (26.6)	163 (21.6)	
Other	16 (0.9)	3 (0.1)	
Initial diagnosis			< 0.001
Sepsis (including pneumonia)	404 (22.3)	132 (17.5)	
Cardiovascular disease	377 (20.8)	221 (29.3)	
Other respiratory condition	279 (15.4)	95 (12.6)	
Neurological condition	332 (18.4)	152 (20.1)	
Renal condition	27 (1.5)	1 (0.1)	
Other	390 (21.6)	154 (20.4)	
COPD	102 (5.6)	35 (4.6)	0.351
Smoking	857 (48.0)	344 (46.9)	0.018
Elixhauser comorbidity score	6 (2–12)	6 (0–11)	0.026
Support in the first 24 hours			
Vasopressor	818 (45.2)	444 (58.8)	< 0.001
Renal replacement therapy	99 (5.5)	35 (4.6)	0.441
Limitation of support	461 (27.2)	155 (22.0)	0.009
Severity of illness			
SAPS II	43 (34–53)	43 (33–55)	0.858
OASIS	38 (33–44)	37 (32–43)	0.001
SOFA	6 (4–8)	7 (4–9)	< 0.001

Data are median (quartile 25% - quartile 75%) or No (%). BMI: body mass index; PBW: predicted body weight; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; SAPS: Simplified Acute Physiology Score; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; bpm: beats per minute.

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Table S6 Vital signs and laboratory tests according to more strict groups

	Always Spontaneous Breathing (n=1809)	Never Spontaneous Breathing (n=755)	Absolute Difference* (95% Confidence Interval)	P value
First day of ventilation				
SAS	3.0 (2.9–3.4)	3.0 (2.2–3.2)	0.34 (0.26 to 0.42)	< 0.001
Heart rate, bpm	92 (81–104)	92 (79–104)	0.38 (-0.94 to 1.71)	0.573
Mean arterial pressure, mmHg	80 (73–89)	81 (73–90)	-0.81 (-1.91 to 0.29)	0.149
SpO_2, %	96 (94–98)	96 (94–98)	0.42 (0.11 to 0.73)	0.007
Temperature, ºC	37.2 (36.6–37.7)	36.9 (36.4–37.4)	0.24 (0.18 to 0.30)	< 0.001
pH	7.38 (7.33–7.42)	7.36 (7.31–7.40)	0.02 (0.02 to 0.03)	< 0.001
PaO_2/FiO_2	261 (186–366)	260 (184–366)	2.46 (-7.82 to 12.78)	0.640
SpO_2/FiO_2	178 (141–210)	161 (136–196)	9.66 (6.38 to 12.96)	< 0.001
$PaCO_2$, mmHg	39 (34–44)	40 (36–44)	-1.20 (-1.93 to -0.46)	0.001
Second day of ventilation				
SAS	3.1 (3.0–3.7)	3.0 (2.2–3.3)	0.39 (0.30 to 0.47)	< 0.001
Heart rate, bpm	90 (79–102)	89 (78–101)	1.28 (0.01 to 2.55)	0.048
Mean arterial pressure, mmHg	80 (73–90)	80 (73–89)	0.13 (-0.82 to 1.08)	0.786
SpO_2, %	97 (95–98)	97 (95–98)	-0.02 (-0.28 to 0.24)	0.888
Temperature, ºC	37.3 (36.9–37.8)	37.2 (36.7–37.7)	0.11 (0.06 to 0.17)	< 0.001
pH	7.40 (7.36–7.43)	7.41 (7.36–7.44)	-0.01 (-0.01 to 0.00)	0.057
PaO_2/FiO_2	247 (187–325)	238 (182–319)	4.12 (-3.76 to 12.04)	0.307
SpO_2/FiO_2	213 (184–244)	199 (175–242)	5.75 (2.12 to 9.40)	0.002
$PaCO_2$, mmHg	38 (34–44)	38 (34–42)	0.67 (-0.03 to 1.36)	0.060

Data are median (quartile 25% - quartile 75%). SpO_2: pulse oximetry; SAS: sedation agitation scale; * mean difference from a univariable mixed-effect linear model with year as random effect.

