Original Article

Role of a successful spontaneous breathing trial in ventilator liberation in brain-injured patients

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Background: Spontaneous breathing trials (SBTs) have been shown to improve outcomes in critically ill patients. However, in patients with brain injury, indications for intubation and mechanical ventilation are different from those of non-neurological patients, and the role of an SBT in patients with brain injury is less established. The aim of the present study was to compare key respiratory variables acquired during a successful SBT between patients with successful ventilator liberation versus failed ventilator liberation.

Methods: In this prospective study, patients with brain injury (≥18 years of age), who completed a 30-min SBT, were enrolled. Airway pressure, flow, esophageal pressure, and diaphragm electrical activity (ΔEAdi) were recorded before (baseline) and during the SBT. Respiratory rate (RR), tidal volume, inspiratory muscle pressure (ΔPmus), ΔEAdi, and neuromechanical efficiency (ΔPmus/ΔEAdi) of the diaphragm were calculated breath by breath and compared between the liberation success and failure groups. Failed liberation was defined as the need for invasive ventilator assistance within 48 h after the SBT.

Results: In total, 46 patients (51.9±13.2 years, 67.4% male) completed the SBT. Seventeen (37%) patients failed ventilator liberation within 48 h. Another 11 patients required invasive ventilation within 7 days after completing the SBT. There were no differences in baseline characteristics between the success and failed groups. In-depth analysis showed similar changes in patterns and values of respiratory physiological parameters between the groups.

Conclusions: In patients with brain injury, ventilator liberation failure was common after successful SBT. In-depth physiological analysis during the SBT did not provide data to predict successful liberation in these patients.

Trial registration: The trial was registered at ClinicalTrials.gov (No. NCT02863237).

Keywords: Brain injury; mechanical ventilation; spontaneous breathing trial; ventilator liberation

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Introduction

In critically ill patients with brain injury, mechanical ventilation aims to minimize secondary brain injury (e.g., due to ischemia and edema) by securing oxygenation and preventing hypercapnic acidosis (1-5). However, the time-dependent nature of ventilator-related complications requires timely ventilator liberation (6-10). Protocolized weaning, including the use of a spontaneous breathing trial (SBT), improves outcomes and is recommended in international guidelines (11-15).

Indications for endotracheal intubation and mechanical ventilation in patients with brain injury are largely different from those of critically ill patients without brain injury (further referred to general critically ill patients) (8,16-18). The predictive value of a successful SBT for ventilator liberation in patients with brain injury is largely unknown. Recent studies have demonstrated higher extubation failure rates after a successful SBT in patients with brain injury compared with general critically ill patients (19-23). After a successful SBT, extubation failure rates between 31% and 46% have been reported in patients with brain injury. In contrast, 10–14% of general critically ill patients completing an SBT failed ventilator liberation (24-27). Reasons for the high failure rates in patients with brain injury may be related to upper airway function or neurological status (19,21,23). Therefore, guidelines specifically recommend assessment for airway protective ability, including suctioning frequency, cough strength, and mental status (11,28). However, the role of impaired respiratory reserve has not been systematically evaluated in this population. This is important, as ventilator reconnection is frequent in tracheostomized patients with brain injury, indicating that factors other than upper airway protection may be involved (29). Therefore, the aim of the current study was to investigate patients with brain injury and to determine if the respiratory physiological parameters during a successful SBT are different between patients with successful liberation versus failed ventilator liberation.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6407).

Methods

Study design and patients

The present prospective study was conducted in the neurocritical intensive care unit (ICU) of the Beijing Tiantan Hospital, Capital Medical University, Beijing, China. Patients with brain injury (≥18 years old), who were mechanically ventilated for >48 h, were screened daily between 9 AM and 10 AM (from Monday to Friday) (Appendix S1). The readiness criteria for an SBT were as follows: (I) intracranial pressure <20 mmHg, or no clinical evidence of elevated intracranial pressure; (II) adequate oxygenation (P_{O2}/F_{IO2} >200 mmHg or pulse oximetry >95% with F_{IO2} ≤0.5) and low level of ventilator support [positive end-expiratory pressure (PEEP) ≤5 cmH_2O, and pressure support ≤8 cmH_2O); (III) hemodynamic stability (no vasopressor support and systolic blood pressure between 90 and 160 mmHg); and (IV) no sedatives or intermittent dosing of sedatives. Patients were excluded if they were moribund or brain dead, had spinal cord injury or any contraindications for esophageal catheter placement, or were tracheostomized before or within 48 h after the SBT (as it affects weaning strategies).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the institutional ethics board of Beijing Tiantan Hospital (No. KY2016-018-02). Informed consent was obtained from all patients or legal representatives.

Study protocol

Patients were ventilated with a Servo-i ventilator (Maquet Critical Care, Sölna, Sweden). Nasogastric catheters for diaphragmatic electrical activity (EAdi) (Maquet Critical Care, Sweden) were inserted to replace the standard nasogastric feeding tube, and esophageal pressure (Pes) monitoring (SensorMedics, Yorba Linda, CA, USA) was conducted. Details for the catheter placement have been described previously (30-35). Baseline data were collected just before the SBT in pressure support ventilation (PSV) mode (inspiratory support: 8 cmH_2O, PEEP: 5 cmH_2O). Subsequently, patients underwent a 30-min SBT at continuous positive airway pressure (CPAP) of 5 cmH_2O, with no inspiratory pressure support and without changing F_{IO2}. At 1, 5, 10, 20, and 30 min after the start of SBT, an end-expiratory occlusion (EEO) maneuver was applied on the ventilator for at least 3 consecutive breathing efforts to determine neuromechanical efficiency. Criteria for terminating the SBT are listed in Table S1 (6).

After completing the SBT, patients were disconnected from the ventilator, either breathing through a T-tube circuit with humidified oxygen or extubated as decided by the clinical team using a screen checklist (Table S2) (36,37). Reconnection to the ventilator support was solely decided by the clinical team, who were unaware of the physiological

data obtained for study purposes (especially data derived from EAdi and Pes). Reasons for resuming mechanical ventilation and/or reintubation were recorded. As per the clinical protocol, reintubation and/or reconnection to the ventilator was performed in patients meeting at least 1 of the following criteria: (I) decreased mental status compared with pre-SBT level of consciousness; (II) peripheral oxygen saturation <90%, despite F_{IO2} >0.5; (III) increased respiratory effort, such as tachypnea, accessory respiratory muscle recruitment, or thoracic–abdominal paradox (36). Failed ventilator liberation was defined as the need for invasive ventilator support within 48 h after the SBT, independent of the presence of an artificial airway (tracheostomy or endotracheal tube). The Glasgow Coma Scale (GCS) score was recorded before ventilator disconnection to assess neurological status. The verbal score was counted as 1 for patients with an artificial airway (38). Arterial blood samples and hemodynamic parameters (i.e., non-invasive blood pressure and heart rate) were collected before and at the end of the SBT. Patients were followed up until they were reconnected to ventilation, extubated, tracheostomized, discharged from the hospital, or 28 days after the first successful SBT, whichever came first.

Data acquisition during SBT

Flow was measured with a heated Fleisch pneumotachograph (Vitalograph, Lenexa, KS, USA) placed between the Y-piece of the ventilator circuit and the endotracheal tube. Two differential pressure transducers (KT 100D-2; KleisTEK di Cosimo Micelli, Monopoli, Italy; range: ±100 cmH_2O) were used to measure the airway opening pressure (Pao) and the Pes. The transducers were connected proximal to the endotracheal tube (Pao) and to the esophageal catheter (Pes), respectively. Flow and pressures signals were recorded by an ICU-Lab pressure box (ICU Lab, KleisTEK Engineering, Bari, Italy), with a sample frequency of 100 Hz. The pressure transducers were calibrated with a water column and the pneumotachograph with a 1-L calibration syringe (SN: 554–2266; Hans Rudolph, Shawnee, KS, USA) prior to each measurement (30). The EAdi catheter was connected to the Servo-i ventilator. EAdi signals were recorded at a sample frequency of 100 Hz using dedicated software (Servo-tracker version 4.1. Maquet, Sweden). All recordings were saved and synchronized for offline analysis in a software developed for the ICU-Lab monitoring system (DigimaClic-1, ICU-Lab System, KleisTEK, Italy).

Data analysis

As per the study design, only patients completing the SBT were included for further analysis. Data were analyzed on a breath-by-breath basis at 6 time points as follows: at baseline (PSV prior to the SBT), and at 1, 5, 10, 20, and 30 min after start of the SBT. These time points were arbitrarily selected, as used previously (39,40). For each time point, 5 consecutive breaths without artifacts (e.g., esophageal contractions) were selected.

Inspiratory time, expiratory time, respiratory rate (RR), minute ventilation, and duty cycle were derived from the flow signal. Tidal volume (Vt) was computed as the time integral of inspiratory flow. Intrinsic PEEP was calculated as the decrease in Pes until the start of inspiratory flow (41). The chest wall recoil pressure (Pcw) was calculated as the product of lung volume and the predicted elastance of the chest wall (4% of vital capacity). The effort of the inspiratory muscles was quantified by calculating the global inspiratory muscle pressure (Pmus) and the inspiratory esophageal pressure–time product (PTPes,insp). Pmus was calculated as the peak difference between Pcw and Pes during inspiration (ΔPmus). PTPes,insp was calculated as the time interval of the difference between Pes and Pcw (Figure S1) (42).

Neural respiratory drive was measured as the inspiratory increase in EAdi from basal activity (ΔEAdi). The static neuromechanical efficiency (NMEoccl) of the diaphragm was computed as ΔPao/ΔEAdi during an EEO maneuver (31). The NMEoccl was calculated from the first occluded breathing effort. In the presence of artifacts in the EAdi waveform, the second or third breathing effort of the same series was selected (Figure S2). This was acceptable, as we have demonstrated that NMEoccl remains stable during a 20-s occlusion. The dynamic neuromechanical efficiency of the diaphragm was defined as ΔPmus/ΔEAdi measured during tidal breathing (Figure S3). As the respiratory centers are located in the brainstem, we performed χ^2-test analysis to determine if responses were different between patients with or without brainstem involvement (43).

