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	$\frac{N_M\ SB}{N_O} \therefore \left(\frac{0}{7}\right) \times 100 = 00\%$
02	5	11	11	24	24	No	
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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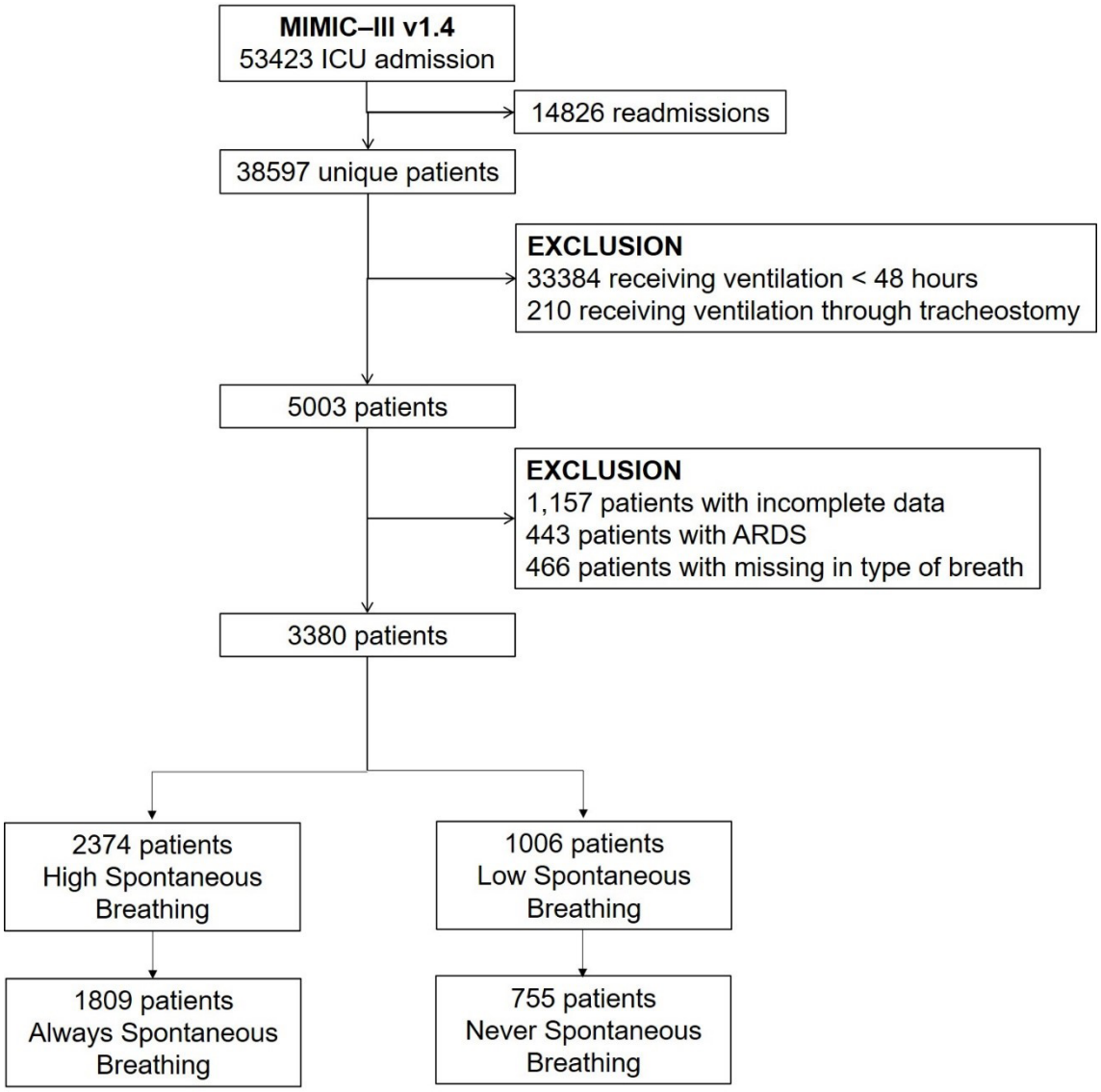

Figure S1 Flowchart of the study in the MIMIC-III dataset.