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Table S7 Ventilatory characteristics of the patients included according to more strict groups

	Always Spontaneous Breathing (n=1809)	Never Spontaneous Breathing (n=755)	Absolute Difference*** (95% Confidence Interval)	P value
Percentage of spontaneous breathing	100 (100–100)	0 (0–0)	–	–
First day of ventilation				
Tidal volume, ml/kg PBW	8.9 (7.9–10.1)	8.8 (7.9–10.0)	0.09 (-0.07 to 0.25)	0.249
PEEP, cmH_2O	5 (5–7)	6 (5–10)	-0.87 (-1.07 to -0.68)	<0.001
Peak pressure, cmH_2O	24 (20–29)	28 (24–33)	-3.59 (-4.06 to -3.13)	<0.001
Driving pressure, cmH_2O*	14 (11–17)	15 (12–17)	-0.89 (-1.22 to -0.56)	<0.001
Respiratory rate, mpm	20 (18–24)	19 (17–21)	1.76 (1.35 to 2.17)	<0.001
Mechanical power, J/min**	23.3 (17.6–30.6)	24.1 (18.5–31.5)	-0.85 (-1.78 to 0.09)	0.076
Minute ventilation, L/min	12.1 (10.2–14.3)	11.1 (9.6–12.8)	1.00 (0.70 to 1.31)	<0.001
FiO_2, %	55 (45–70)	60 (50–70)	-2.69 (-3.68 to -1.70)	<0.001
Second day of ventilation				
Tidal volume, ml/kg PBW	8.7 (7.6–9.8)	8.6 (7.6–9.6)	0.03 (-0.12 to 0.19)	0.651
PEEP, cmH_2O	5 (5–8)	7 (5–10)	-1.07 (-1.33 to -0.81)	<0.001
Peak pressure, cmH_2O	24 (20–29)	28 (24–32)	-3.48 (-3.96 to -3.00)	<0.001
Driving pressure, cmH_2O*	13 (11–16)	14 (12–16)	-0.63 (-0.95 to -0.32)	<0.001
Respiratory rate, mpm	20 (17–23)	18 (15–21)	1.71 (1.32 to 2.10)	<0.001
Mechanical power, J/min**	21.0 (15.7–27.8)	21.6 (16.5–27.9)	-0.38 (-1.14 to 0.38)	0.325
Minute ventilation, L/min	11.3 (9.4–13.4)	10.3 (8.6–12.3)	1.04 (0.78 to 1.29)	<0.001
FiO_2, %	45 (40–50)	50 (40–55)	-1.46 (-2.37 to -0.56)	0.002

Data are median (quartile 25% - quartile 75%). PEEP: positive end-expiratory pressure; FiO_2: inspired fraction of oxygen; * calculated when plateau pressure is available and as plateau pressure – PEEP; ** calculated when plateau pressure is available and as: 0.098× tidal volume × respiratory rate ×(peak pressure – driving pressure/2); *** mean difference from a univariable mixed–effect linear model with year as random effect.

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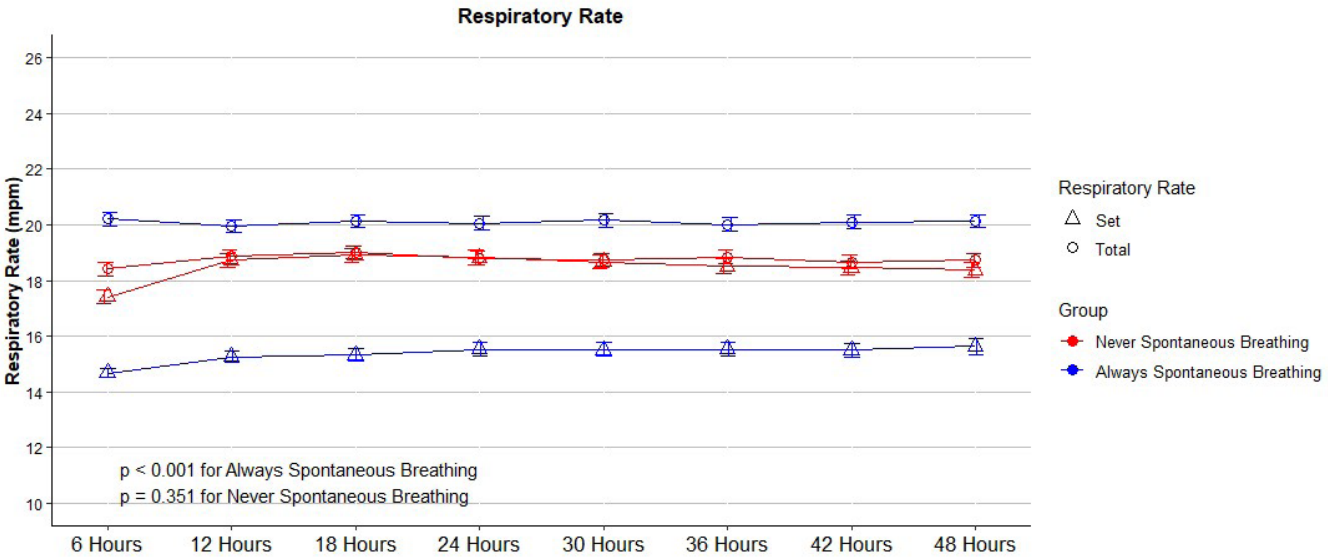