Statistical analysis

Data were analyzed with IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 7.0 (GraphPad Software, Inc., San Diego, CA, USA). Assumption of normality was tested using the Shapiro-Wilk normality test. Differences in patient characteristics between two groups were analyzed using the

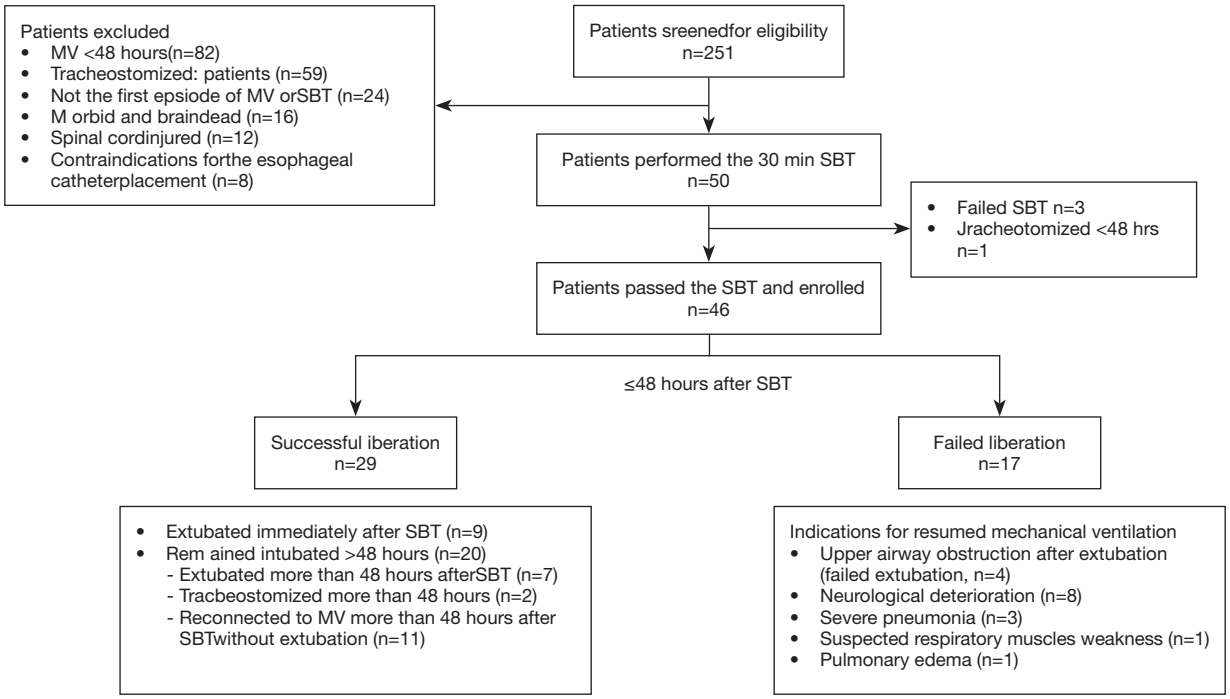

Figure 1 Flowchart of patient enrollment in the study. MV, mechanical ventilation; SBT, spontaneous breathing trial.

t-test, Mann-Whitney U-test, or χ^2-test, as appropriate.

To analyze the effects of time and group (failure and success) on each respiratory parameter, a linear mixed model design was used with a fixed effect of time, group, and group-by-time interaction, and a random effect of patient. For nonparametric respiratory parameters, an appropriate mathematical transformation was applied. Post-hoc pairwise comparisons of estimated means over time and between groups at each time point were performed after applying Bonferroni correction (34). Sensitivity analyses were performed in a subgroup analysis by defining the failed ventilator liberation as the need for invasive ventilator support within 7 days after the SBT.

For all tests, a 2-tailed P value <0.05 was considered to be statistically significant. Values were given as mean ± standard deviation or median (interquartile range) for continuous variables, and as number and percentage for categorical variables. Because of the exploratory nature of this study, convenience sampling was used (39,40).

Results

During the 12-month study period, 251 patients were screened, and 46 were included for analysis (*Figure 1*). Reasons for exclusion included mechanical ventilation <48 h (n=82) and early tracheostomy (n=59). Patient characteristics at baseline are reported in *Table 1*. Seventeen (37%) patients failed ventilator liberation within 48 h after a successful SBT. Of these patients, 4 were reintubated and 13 were reconnected to the ventilator before extubation. Reasons for failing ventilator liberation within 48 h were postextubation upper airway obstruction (n=4), neurological deterioration (n=8), and respiratory-related issues (n=5). Clinical characteristics of patients failing ventilator liberation within 48 h were not different from patients with successful liberation (*Table 1*). The proportion of patients that remained liberated from mechanical ventilation decreased rapidly within 7 days after the first SBT and remained stable thereafter (*Figure 2*). In total, 28 patients were reconnected to the ventilator within 7 days after the first SBT. The median time until reconnection was 1.4 (0.4–3) days. Further patient details are presented in Table S3.

Breathing pattern during SBT in successful and failed liberation

Immediately after the transition from PSV to SBT, Vt decreased and RR increased in both groups, but remained

Table 1 Baseline characteristics of all patients in the successful and failed ventilator liberation groups

Variables	All patients (n=46)	Successful liberation (n=29)	Failed liberation (n=17)	P value
Age (years)	51.9±13.2	54.3±11.7	47.8±11.7	0.104
Sex (male/female)	31/15	18/11	13/4	0.251
Acute Physiology and Chronic Health Evaluation II	16.2±4.1	15.7±4.4	17.2±3.3	0.262
Time of starting mechanical ventilation after surgery (days)	1.7 (0.4–3.4)	1.9 (0.6–3.7)	1.1 (0.1–1.9)	0.112
Mechanical ventilation duration before SBT (days)	4.6±2.0	4.9±2.2	4.2±1.5	0.278
P_{aO2}/F_{IO2} ratio at the beginning of SBT	262.8±56.9	266.6±54.8	256.5±61.5	0.568
Glasgow Coma Scale at the beginning of SBT	8.5 (7.0–10.0)	9.0 (8.0–10.0)	8.0 (5.5–10.0)	0.447
Main diagnosis for neurosurgery (n)				0.174
Tumor	33 (71.7)	19 (65.5)	14 (82.4)	
Intracranial vascular malformation or aneurysm	4 (8.7)	3 (10.3)	3 (17.6)	
Intracerebral/subarachnoid hemorrhage	6 (13.0)	4 (13.8)	0 (0)	
Other	3 (6.5)	3 (10.3)	0 (0)	
Anatomic location of the lesion				0.45
Brainstem involvement	10 (21.7)	7 (24.1)	3 (17.6)	
Nonbrainstem involvement	36 (78.3)	22 (75.9)	14 (82.4)	
Primary indication for mechanical ventilation (n)				0.059
Neurological indications	30 (65.2)	16(55.2)	14 (82.4)	
Non-neurological indications	16 (34.8)	13 (44.8)	3 (17.6)	

Data are presented as mean ± standard deviation, median (interquartile range), or n (%). SBT, spontaneous breathing trial.

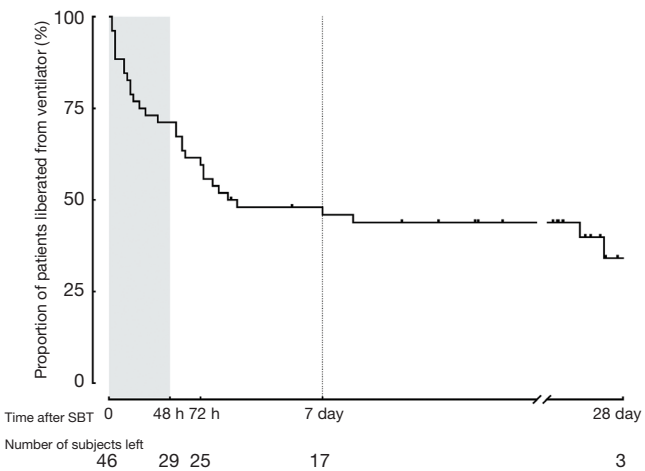

Figure 2 Proportion of patients liberated from mechanical ventilation after a successful spontaneous breathing trial (SBT). Number of patients left at the time of observation is shown below the x-axis. Patients were followed up until they were reconnected to ventilation, extubated, tracheostomized, discharged from the hospital, or 28 days after the first successful SBT, whichever came first.

stable during the rest of the SBT (*Table 2*). Minute ventilation decreased in the successful liberation group only [9.0 (7.7–10.4) to 7.8 (6.1–10.0) L/min, P<0.05]. There was no difference in respiratory pattern between the groups. Other respiratory physiological parameters are shown in Table S4.

Respiratory muscle effort during SBT in successful and failed liberation

As shown in *Figure 3*, parameters of inspiratory muscle effort including ΔPmus, PTPes,insp, and ΔEAdi increased after the transition from PSV to SBT in both groups, but remained stable during the SBT. There were no significant differences between groups.

NMEoccl, a measure for neuromechanical efficiency of the diaphragm, did not change after the transition from PSV to the SBT and remained stable during the SBT. No difference was found in NMEoccl between the two groups (*Figure 4*).