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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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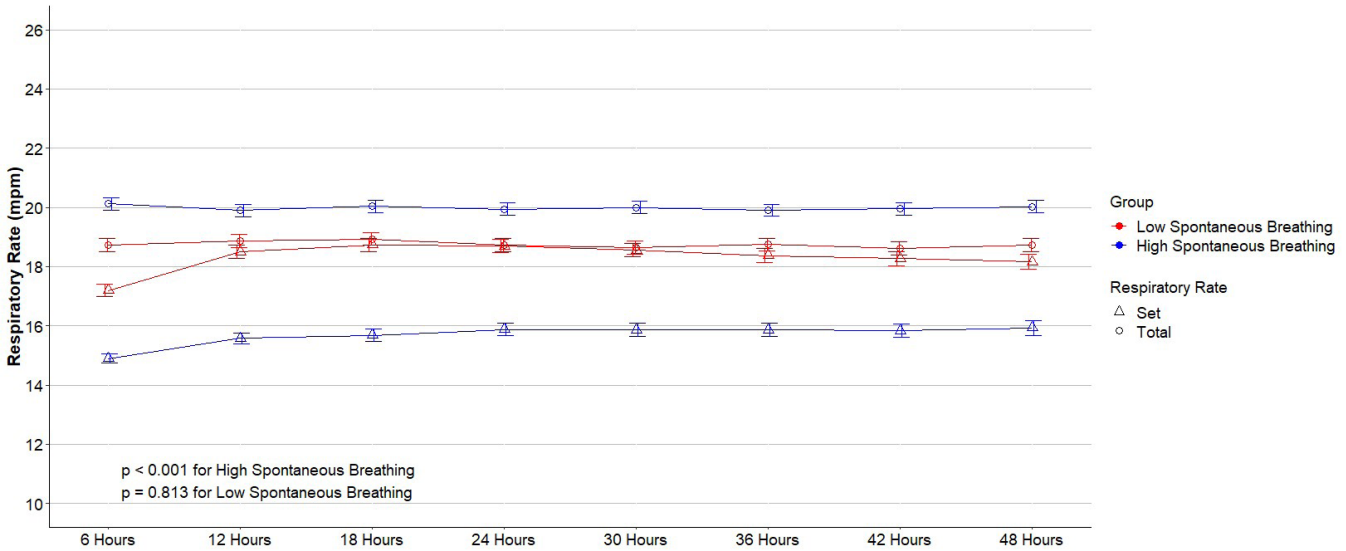

Figure S2 Comparison of set and total respiratory rate among groups. Symbols and bars are mean and 95% confidence interval. Mixed-effect longitudinal models with random intercept for patients and year of admission, and with group, time and the interaction of group x time as fixed effects. P values reported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

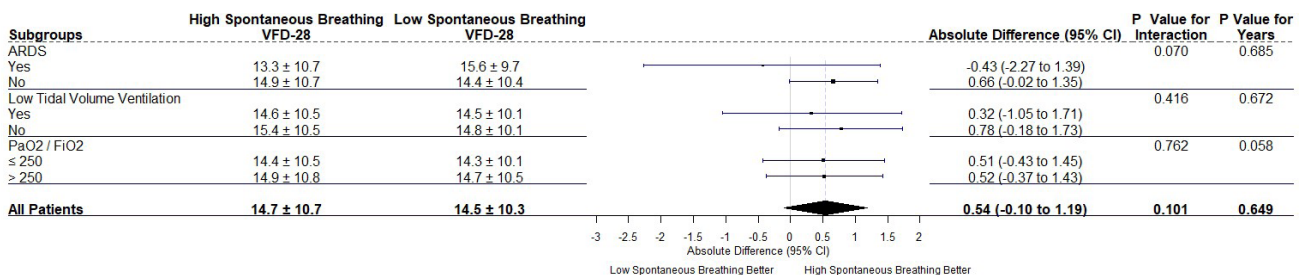

Figure S3 Subgroup analyses.

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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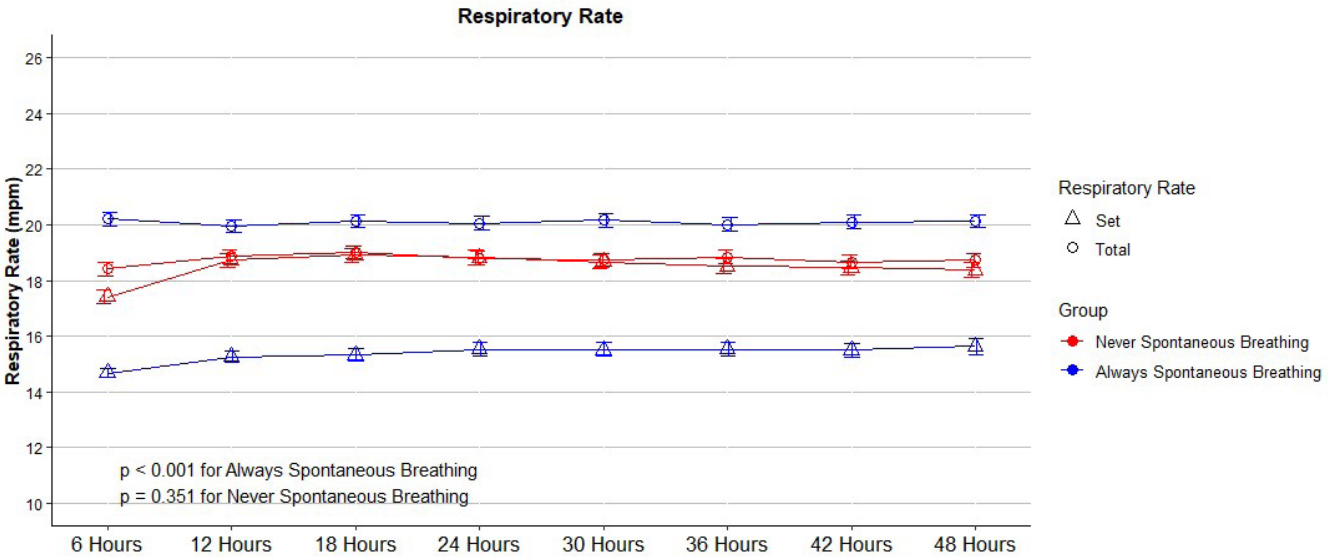