Figure S4 omparison of set and total respiratory rate among more strict groups Symbols and bars are mean and 95% confidence interval. Mixed-effect longitudinal models with random intercept for patients and year of admission, and with group, time and the interaction of group x time as fixed effects. P values reported are for the group and reflect the overall test for difference between groups across the 48 hours.

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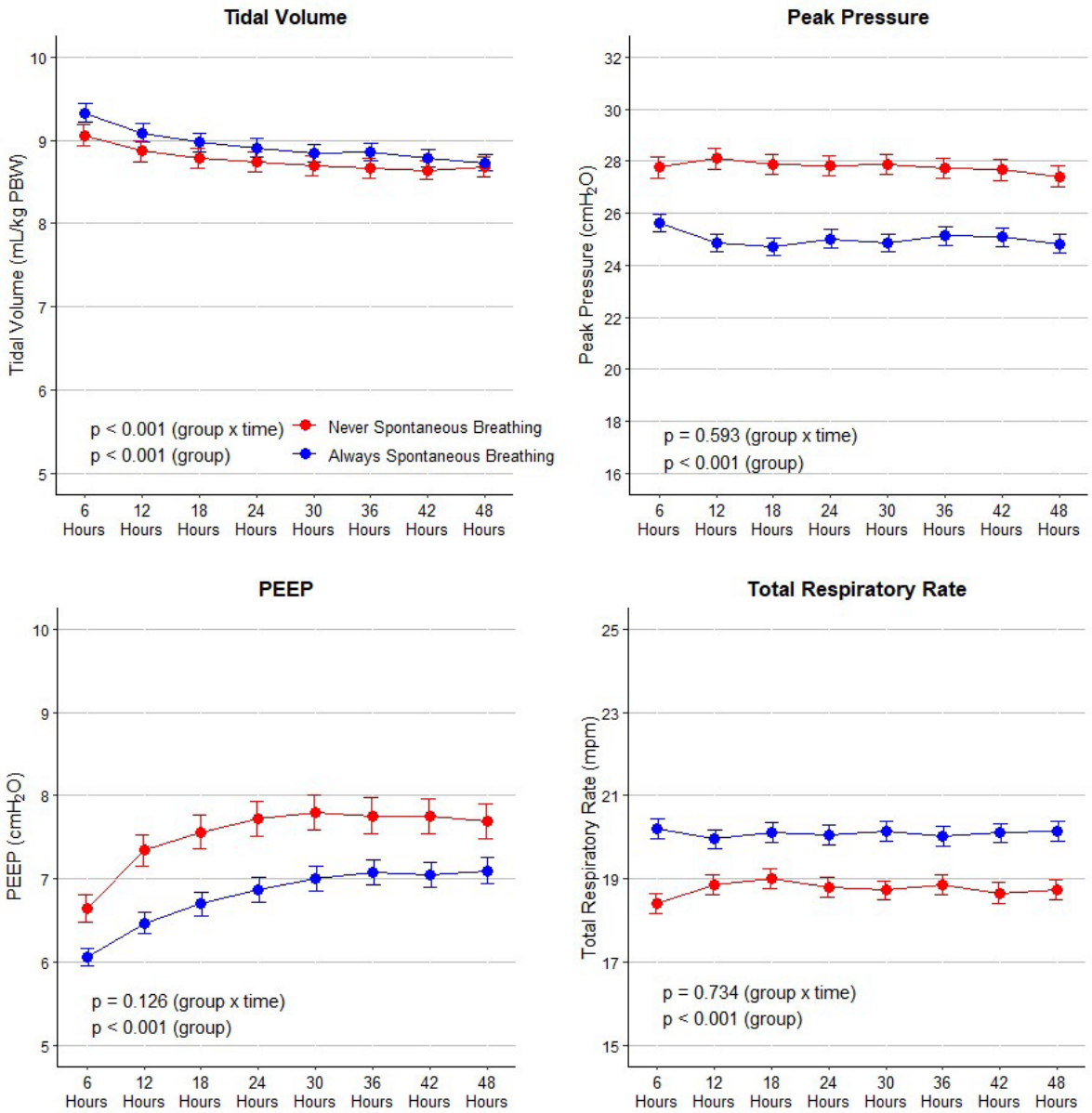