Table 2 Changes in respiratory parameters during the spontaneous breathing trial in the successful (S) and failed (F) ventilator liberation groups

Parameters	Baseline	1 min	5 min	10 min	20 min	30 min	P value		
							Main effects		Interaction
							Time	Group	Time*Group
VT, mL									
S	474.5 (352.2–597.1)	403.0 (278.8–524.3)**	437.4 (336.3–541.9)	438.7 (321.0–538.6)	388.0 (340.1–537.4)	446.8 (341.9–533.3)	0.035	0.417	0.731
F	450.9 (395.9–724.7)	390.1 (318.8–561.3)*	415.6 (335.0–600.7)	449.0 (336.9–602.9)	397.9 (348.9–613.5)	397.2 (340.1–616.6)			
RR, min^{-1}									
S	19.0 (16.0–22.0)	21.0 (17.0–25.5)*	21.0 (17.0–25.5)	23.0 (14.5–24.5)	21.0 (15.5–25.0)	22.0 (17.0–25.8)	0.055	0.691	0.967
F	19.0 (14.8–25.8)	22.0 (17.0–27.8)*	21.0 (16.0–29.0)	20.0 (17.5–28.5)	21.0 (16.5–29.0)	20.0 (18.0–28.0)			
VE, L/min									
S	9.0 (7.7–10.4)	7.8 (6.4–10.0)*	8.6 (7.1–9.9)	8.3 (7.1–9.8)	8.4 (7.6–10.2)	8.4 (7.8–10.1)	0.051	0.173	0.808
F	10.5 (6.7–12.3)	10.0 (6.9–11.0)	9.7 (7.8–10.7)	9.0 (7.6–11.3)	9.1 (7.3–11.4)	9.5 (7.7–11.3)			
RR/VT, $min^{-1}·L^{-1}$									
S	41.5 (26.0–61.0)	53.0 (30.5–88.0)**	46.0 (30.5–78.5)	43.0 (25.5–83.5)	53.0 (29.0–75.0)	48.0 (32.0–75.0)	0.026	0.391	0.758
F	39.0 (17.8–54.5)	51.5 (26.8–78.3)*	52.0 (24.5–70.0)	50.0 (26.0–66.5)	48.0 (28.0–71.5)	48.0 (29.0–69.0)			

Data are presented as median (interquartile range). No significant differences between the 2 groups were observed at baseline and each time point during the spontaneous breathing trial. Within each group, comparisons were made between the baseline and the first minute of the spontaneous breathing trial. *P<0.05, **P<0.001. RR, respiratory rate; VE, minute ventilation; VT, tidal volume.

A subgroup analysis was performed to compare respiratory physiological parameters between patients that were successfully liberated from mechanical ventilation and patients failing ventilator liberation within 7 days. This, however, did not change the results compared with failure within 48 h after successful SBT (Table S5). Subgroup analysis was also performed in patients remaining intubated within 48 h. First, the rate of liberation failure was comparable to that of patients who were extubated (39.4% *vs.* 30.8%, P=0.74). Second, the respiratory physiological variables showed no difference between patients who failed and those were successfully liberated from the ventilator within 48 h (Table S6).

Arterial blood gas variables and hemodynamic variables

Arterial blood gas and hemodynamic variables are shown in *Table 3*. The arterial HCO3– at the start of the SBT was significantly higher in the successful liberation group compared with the failed liberation group (28.4±2 *vs.* 26.1±2.7 mmol/L, P=0.001). There were no differences between groups in hemodynamic variables at baseline or during the SBT.

Clinical outcomes

Clinical outcomes are shown in *Table 4*. There were no significant differences between the failed liberation and successful liberation groups with regard to discharge status, ICU length of stay, and hospital length of stay. At the time of hospital discharge, 40 (87.0%) patients were liberated from the ventilator in a median of 3.4 (0–6.2) days after the first successful SBT. In these patients, the median number of SBTs before final ventilator liberation was 2 [1–5]. Two patients died before ventilator liberation and 4 patients were

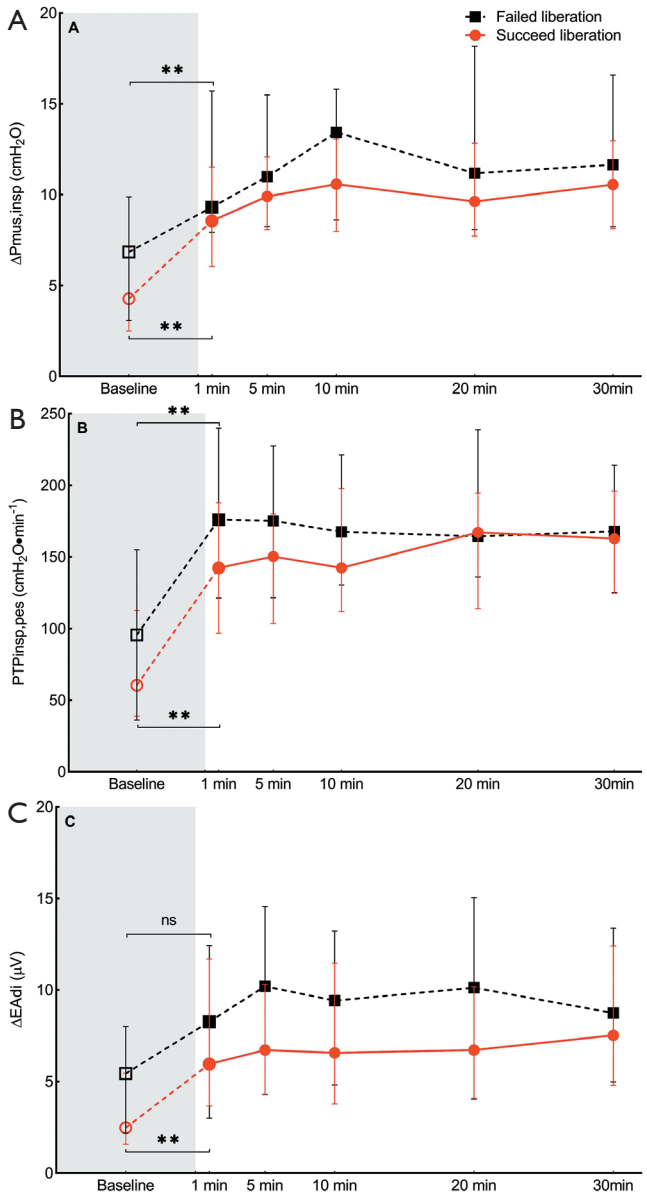

Figure 3 Respiratory muscle effort quantified as (A) inspiratory muscle pressure (ΔPmus,insp), (B) inspiratory esophageal pressure-time product (PTPes,insp), and (C) diaphragm electrical activity (ΔEAdi) during pressure support ventilation (baseline, gray area) prior to the spontaneous breathing trial (SBT) and during the course of the SBT for the successful (red dots) and failed (black boxes) liberation groups. In 9 patients, Pes-derived parameters could not be analyzed due to the low quality of the signals (1 in the failure group and 8 in the success group). Data are presented as median (interquartile range). **P<0.001, difference between the first minute of SBT and baseline. No significant differences between the 2 groups were observed at any time point.

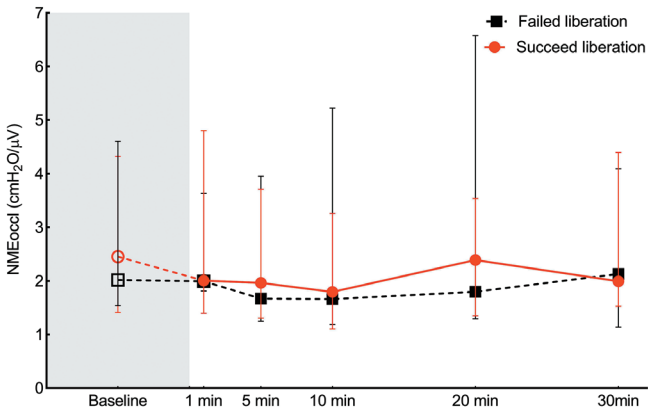

Figure 4 Changes in neuromechanical efficiency (NMEoccl) during pressure support ventilation (baseline, gray area) and during the course of the spontaneous breathing trial (SBT) in the successful (red dots) and failed (black boxes) liberation groups. Data are presented as median (interquartile range). No significant differences were observed at any time point within and between the 2 groups.

transferred to a local hospital for end-of-life care.

Discussion

In the current study, we demonstrated that, in patients with brain injury completing a 30-min SBT, 37% required invasive ventilator support within 48 h and 61% within 7 days. In-depth analysis of respiratory muscle effort and breathing patterns during the SBT did not provide any predictive information for ventilator liberation failure. Therefore, the clinical usefulness of a successful SBT in this patient category is debatable.

Successful SBT and failed ventilator liberation

Our study demonstrated that, in patients with brain injury, ventilator liberation failure within 48 h after a successful SBT was more common (37%) compared with general critically ill patients (24-27,44). In general critically ill patients, Subira *et al.* reported 12% of extubation failure within 48 h after a successful SBT (24), and Burns *et al.* reported that the reintubation rate was 13% in younger patients (age <65 years) and 10.8% in patients aged ≥65 years (25). The differences in ventilator reconnection may be related to underlying illness (45). Reasons for

Table 3 Arterial blood gas variables and hemodynamic variables before and after the spontaneous breathing trial for the successful (S) and filed (F) ventilator liberation groups

Variables	Group	SBT start	SBT end	P value		
				Main effect		Interaction (time × group)
				Time	Group	
Arterial blood pH	S	7.49±0.03	7.49±0.03	0.351	0.13	0.06
	F	7.47±0.04	7.48±0.04			
P_{aO2}, mmHg	S	103.5±25.4	98.6±30.9	0.499	0.528	0.799
	F	97.3±28.5	96±34.4			
P_{aCO2}, mmHg	S	36.7±5.0	37.2±5.2	0.552	0.233	0.269
	F	35.6±6.7	34.5±5.9			
Bicarbonate (HCO_3^-), mmol/L	S	28.4±2.0*	28.5±2.3*	0.373	0.004	0.441
	F	26.1±2.7	26.9±2.6			
P_{O2}/F_{IO2} ratio	S	258.7±63.5	246.5±77.3	0.499	0.528	0.799
	F	243.2±71.2	240±86.0			
Mean arterial pressure, mmHg	S	98.2±12.0	99.1±13.0	0.775	0.973	0.489
	F	98.8±7.2	98.4±8.8			
Heart rate, beats/min	S	89.0±20.6	94.3±15.5	0.659	0.776	0.095
	F	94.5±12.6	91.4±13.1			

Data are presented as mean ± standard deviation. Comparison between the S and F ventilator liberation groups: *P<0.05. No significant differences were observed within each group before and after SBT. SBT, spontaneous breathing trial.