Figure S4 omparison of set and total respiratory rate among more strict groups Symbols and bars are mean and 95% confidence interval. Mixed-effect longitudinal models with random intercept for patients and year of admission, and with group, time and the interaction of group x time as fixed effects. P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

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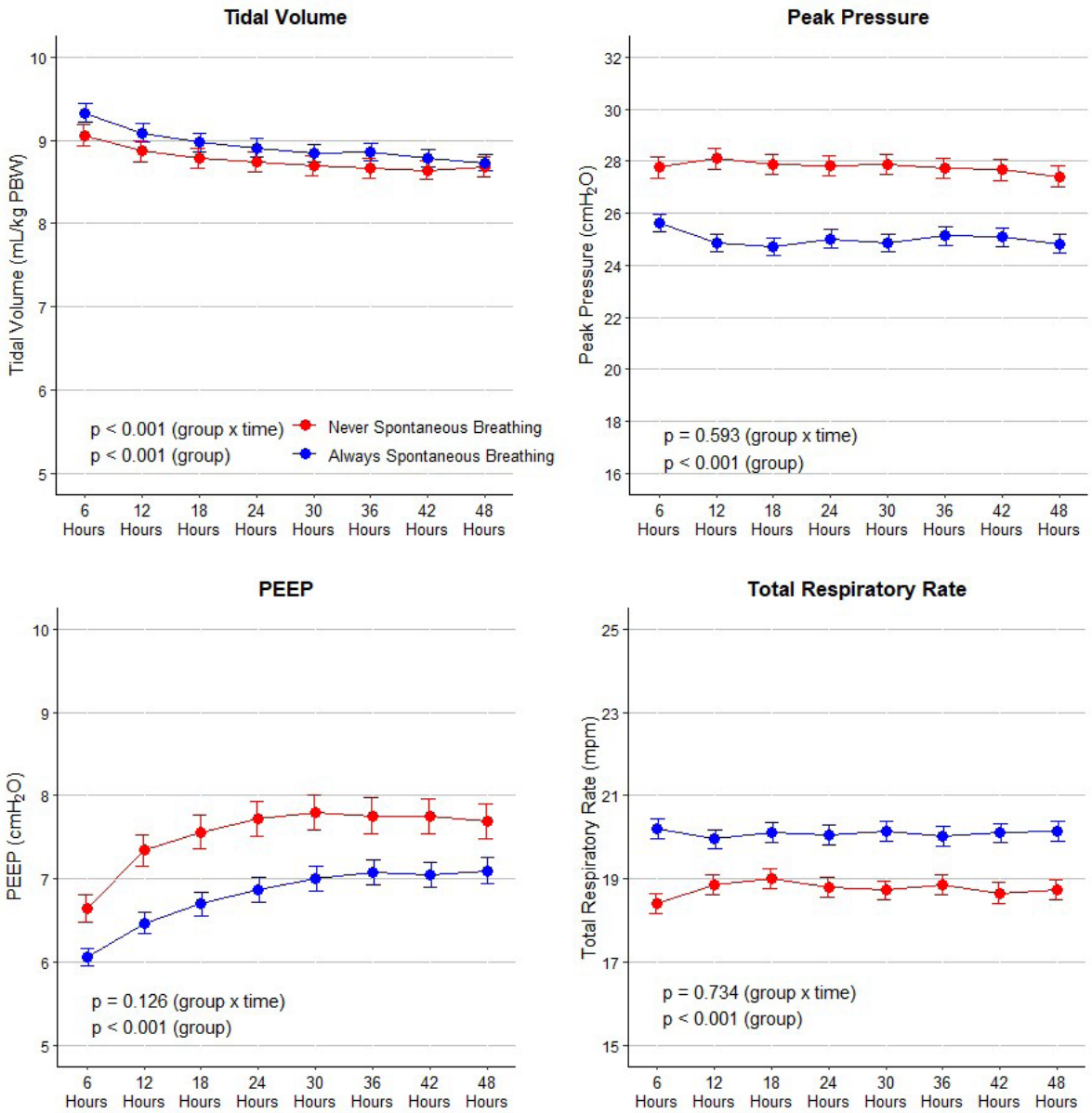

Figure S5 Measurements of ventilatory parameters every 6 hours for the first 48 hours of ventilation according to more strict groups. Circles and bars are mean and 95% confidence interval. Mixed-effect longitudinal models with random intercept for patients and with group, time and the interaction of 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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