Figure S5 Measurements of ventilatory parameters every 6 hours for the first 48 hours of ventilation according to more strict groups. Circles and bars are mean and 95% confidence interval. Mixed-effect longitudinal models with random intercept for patients and with group, time and the interaction of group x time as fixed effects. P values for the group reflect the overall test for difference between groups across the 48 hours while P values for the group x time interaction evaluate if change over time differed by group.

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Table S8 Unadjusted analyses for the primary and secondary outcomes according to more strict groups

	Always Spontaneous Breathing (n=1809)	Never Spontaneous Breathing (n=755)	Absolute Difference* (95% Confidence Interval)	P value
Ventilator–free days at day 28	20 (0–24)	18 (0–23)	0.72 (-0.19 to 1.63)	0.119
Duration of ventilation in survivors, days	5.9 (3.6–10.4)	5.0 (2.9–9.8)	0.80 (-0.03 to 1.63)	0.058
ICU length of stay, days	9.5 (5.9–15.6)	10.1 (6.0–17.4)	-1.04 (-1.92 to -0.14)	0.022
Hospital length of stay, days	15.5 (9.7–24.4)	15.4 (9.2–25.8)	-0.83 (-2.20 to 0.55)	0.235
ICU mortality	470 (26.0)	203 (26.9)	-0.91 (-4.64 to 2.83)	0.635
Hospital mortality	561 (31.0)	229 (30.3)	0.68 (-3.24 to 4.60)	0.734
30–day mortality	546 (30.2)	230 (30.5)	-0.28 (-4.18 to 3.62)	0.888

Data are median (quartile 25% - quartile 75%) or N (percentage). ICU: intensive care unit. * absolute difference from a univariable mixed–effect linear model with year as random effect; [a] effect estimate is mean difference; [b] effect estimate is risk ratio.

Table S9 Adjusted analyses for the primary and secondary outcomes according to more strict groups

	Always Spontaneous Breathing (n=1809)	Never Spontaneous Breathing (n=755)	Absolute Difference*,** (95% Confidence Interval)	P value
Ventilator–free days at day 28	20 (0–24)	18 (0–23)	0.96 (0.20 to 1.72)	0.014
Duration of ventilation in survivors, days	5.9 (3.6–10.4)	5.0 (2.9–9.8)	0.77 (-0.16 to 1.70)	0.109
ICU length of stay, days	9.5 (5.9–15.6)	10.1 (6.0–17.4)	-0.86 (-1.83 to 0.10)	0.080
Hospital length of stay, days	15.5 (9.7–24.4)	15.4 (9.2–25.8)	-0.29 (-1.74 to 1.17)	0.700
ICU mortality	470 (26.0)	203 (26.9)	-1.27 (-4.40 to 1.86)	0.428
Hospital mortality	561 (31.0)	229 (30.3)	-1.02 (-4.19 to 2.13)	0.530
30–day mortality	546 (30.2)	230 (30.5)	-1.66 (-4.86 to 1.54)	0.313

Data are median (quartile 25% - quartile 75%) or N (percentage). ICU: intensive care unit. * absolute difference from a multivariable mixed–effect linear model with year as random effect and adjusted for: age, gender, weight, initial diagnosis, Elixhauser comorbidity score, use of vasopressor in the first day, limitation of support, SAPS II, OASIS, SOFA at day 1, heart rate at day 1 and 2, mean arterial pressure at day 1 and 2, and SpO_2 / FiO_2 at day 1 and 2; ** continuous variables were standardized before inclusion to improve convergence; [a] effect estimate is mean difference; [b] effect estimate is risk ratio.

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