Table 4 Clinical outcomes of all patients in the successful and failed ventilator liberation groups

Outcomes	Patients (n=46)	Successful liberation (n=29)	Failed liberation (n=17)	P value
Received tracheostomy	11 (21.7)	4 (13.8)	7 (41.2)	0.07
Length of stay in ICU (days)	13.5 (11.0–20.0)	14.0 (11.0–18.5)	13.0 (10.5–20.5)	0.793
Length of stay in hospital (days)	34.0 (23.8–54.0)	30.0 (22.0–50.5)	44.0 (28–57.5)	0.175
Successful ventilator liberation at time of discharge	40 (87.0)	26 (89.7)	14.0 (82.4)	0.389
Died on mechanical ventilation	2 (4.3)	1 (3.4)	1 (5.9)	0.608

Data are presented as median (interquartile range) or n (%). Four patients (2 in each group) were transferred to the local hospital in their hometown for end-of-life care. ICU, intensive care unit.

resuming ventilator support may be different between general critically ill patients and patients with brain injury. In general critically ill patients, reasons for resuming ventilator support are mainly related to cardiorespiratory function (24,25,46,47). In our study, 4 of 17 (24%) patients were reconnected to a ventilator because of upper airway obstruction and 8 of 17 (47%) patients for neurological reasons. These data are in line with previous studies on patients with brain injury (21,48). Karanjia *et al*. retrospectively investigated the cause of reintubation in 99 patients with brain injury reintubated within 72 h after a successful SBT (48). They found that the primary cause for reintubation was respiratory distress associated with decreased mental status, without signs of aspiration or pneumonia. Given that most patients with brain injury are intubated and mechanically ventilated for neurological

reasons, these results are not surprising. Accordingly, in patients with brain injury, the predictive value of a successful SBT for ventilator liberation appears limited. Possibly, well-known parameters provided by an SBT may not be as relevant in patients with brain injury. Neurological dysfunction may not affect the ability to breathe (tested with SBT), but may affect ventilator liberation success.

We explored if more advanced respiratory physiological parameters collected during the SBT were helpful in predicting ventilator liberation outcome. Similar respiratory parameters have been systematically measured during a 30-min SBT in general critically ill patients (39,40). In these studies, variables of breathing pattern (RR, Vt, minute ventilation, and RR/Vt), EAdi and its derived parameters (neuromechanical and neuroventilatory efficiency) were reliable and early predictors for ventilator liberation outcome. In contrast, we did not find differences in physiological parameters related to breathing pattern or respiratory muscle effort between liberation success and failure patients with brain injury in our study. Interestingly, the values of the respiratory parameters assessed in our study were similar to the values earlier reported in successfully liberated general critically ill patients (39,40). Immediate changes occurred after the transition from PSV to the SBT, but remained relatively stable during the course of the SBT. This indicates that limited cardiorespiratory physiological reserve was not the main reason of ventilator liberation failure. Although the cardiorespiratory reserve and neurorespiratory drive can be assessed during an SBT, it is unlikely that neurological deterioration affects the course of an SBT. Therefore, the clinical usefulness of a successful SBT in patients with brain injury can be challenged or even considered misleading. In patients with brain injury, both neurological and non-neurological features should be evaluated before the decision of ventilator liberation. Therefore, other valid tools to assess underlying neurological conditions need to be developed and prospectively evaluated to predict the success of ventilator liberation.

Neurological status is one of the major concerns before the decision of ventilator liberation is made for patients with brain injury. Investigators have used the GCS to decide on extubation in these patients (49,50). However, the role of the consciousness level on extubation outcome remains controversial (20,38,51,52). Whether a low level of consciousness affects the breathing pattern in brain-injured patients is unclear. In our study, the GCS at the time of ventilator disconnection was similar for successful and failed patients. Moreover, half of the patients with a GCS <8 were successfully liberated from the ventilator. Accordingly, the level of consciousness appears not a main predictor for ventilator liberation outcome in these patients. Studies have demonstrated that together with visual pursuit, adequate swallowing function may improve ventilator liberation outcome (50), although no recommendations on this topic are available in recent guidelines (28). Therefore, further studies are required to investigate more specific parameters, rather than the level of consciousness, to assess neurological status during the SBTs.

High rate of liberation failure

Compared with other studies in patients with brain injury, the liberation failure rate in our patients appeared rather high (20,21,50,53). This may be related to the anatomical site of the injury. In our study, 54% (25/46) of the patients had infratentorial lesions and 10 of these patients had lesions that involved the brainstem. Infratentorial lesions include lesions located in the cerebellum and/or brainstem, which puts patients at high risk of respiratory compromise by involving primary neural respiratory centers, lower cranial nerve nuclei, and reticular activating pathways (43,54).

In addition, the type of SBT used may affect extubation outcome. SBT with low inspiratory support reduces patient respiratory effort. However, this technique may overestimate patients' ability to breathe without assistance. Conversely, an SBT with a T-piece provides no inspiratory (and expiratory) support, which more accurately reflects the physiological condition after extubation (55). However, the sudden drop in PEEP may induce cardiac dysfunction (56,57). It has been suggested that, as an inspiratory pressure support, SBT improves extubation outcomes compared with T-piece SBT (24,58). In our study we did not apply inspiratory support, but CPAP only. We chose this strategy as it better reflects breathing effort after extubation (55,57).

Strengths and limitations

The present study has several strengths, including the in-depth analysis of breathing pattern and respiratory muscle effort during an SBT. This has not been evaluated in earlier studies in patients with brain injury. In addition, half of the patients had an infratentorial lesion, 10 of which had brainstem involvement. This provided an opportunity to explore the impact of the anatomical location on the liberation outcome, especially brainstem injury. Our study suggests that, for patients completing an SBT, the anatomic

location of the lesion is not associated with the rate of liberation failure.

However, several limitations should be acknowledged. First, this was a single-center study, possibly challenging the generalizability of the data. Nevertheless, the study was performed in the largest neurological ICU in China, admitting the full spectrum of patients with brain injury. Second, we did not perform a formal sample size analysis. This is reasonable given the explorative nature of the study, and the current sample size was comparable to earlier studies (39,40). The results of the current study are helpful for sample size calculation in future studies with this specific patient population. Third, although all patients completing the SBT were disconnected from the ventilator, not all patients were extubated directly after the SBT. Therefore, the difference between ventilator liberation and extubation should be acknowledged. However, our study showed that the liberation failure rate in patients not extubated was comparable to patients immediately extubated. Moreover, respiratory physiological parameters were not different between the liberation success and failure groups in these subgroups of patients. Breathing without ventilator assistance through an endotracheal tube after a successful SBT is common in our ICU, especially in patients with anatomical injury at the brainstem level. This strategy allows for the recovery of upper airway protective reflexes before the decision of early tracheostomy. The prerequisite for this decision-making period is that patients are awake and mobilized.

Conclusions

A successful SBT does not predict ventilator liberation in patients with brain injury, indicating that factors other than respiratory dysfunction are involved in this specific population. Given the high rate of ventilator liberation failure in patients with brain injury, further studies focusing on nonrespiratory parameters to predict liberation success are warranted.

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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) and was approved by the institutional ethics board of Beijing Tiantan Hospital (No. KY2016-018-02). Informed consent was obtained from all patients.

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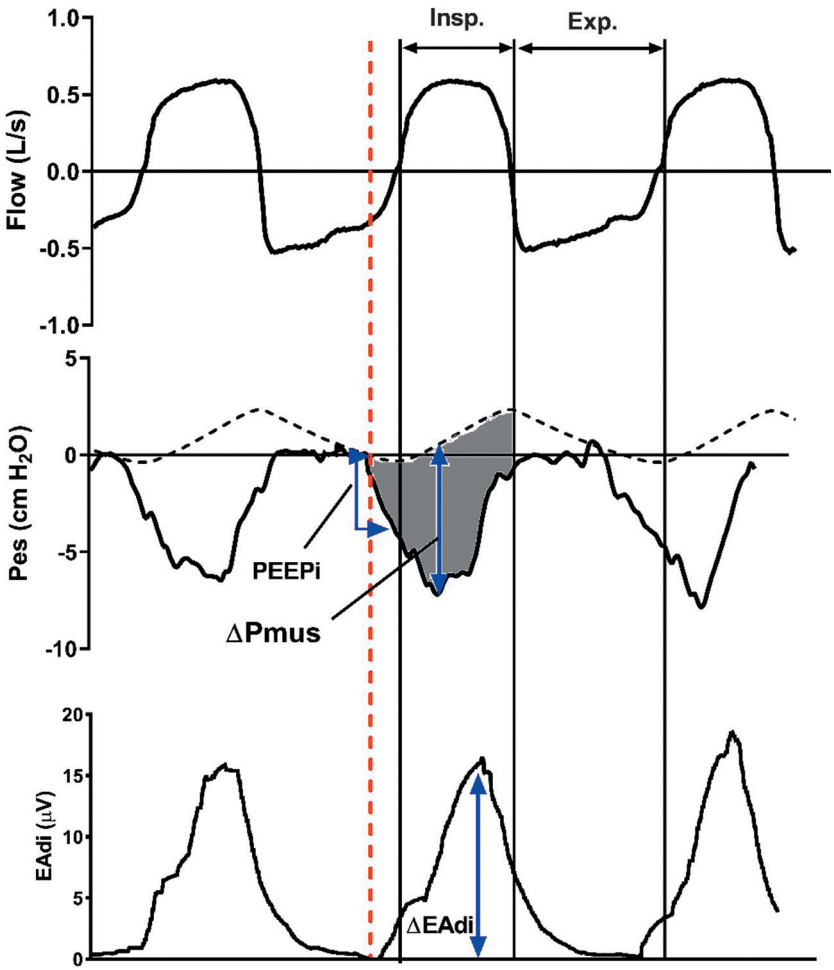

Figure S1 Calculation illustration of the pressure generated by global inspiratory muscles (ΔPmus), the inspiratory pressure-time product (PTPpes,insp), and the electrical activity of diaphragm (ΔEAdi). The recoil pressure of the chest wall (dotted black curve line) is calculated from the predicted elastance of chest wall (4% vital capacity) and the lung volume. The recoil pressure starts from the onset of the Pes dropping. The broken vertical red line indicates the onset of the decrease in Pes. The following three solid lines indicate the start and end of the inspiration and expiration of one breathing circle. The ΔPmus,insp is the difference between the nadir of the Pes tracing and the chest recoil pressure at the same time (blue arrow). The intrinsic positive end expiratory pressure (PEEPi) is the part between the onset of Pes dropping and the start of the inspiratory flow. The PTPpes,insp is calculated as the area between the chest wall recoil pressure and the esophageal pressure (gray area). The amplitude of electrical activity of the diaphragm (ΔEAdi) is the difference between the onset of EAdi rising and the peak of the EAdi (blue arrow).

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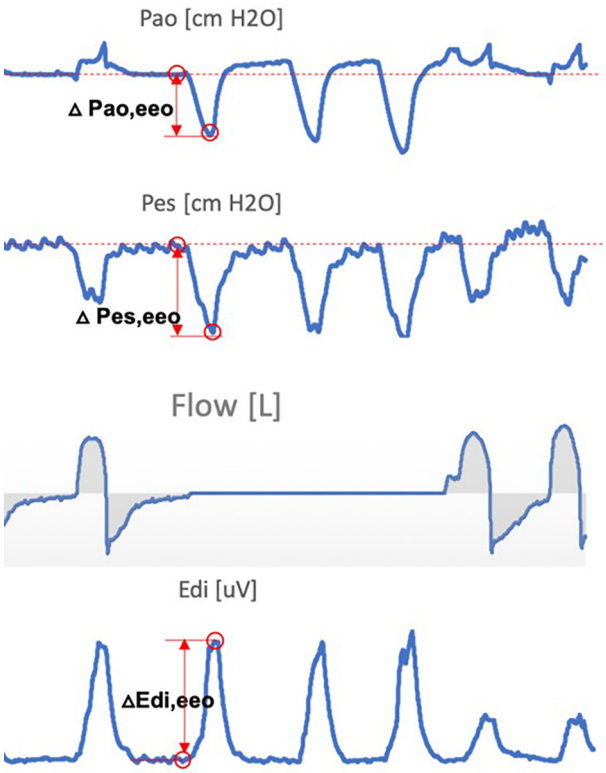

Figure S2 Calculation illustration of the neuro-mechanical efficiency during the end-expiratory occlusion (NMEoccl). From top to bottom are the airway pressure (Pao), esophageal pressure (Pes), flow, and electrical activity of diaphragm (EAdi) tracing. The end-expiratory occlusion includes three breathing efforts. The calculation is performed with the fist breath, both the Pes and Pao could be used to calculate the NMEoccl. Amplitude of inspiratory Pes (ΔPes,eeo) and EAdi (ΔEAdi,eeo) are same as described in the Fig. S1. The NMEoocl is defined as the ΔPao,eeo divided by the ΔEAdi,eeo.

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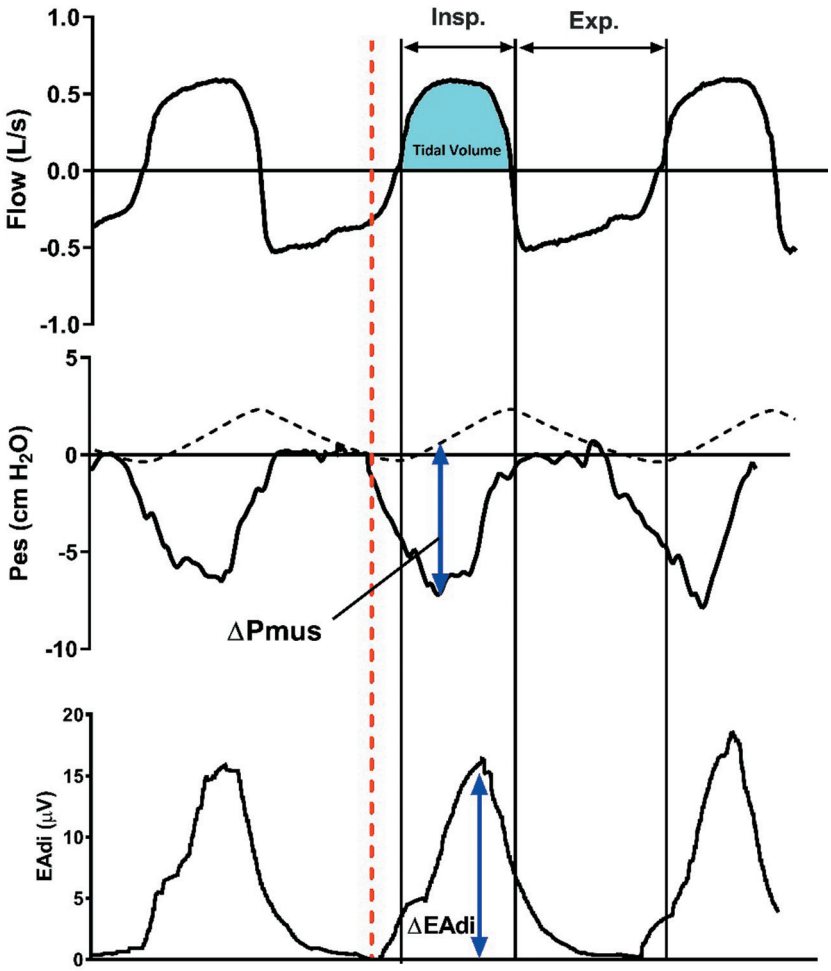

Figure S3 Calculation illustration of the dynamic neuro-mechanical efficiency (NMEdyn) and neuro-ventilatory efficiency (NVE) during tidal breathing. Inspiratory tidal volume (Vt) is integrated from flow signal during the inspiration. The ΔEAdi and ΔPmus calculated as mentioned in Fig. S1. The NMEdyn is the ratio of ΔPmus divided by the ΔEAdi. The NVE is the ratio of tidal volume divided by the ΔEAdi.

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Table S1 Protocolized criteria for failed spontaneous breathing trial

Tachypnea: respiratory rate >35 breaths/min for ≥5 min
Hypoxemia: pulse oximeter <90% despite increasing F_{IO2} to 0.5 for ≥30 s
Heart rate: >140 beats/min or a 20% change from baseline for ≥1 min
Hypertension or hypotension: systolic blood pressure >180 or <90 mmHg for ≥1 min
Agitation, diaphoresis, or anxiety confirmed as a change from baseline and present for >5 min

Table S2 Screening checklist used to determine the patient's suitability for extubation

Question	Answer
1. Awake and alert with cerebral function adequate for patient co-operation or equivalent pre SBT state of consciousness?	Yes □ No □
2. Haemodynamic stability (lack of vasopressor support and mean arterial pressure within 10–15% of baseline)?	Yes □ No □
3. Adequate recovery of muscle strength?	Yes □ No □
4. Normal tidal volumes, normocapnia (end-tidal carbon dioxide 30–45 mm Hg), minimum pulse oximetry >95% with F_{IO2} 0.5?	Yes □ No □
5. Intact gag reflex and swallow function (presence of clearly audible cough during suctioning)?	Yes □ No □
The answer to all questions must be "yes" in order for extubation to be approved.	

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Table S3 Characteristics of subjects in the ventilator failed liberation (A) and successful ventilator liberation (B) groups.

A Subjects failed ventilator liberation (Defined as reconnection to the ventilator or reintubation within 48 hours)

Patients No.	Age (yr)	Sex (M/F)	Location of lesion	MV indications	Failed extubation or separation (hours)	Reasons for reconnection to MV
1	52	Male	Supratentorial, frontal lobe (right)	Intracerebral hemorrhage, Stroke	12.3	Neurological deterioration
3	52	Male	Infratentorial, petroclival region (left)	Neurogenic pulmonary edema	0.2	Upper airway obstruction after extubation
4	61	Male	Infratentorial, ventral medulla (right)	Respiratory center involvement	0.5	Upper airway obstruction after extubation
5	51	Male	Supratentorial, middle cranial fossa	Coma	29.9	Severe pneumonia
6	55	Male	Infratentorial, cerebellopontine angle (left)	Pulmonary embolism	3.1	Upper airway obstruction after extubation
12	32	Male	Supratentorial, temporal lobe, basal segment region (right)	Intracerebral hemorrhage, Stroke	4.4	Neurological deterioration
13	53	Female	Infratentorial, cerebellum (bilateral)	Post cardiac arrest hypoxic ischemic brain injury	20.2	Pulmonary edema
14	61	Female	Infratentorial, petroclival region (right)	Lung atelectasis	14.0	Severe pneumonia
17	39	Male	Supratentorial, temporal lobe (right)	Cerebral herniation	11.8	Neurological deterioration
18	50	Female	Infratentorial, hypothalamus (right)	Coma	0.9	Neurological deterioration
21	67	Male	Supratentorial, occipital lobe (right)	Cerebral infarction	37.3	Neurological deterioration
25	55	Male	Supratentorial, middle cranial fossa	Acute respiratory distress syndrome	4.8	Severe pneumonia
31	39	Female	Infratentorial, jugular foramen region (right)	Respiratory center involvement	39	Upper airway obstruction after extubation
49	52	Male	Infratentorial, ventral medulla (left)	Respiratory center involvement	1.3	Neurological deterioration
59	33	Male	Infratentorial, ventral medulla (left)	Respiratory center involvement	5.0	Respiratory muscle weakness
64	30	Male	Infratentorial, cerebellum (right)	Respiratory center involvement	4.0	Neurological deterioration
65	30	Male	Supratentorial, frontal, temporal lobe (right)	Intracerebral hemorrhage, Stroke	1.0	Neurological deterioration

B Subjects with successful ventilator liberation (Defined as remained liberated form the ventilator 48 hours after the SBT).

Patient No.	Age (yr)	Sex (M/F)	Location of lesion	MV indications	Time between end of the SBT and the reconnection to MV (hours)	Reasons for reconnection to MV
2	69	Male	Infratentorial, ventral medulla	Neurogenic pulmonary edema	99.9	Hospital acquired pneumonia (Aspiration)
7	72	Male	Infratentorial, dorsal medulla	Respiratory center involvement	192.9	Hospital acquired pneumonia (Aspiration)
8	68	Male	Carotid artery (right)	Cerebral infarction	109.5	Neurologic deterioration
9	65	Male	Middle cerebral artery (right)	Acute respiratory distress syndrome	---	---
10	52	Male	Middle meningeal artery (right)	Coma	---	---
15	37	Male	Supratentorial, frontal, temporal lobe (left)	Lung atelectasis	---	---
16	38	Male	Supratentorial, basal ganglia (left)	Aspiration pneumonia	74.5	Hospital acquired pneumonia (Aspiration)
19	59	Female	Supratentorial, hypothalamus (right)	Hypothalamic dysfunction	---	---
20	73	Female	Supratentorial, parietal, temporal lobe (left)	Postoperative epilepsy	---	---
22	53	Male	Infratentorial, cerebellum (left)	Neurogenic pulmonary edema	53.0	Post-extubation respiratory failure
24	52	Male	Infratentorial, cerebellum (left)	Pneumonia	---	---
26	61	Female	Infratentorial, cerebellopontine angle (right)	Sepsis (central nervous system)	588.2	Septic shock (Catheter-related bloodstream infection)
27	33	Female	Infratentorial, cerebellum	Acute respiratory distress syndrome	75.2	Lung atelectasis
29	59	Male	Infratentorial, midbrain, pons	Respiratory center involvement	---	---
30	36	Male	Infratentorial, ventral medulla	Lung atelectasis	---	---
32	56	Male	Supratentorial, middle cranial fossa	Pulmonary embolism	---	---
33	44	Female	Infratentorial, ventral medulla	Neurogenic pulmonary edema	53.3	Septic shock (Catheter-related bloodstream infection)
34	51	Male	Supratentorial frontal lobe (right)	Non neurological upper airway occlusion	168.0	Hospital acquired pneumonia
41	22	Male	Infratentorial, cerebellopontine angle (right)	Respiratory center involvement	58.5	Septic shock (Catheter-related bloodstream infection)
43	64	Male	Supratentorial, ventricular (right)	Postoperative epilepsy	---	---
45	33	Female	Supratentorial, ventricular (right)	Hydrocephalus, Intracranial hypertension	---	---
46	68	Female	Supratentorial, frontal lobe (left)	Intracranial hypertension	---	---
50	46	Female	Infratentorial, petroclival region (left)	Acute respiratory distress syndrome	---	---
52	50	Male	Infratentorial, ventral medulla (left)	Pneumonia	---	---
54	66	Female	Infratentorial, cerebellopontine angle (left)	Respiratory center involvement	58.0	Neurologic deterioration
55	53	Male	Infratentorial, ventral medulla (left)	Respiratory center involvement	---	---
57	72	Female	Infratentorial, cerebellum (right)	Acute respiratory distress syndrome	93.0	Hospital acquired pneumonia
60	57	Male	Supratentorial, temporal lobe (right)	Pulmonary embolism	---	---
63	67	Female	Carotid artery (right)	Intracranial hypertension	72.0	Neurologic deterioration

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Table S4 Respiratory parameters during the SBT in successful (S) and failed (F) ventilator liberation groups within 48 hours after the SBT

Variables		Baseline	1MIN	5MIN	10MIN	20MIN	30MIN	P Value		
								Main Effects	Interaction	Interaction
								Time	Group	Time*Group
Tidal Volume (ml)	S	474.5 (352.2, 597.1)	403.0 (278.8, 524.3)‡	437.4 (336.3, 541.9) †	438.7 (321.0, 538.6)	388 (340.1, 537.4)	446.8 (341.9, 533.3) †	.035	.42	.73
	F	450.9 (395.9, 724.7)	390.1 (318.8, 561.3)†	415.6 (335.0, 600.7)	449 (336.9, 602.9)	397.9 (348.9, 613.5)	397.2 (340.1, 616.6)			
Respiratory rate (Breath/min)	S	19.1 (15.8, 22.2)	21.4 (16.8, 25.6)‡	20.8 (16.9, 25.6)	22.5 (14.3, 24.7)	21.0 (15.6, 25)	21.7 (16.7, 25.8)	.055	.69	.97
	F	19.1 (14.4, 25.9)	22.1 (17, 27.9)†	20.5 (16.5, 28.9)	20.3 (17.3, 28.6)	20.8 (16.3, 29)	20.4 (17.9, 28.1)			
Minute ventilation (L)	S	9 (7.7, 10.4)	7.8 (6.4, 10.0)†	8.6 (7.0, 9.8)	8.3 (7.1, 9.7)	8.4 (7.6, 10.1)	8.4 (7.8, 10.0) †	.051	.17	.81
	F	10.5 (6.7, 12.2)	9.9 (6.9, 10.9)	9.7 (7.7, 10.7)	9.0 (7.6, 11.3)	9.1 (7.3, 11.4)	9.5 (7.6, 11.3)			
Inspiratory time (sec)	S	1.1 (0.9, 1.3)	1.1 (0.9, 1.2)	1.1 (0.9, 1.3)	1 (0.9, 1.3)	1 (1, 1.2)	1.1 (0.9, 1.2)	.024	.47	.92
	F	0.9 (0.9, 1.2)	1 (0.9, 1.2)	1 (0.8, 1.3)	1 (0.9, 1.3)	0.9 (0.9, 1.2)	1 (0.9, 1.2)			
Expiratory time (sec)	S	2.1 (1.8, 2.6)	1.8 (1.5, 2.3)‡	1.9 (1.6, 2.3)	1.8 (1.5, 2.5)	1.8 (1.6, 2.5)	1.9 (1.4, 2.4)	.002	.87	.81
	F	2.1 (1.4, 2.9)	1.8 (1.3, 2.4)	1.8 (1.2, 2.5)	2 (1.2, 2.3)	1.8 (1.2, 2.5)	1.8 (1.2, 2.3)			
Duty cycle (%)	S	32.7 (31.1, 39.2)	36.8 (34.3, 40.0)‡	36.9 (33.9, 38.5)	37.1 (33.2, 40.7)	36.6 (34.2, 39.6)	37.8 (32.7, 41.3)	.27	.79	.97
	F	33.7 (29.0, 39.4)	37.9 (31.9, 40.6)†	36.1 (31.1, 40.3)	36.7 (30.4, 41.6)	36 (31.1, 41.8)	36.2 (32.2, 42.1)			
RR/VT (Breath•min^{-1}•L^{-1})	S	41.5 (25.8, 60.9)	52.9 (30.5, 87.8)‡	46.1 (30.4, 78.5) †	43.3 (25.6, 83.5) †	52.5 (29.2, 75.2)	48 (32.2, 74.9)	.026	.39	.76
	F	38.6 (17.6, 54.5)	51.2 (26.7, 78.1)†	52.3 (24.5, 70.0)	49.7 (25.7, 66.1)	48.4 (27.9, 71.5)	47.7 (28.8, 69.1)			
PEEPi (cmH_2O)	S	1.0 (0.4, 1.6)	1.3 (0.6, 2)	1.0 (0.5, 2.1)	1.1 (0.5, 1.6)	0.9 (0.4, 1.8)	1.0 (0.3, 1.3)	.06	.42	.97
	F	1.0 (0.1, 1.6)	1.2 (0.5, 2)	1.1 (0.5, 1.5)	0.7 (0.3, 1.7)	0.8 (0.5, 1.2)	0.6 (0.1, 1.4)			
PTP per breath (cmH_2O•sec)	S	4.1 (1.7, 6.4)	7.1 (4.2, 8.5)‡	7 (5.6, 9.3)	8.1 (5.9, 10.0)	7.3 (5.6, 9.7)	8.1 (5.7, 10)	.76	.34	.58
	F	4.7 (2.4, 7.4)	7.5 (5, 10.8)‡	8.4 (6.2, 11.6)	8.2 (5.6, 12.4)	8.5 (5.4, 11.6)	7.4 (5.7, 10.7)			
PTP per liter (cmH_2O•sec•L^{-1})	S	7.4 (4.5, 11.2)	17.1 (11.9, 22.4)‡	17.0 (12.9, 21.3)	18.2 (13.4, 22.6)	18.0 (13.6, 22.7)	18.0 (14.9, 22.6)	.70	.94	.83
	F	7.4 (6.1, 10.3)	16.7 (13.2, 23.7)‡	18.2 (12.3, 22.7)	18.2 (15.8, 22.4)	17.7 (15.2, 21)	17.7 (15.8, 19.9)			
NVE (ml/μV)	S	208.6 (119.5, 324.2)	67.9 (37.4, 125.3)‡	64.9 (44.0, 110.2)	63.2 (45.1, 115.8)	72.2 (41.4, 105.4)	66.1 (36.9, 115.2)	.58	.89	.58
	F	101.9 (64.0, 294.2)	53.0 (39.1, 191.3)	57.5 (29.5, 116.3)	55.1 (33.5, 138.9)	54.7 (30.1, 149.8)	50.1 (38.1, 97.9)			
NMEdyn (cmH_2O/ μV)	S	1.5 (0.8, 2.0)	1.2 (0.8, 1.8)	1.2 (0.9, 1.7)	1.2 (0.9, 2.5)	1.2 (1, 2.4)	1.1 (0.9, 1.8)	.24	.12	.81
	F	1.5 (0.8, 3.7)	1.5 (1.1, 4.2)	1.2 (1.0, 4.0)	1.5 (1.0, 3.6)	1.2 (1.0, 4.2)	1.7 (1.0, 3.0)			
ΔPmus (cmH_2O)	S	6.0 (1.8, 7.8)	8.7 (6.2, 11.5)‡	10.0 (8.3, 12.2)	11.3 (8.1, 13.2)	10.8 (8.0, 12.9) †	11.2 (8.4, 13.3) †	.003	.11	.78
	F	7.9 (3.6, 10.1)	10.3 (8.1, 16.5)‡	11 (8.8, 16.1)	13.4 (8.9, 15.6)	12.5 (8.6, 18.5)	11.7 (8.7, 18.1)			
PTP per min (cmH_2O•min)	S	60.4 (38.9, 112.5)	142.3 (96.7, 187.7)‡	150.2 (103.5, 180)	142.3 (111.7, 197.7)	167.1 (113.9, 194.4)	162.7 (124.5, 195.7)	.60	.22	.58
	F	95.6 (36.1, 154.9)	176.0 (121.2, 239.9)‡	175.1 (121.5, 227.4)	167.5 (130.5, 221.2)	164.3 (136.0, 238.7)	167.8 (125.1, 213.9)			
ΔEAdi (μV)	S	2.4 (1.3, 4.4)	5.8 (3.4, 10.3)‡	6.5 (3.8, 9.9)	6.3 (3.7, 10.9)	5.8 (3.7, 9.7)	6.8 (3.5, 12.3)	.29	.21	.84
	F	5.4 (2.2, 8.0)	8.3 (3.0, 12.4)	10.2 (4.3, 14.6)	9.4 (4.8, 13.2)	10.1 (4.0, 15)	8.7 (5.0, 13.4)			
NMEoocl (cmH_2O/ μV)	S	2.8 (1.5, 4.8)	2.0 (1.4, 5.1)	2.0 (1.3, 3.9)	2.0 (1.1, 3.3)	2.4 (1.4, 3.8)	2.0 (1.6, 4.5)	.89	.75	.34
	F	2.0 (1.5, 4.6)	2.0 (1.8, 3.6)	1.7 (1.2, 4)	1.7 (1.2, 5.2)	1.8 (1.3, 6.6)	2.1 (1.1, 4.1)			

Data are presented as median (interquartile range). No significant differences between two groups were observed at baseline and each time points during the spontaneous breathing trial. Within each group, comparison between the baseline and the first minute of the spontaneous breathing trial: † p <0.05, ‡ p <0.001. And comparison between the first minute after the start of the SBT and other time points after it: † P <0.05, ‡ P <0.001. SBT, spontaneous breathing trial; RR, respiratory rate; VT, tidal volume; PEEPi, intrinsic positive end-expiratory pressure; PTP, pressure-time-product; NVE, neuro-ventilatory efficiency; NMEdyn, dynamic neuro-mechanical efficiency; ΔPmus, global inspiratory muscles pressure; ΔEAdi, electrical activity of the diaphragm; NMEoocl, static neuro-mechanical efficiency.

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Table S5 Respiratory parameters during the SBT in successful (S) and failed (F) ventilator liberation groups within 7 days after the SBT

Variables		Baseline	1MIN	5MIN	10MIN	20MIN	30MIN	P Value		
								Main Effects		Interaction
								Time	Group	Time*Group
Tidal Volume (ml)	S	474.5 (352.2, 597.1)	403.0 (278.8, 524.3)‡	437.4 (336.3, 541.9)†	438.7 (321, 538.6)	388.0 (340.1, 537.4)	446.8 (341.9, 533.3)	.006	.65	.74
	F	450.9 (395.9, 724.7)	390.1(318.8, 561.3)‡	415.6 (335, 600.7)	449.0 (336.9, 602.9)	397.9 (348.9, 613.5)	397.2 (340.1, 616.6)			
Respiratory rate (Breath/min)	S	19.1 (15.8, 22.2)	21.4 (16.8, 25.6)‡	20.8 (16.9, 25.6)	22.5 (14.3, 24.7)	21.0 (15.6, 25.0)	21.7 (16.7, 25.8)	.05	.26	.42
	F	19.1 (14.4, 25.9)	22.1 (17, 27.9)†	20.5 (16.5, 28.9)	20.3 (17.3, 28.6)	20.8 (16.3, 29.0)	20.4 (17.9, 28.1)			
Minute ventilation (L)	S	9.0 (7.7, 10.4)	7.8 (6.4, 10.0)	8.6 (7.0, 9.8)	8.3 (7.1, 9.7)	8.4 (7.6, 10.1)	8.4 (7.8, 10.0)	.02	.50	.89
	F	10.5 (6.7, 12.2)	9.9 (6.9, 10.9)	9.7 (7.7, 10.7)	9 (7.6, 11.3)	9.1 (7.3, 11.4)	9.5 (7.6, 11.3)			
Inspiratory time(sec)	S	1.1 (0.9, 1.3)	1.1 (0.9, 1.2)	1.1 (0.9, 1.3)	1.0 (0.9, 1.3)	1.0 (1.0, 1.2)	1.1 (0.9, 1.2)	.017	.27	.87
	F	0.9 (0.9, 1.2)	1.0 (0.9, 1.2)	1.0 (0.8, 1.3)	1.0 (0.9, 1.3)	0.9 (0.9, 1.2)	1 (0.9, 1.2)			
Expiratory time(sec)	S	2.1 (1.8, 2.6)	1.8 (1.5, 2.3)†	1.9 (1.6, 2.3)	1.8 (1.5, 2.5)	1.8 (1.6, 2.5)	1.9 (1.4, 2.4)	.001	.54	.26
	F	2.1 (1.4, 2.9)	1.8 (1.3, 2.4)†	1.8 (1.2, 2.5)	2 (1.2, 2.3)	1.8 (1.2, 2.5)	1.8 (1.2, 2.3)			
Duty cycle (%)	S	32.7 (31.1, 39.2)	36.8 (34.3, 40.0)†	36.9 (33.9, 38.5)	37.1 (33.2, 40.7)	36.6 (34.2, 39.6)	37.8 (32.7, 41.3)	.22	.55	.32
	F	33.7 (29.0, 39.4)	37.9 (31.9, 40.6)†	36.1 (31.1, 40.3)	36.7 (30.4, 41.6)	36 (31.1, 41.8)	36.2 (32.2, 42.1)			
RR/VT (Breath•min^{-1}•L^{-1})	S	41.4 (25.8, 60.9)	52.9 (30.5, 87.8)‡	46.1 (30.4, 78.5)	43.3 (25.6, 83.5) †	52.5 (29.2, 75.2)	48.0 (32.2, 74.9)	.030	.88	.43
	F	38.6 (17.6, 54.5)	51.2 (26.7, 78.1)‡	52.3 (24.5, 70)	49.7 (25.7, 66.1)	48.4 (27.9, 71.5)	47.7 (28.8, 69.1)			
PEEPi (cmH_2O)	S	1.0(0.4, 1.6)	1.3 (0.6, 2.0)	1.0 (0.5, 2.1)	1.1 (0.5, 1.6)	0.9 (0.4, 1.8)	1.0 (0.3, 1.3)	.030	.60	.84
	F	1.0 (0.1, 1.6)	1.2 (0.5, 2.0)	1.1 (0.5, 1.5)	0.7 (0.3, 1.7)	0.8 (0.5, 1.2)	0.6 (0.1, 1.4)			
PTP per breath (cmH_2O•sec)	S	4.1 (1.7, 6.4)	7.1 (4.2, 8.5)†	7.0 (5.6, 9.3)	8.1 (5.9, 10.0)	7.3 (5.6, 9.7)	8.1 (5.7, 10.0)	.54	.66	.72
	F	4.7 (2.4, 7.4)	7.5 (5.0, 10.8)‡	8.4 (6.2, 11.6)	8.2 (5.6, 12.4)	8.5 (5.4, 11.6)	7.4 (5.7, 10.7)			
PTP per liter (cmH_2O•sec•L^{-1})	S	7.4 (4.5, 11.2)	17.1 (11.9, 22.4)‡	17 (12.9, 21.3)	18.2 (13.4, 22.6)	18 (13.6, 22.7)	18 (14.9, 22.6)	.54	.71	.92
	F	7.4 (6.1, 10.3)	16.7 (13.2, 23.7)‡	18.2 (12.3, 22.7)	18.2 (15.8, 22.4)	17.7 (15.2, 21)	17.7 (15.8, 19.9)			
NVE (ml/μV)	S	208.6 (119.5, 324.2)	67.9 (37.4, 125.3)	64.9 (44.0, 110.2)	63.2 (45.1, 115.8)	72.2 (41.4, 105.4)	66.1 (36.9, 115.2)	.55	.45	.62
	F	101.9 (64.0, 294.2)	53.0 (39.1, 191.3)	57.5 (29.5, 116.3)	55.1 (33.5, 138.9)	54.7 (30.1, 149.8)	50.1 (38.1, 97.9)			
NMEdyn (cmH_2O/ μV)	S	1.5 (0.8, 2.0)	1.2 (0.8, 1.8)	1.2 (0.9, 1.7)	1.2 (0.9, 2.5)	1.2 (1.0, 2.4)	1.1 (0.9, 1.8)	.25	.26	.82
	F	1.5 (0.8, 3.7)	1.5 (1.1, 4.2)	1.2 (1.0, 4.0)	1.5 (1.0, 3.6)	1.2 (1.0, 4.2)	1.7 (1.0, 3.0)			
ΔPmus (cmH_2O)	S	6.0 (1.8, 7.8)	8.7 (6.2, 11.5)‡	10.0 (8.3, 12.2)	11.3 (8.1, 13.2) †	10.8 (8.0, 12.9)	11.2 (8.4, 13.3)	.001	.23	.65
	F	7.9 (3.6, 10.1)	10.3 (8.1, 16.5)‡	11.0 (8.8, 16.1)	13.4 (8.9, 15.6)	12.5 (8.6, 18.5)	11.7 (8.7, 18.1)			
PTP per min (cmH_2O•min)	S	60.4 (38.9, 112.5)	142.3 (96.7, 187.7)‡	150.2 (103.5, 180.0)	142.3 (111.7, 197.7)	167.1 (113.9, 194.4)	162.7 (124.5, 195.7)	.47	.29	.93
	F	95.6 (36.1, 154.9)	176 (121.2, 239.9)‡	175.1 (121.5, 227.4)	167.5 (130.5, 221.2)	164.3 (136, 238.7)	167.8 (125.1, 213.9)			
ΔEAdi (μV)	S	2.4 (1.3, 4.4)	5.8 (3.4, 10.3)†	6.5 (3.8, 9.9)	6.3 (3.7, 10.9)	5.8 (3.7, 9.7)	6.8 (3.5, 12.3)	.39	.87	.47
	F	5.4 (2.2, 8)	8.3 (3, 12.4)‡	10.2 (4.3, 14.6)	9.4 (4.8, 13.2)	10.1 (4.0, 15.0)	8.7 (5.0, 13.4)			
NMEoocl (cmH_2O/ μV)	S	2.8 (1.5, 4.8)	2.0 (1.4, 5.1)	2.0 (1.3, 3.9)	2.0 (1.1, 3.3)	2.4 (1.4, 3.8)	2.0 (1.6, 4.5)	.69	.40	.81
	F	2.0 (1.5, 4.6)	2.0 (1.8, 3.6)	1.7 (1.2, 4.0)	1.7 (1.2, 5.2)	1.8 (1.3, 6.6)	2.1 (1.1, 4.1)			

Data are presented as median (interquartile range). No significant differences between two groups were observed at baseline and each time points during the spontaneous breathing trial. Within each group, comparison between the baseline and the first minute of the spontaneous breathing trial: † P<0.05, ‡ P<0.001. And comparison between the first minute after the start of the SBT and other time points after it: † P<0.05, ‡ P<0.001. SBT, spontaneous breathing trial; RR, respiratory rate; VT, tidal volume; PEEPi, intrinsic positive end-expiratory pressure; PTP, pressure-time-product; NVE, neuro-ventilatory efficiency; NMEdyn, dynamic neuro-mechanical efficiency; ΔPmus, global inspiratory muscles pressure; ΔEAdi, electrical activity of the diaphragm; NMEoocl, static neuro-mechanical efficiency.

Early and delayed extubation after the first SBT

Within 48 hours after the first SBT, 13 (28.3%) subjects were extubated, and 33 (71.7%) subjects were remained breathing through a T-tube circuit with humidified oxygen. The rate of failed ventilator liberation in subjects extubated and subjects without extubation were not different (4/13 (30.8%) *vs.* 13/33 (39.4%), respectively, P=0.74).

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Table S6 Respiratory parameters during the SBT in successful (S) and failed (F) ventilator liberation groups within 48 hours after the SBT in subjects remaining intubated within 48 hours

Variables		Baseline	1MIN	5MIN	10MIN	20MIN	30MIN	P Value		
								Main Effects		Interaction
								Group	Time*Group	Time*Group
Tidal Volume (ml)	S	511.2(376.7-592.8)	440.2(284.8-525) ‡	454.4(349.8-550)	445.0(347.8-539.9)	462.1(340.7-540.2) †	485.6(364.8-535.7) †	<.001	.83	.57
	F	450.9(400.8-686.7)	370.0(309.5-517.5) ‡	412(335-571.9)	392.7(330.1-583.9)	397.9(348.9-613.5)	388.8(340.1-616.6) †			
Respiratory rate (Breath/min)	S	18.7(16-22.2)	20.8(17-23.1) †	20.2(17.6-22.3)	20.6(15.1-23.4)	20.8(16.7-24)	20.0(16.9-24.4)	.44	.17	.72
	F	20.4(16.5-27)	23.3(18.7-29) †	24.0(17.1-29.6)	23.1(17.8-29.1)	22.9(18.1-29.3)	20.9(18.5-29.9)			
Minute ventilation (L)	S	9.2(8.2-10.5)	7.9(6.4-10.1)	9.4(7.5-9.9)	8.5(7.3-10.1)	8.9(7.8-10.3)	8.7(7.9-10.6) †	.002	.23	0.91
	F	10.5(7.2-12.1)	10.3(7.0-11.5) †	10.1(7.7-10.8)	10.0(7.6-11.7)	10.5(7.8-11.9)	10.6(7.6-11.4)			
Inspiratory time(sec)	S	1.14(0.97-1.29)	1.13(1.01-1.23)	1.13(0.98-1.35)	1.08(0.92-1.4)	1.05(0.98-1.25)	1.09(1.02-1.38)	.18	.09	.28
	F	0.91(0.89-1.18)	0.93(0.84-1.12)	0.95(0.83-1.16)	0.98(0.85-1.17)	0.94(0.84-1.15)	0.97(0.86-1.14)			
Expiratory time(sec)	S	2.13(1.87-2.48)	1.85(1.58-2.22) †	1.9(1.77-2.23)	1.80(1.60-2.42)	1.83(1.59-2.28)	1.91(1.49-2.29)	.08	.28	.51
	F	2.05(1.32-2.61)	1.58(1.2-1.95) †	1.54(1.17-2.2)	1.64(1.17-2.23)	1.7(1.16-2.05)	1.71(1.12-2.17)			
Duty cycle (%)	S	32.7(32.2-39.7)	36.6(32.2-40)	37.0(34.5-38.4)	36.9(33.6-41.1)	36.7(35.3-39.7)	37.9(33.6-41.6)	.62	.49	.75
	F	35.9(29.8-40.1)	39.1(34.8-41.4) †	37.7(33.3-40.6)	38.8(31.7-42.1)	38.6(33.3-42.1)	36.5(33.9-42.4)			
RR/VT (Breath•min^{-1}•L^{-1})	S	41.0(26-60.6)	49.4(29.6-80.2) ‡	42.4(33.9-69.2) †	43.0(27.3-76.1)	43.1(31.3-73.5)	46.8(32.4-59.8)	.017	.85	.59
	F	40.4(21.4-55.4)	62.2(34.5-84.5) ‡	52.3(30.7-80.2)	54.8(29.2-71.8)	48.4(29.4-74)	47.7(28.9-71)			
PEEPi (cmH_2O)	S	1.0(0.4-1.5)	1.3(0.6-1.9)	1.0(0.5-1.9)	1.1(0.3-1.6)	0.9(0.3-1.7)	0.7(0.2-1.1)	.08	.72	.83
	F	1.1(0.0-1.7)	1.2(0.5-2)	1.1(0.6-1.5)	1.3(0.2-2)	0.7(0.5-1.2)	0.5(0.1-1.2)			
PTP per breath (cmH_2O•sec)	S	4.1(1.4-6.4)	7.5(5-8.5) ‡	7.1(6.5-9.3)	8.1(5.9-10)	7.7(5.8-9.7)	8.4(7.4-10.5)	.021	.84	.52
	F	5.0(2.9-7.7)	7.1(4.3-10.2) †	8.4(3.9-11.6)	7.7(5-12.2)	8.5(5.6-11.6)	7.4(5.7-10.7) †			
PTP per liter (cmH_2O•sec•L^{-1})	S	7.4(3.5-10.8)	17.1(11.5-19.4) ‡	17.0(12.8-21.0)	19.0(13.1-21.0)	18.0(12.9-22.1)	19.0(12.4-21.9)	.27	.82	.79
	F	8.5(5.5-12.3)	16.1(12.5-23.3) ‡	17.8(11.2-22.7)	18.6(13.7-23.2)	17.7(11.9-23.1)	17.5(14.1-19.9)			
NVE (ml/μV)	S	203.9(127.8-343.5)	76.7(39.9-136.7)	72.3(48.3-127.5)	80.7(56.6-119.1)	86.4(46.8-126.4)	79.8(51.6-115.4)	.70	.56	.54
	F	101.9(61-232.4)	48.6(40.1-161.6) †	57.5(27.4-116.3)	45.8(31-138.9)	41.5(27.5-149.8)	50.1(34.6-97.9)			
NMEdyn (cmH_2O/ μV)	S	1.6(1-2.1)	1.2(0.9-2.4)	1.2(1-2.8)	1.3(1-3)	1.4(1-3)	1.2(0.9-2.4)	.029	.42	.80
	F	1.2(0.8-4.1)	1.4(1.1-3.9)	1.3(1.1-4)	1.6(1-3.6)	1.2(1-4.2)	1.6(0.9-2.8)			
ΔPmus (cmH_2O)	S	6.4(2.6-7.8)	8.8(6.2-11.3) †	10(8.9-12.2)	11.4(8.1-13.2)	11.1(7.7-12.9)	11.6(9.1-14.1) †	.002	.17	.50
	F	7.9(4.6-11.2)	9.1(7.8-15.9)	11.1(7.7-16.1)	13.7(8.6-15.6)	13.8(9.7-18.5)	12(9-17.3)			
PTP per min (cmH_2O•min)	S	76.8(29.4-112.5)	142.3(91.1-186.9) ‡	154.8(142-174.2)	177.7(104.5-199.9)	172.1(117.2-206.2)	172.2(134.5-199.7) †	.071	.29	.30
	F	101.8(50.1-156.7)	198.6(98.9-237.2) ‡	178.7(121.5-227.4)	186.1(134.0-235.2)	182.0(152.8-268.3)	177.3(130.7-213.9)			
ΔEAdi (μV)	S	2.3(1.1-4.4)	5.9(2.8-8.5)	6.6(3.5-8.5)	4.5(3.7-10.1)	5.5(3.5-9.4)	6.0(3.2-11.7)	.17	.10	.48
	F	5.4(2.5-7.6)	8.1(3.8-11.0) †	9.3(4.3-13.7)	9.4(4.8-12.2)	10.1(4.0-15.5)	8.7(5.0-11.2)			
NMEoocl (cmH_2O/ μV)	S	3.2(1.7-4.4)	2.1(1.5-6.9)	2.0(1.4-4.5)	2.2(1.3-3.3)	2.7(1.7-4.9)	2.4(1.6-4.7)	.83	.48	.31
	F	1.8(1.5-4.4)	2.0(1.9-3.3)	1.7(1.3-4.0)	1.6(1.2-5.2)	1.9(1.3-6.6)	2.3(1.2-4.1)			

Data are presented as median (interquartile range). No significant differences between two groups were observed at baseline and each time points during the spontaneous breathing trial. Within each group, comparison between the baseline and the first minute of the spontaneous breathing trial: † P <.05, ‡ P <.001. And comparison between the first minute after the start of the SBT and other time points after it: † P <.05, ‡ P <.001. SBT, spontaneous breathing trial; RR, respiratory rate; VT, tidal volume; PEEPi, intrinsic positive end-expiratory pressure; PTP, pressure-time-product; NVE, neuro-ventilatory efficiency; NMEdyn, dynamic neuro-mechanical efficiency; ΔPmus, global inspiratory muscles pressure; ΔEAdi, electrical activity of the diaphragm; NMEoocl, static neuro-mechanical efficiency.

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Appendix S1

Definition of the brain-injured patients screened:

Potential candidates for this study are brain-injured patients including:

- Traumatic brain injury (TBI, including contusion, brain hemorrhages, shearing lesions, and subdural and epidural hematomas)
- Stroke
- Global cerebral ischemia (for example, after cardiac arrest)
- Infections of the brain
- Brain tumor (including post neurosurgical status)

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