Comparison of Success Rate of Extubation Between Spontaneous Breathing Trial with Pressure Support Ventilation and T-piece in Patients with Expiratory Flow Limitation

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Background: Expiratory flow limitation (EFL) is an inability to exceed a certain flow regardless of the pressure exerted, which appears in 60% of patients with extubation failure. However, an appropriate weaning method for the patients with EFL remains unknown.

Objectives: We aimed to evaluate an effect of different techniques of spontaneous breathing trials (SBT) on a success rate of extubation in the patients with EFL.

Methods: We conducted a non-inferiority randomized controlled trial comparing between 30-minute pressure support ventilation (PSV) and 30-minute T-piece in ventilated patients with EFL who got ready to wean. The primary outcome was successful extubation during a 72-hour post-extubation period. Secondary outcomes were a reintubation rate within 7 days, time to reintubation, and a SBT success rate.

Results: A total of 99 ventilated patients with EFL consisting of male (50.5%) with the median age of 70 [23] years were recruited. The most common cause of acute respiratory failure was intrapulmonary cause (68.7%). The eligible patients were randomized into 2 groups with a ratio of 1:1. The success rate of extubation during the 72-hour period in the PSV group was non-inferior to the T-piece group: 82% and 81.63%, respectively (95%CI -0.148 to 0.156, p=0.0475). There was also non-inferiority in the reintubation rate within 7 days (22.9% in the PSV group VS 15.2% in the T-piece group; 95%CI -0.081 to 0.235, p=0.005) and the SBT success rate (96% in the PSV group VS 93.9% in the T-piece group; 95%CI -0.065 to 0.108, p<0.001). There was no significant difference in the median time to reintubation between these 2 groups (55 [95.5] hours in PSV VS 25.33 [48] hours in the T-piece group, p=0.683).

Conclusions: Among patients with EFL, the 30-minute SBT with PSV was non-inferior to the T-piece SBT in terms of the successful extubation during the 72-hour period, successful SBT, and reintubation rate within 7 days. This was the first study demonstrating that the different techniques of SBT did not affect the weaning outcomes in the patients with EFL.

Keywords: Expiratory Flow Limitation, Spontaneous Breathing Trial, Extubation Outcome

Trial registration: Thai Clinical Trial Registry TCTR20200604003. Registered 23 May 2020.

Introduction

Expiratory flow limitation (EFL) is an inability to exceed a certain expiratory flow regardless of the intraluminal pressure gradient or breathing effort of patients[1-6]. This was first documented in 1983, which appeared in 38% of patients with respiratory failure[1,7-8]. Moreover, it presents in many medical conditions, such as ARDS, heart failure, obesity, and COPD[9]. The EFL affects respiratory physiology by increased air trapping, which is associated with several clinical consequences, for examples, more severe symptoms in COPD patients, increasing risk of post-operative complications, and increasing rate of extubation failure[9-15].

Theoretically, EFL might play an important role in liberation from mechanical ventilation. However, the evidence of suitable techniques for weaning in the patients with EFL was limited. Practically, SBT is considered as a standard and effective weaning method[16,17] which consists of low-level pressure support ventilation (PSV) and T-piece. The majority of previous randomized controlled trials of different weaning methods demonstrated the similar extubation outcomes between the PSV and T-piece[18,19,21-25]. In contrast, the recent multicenter study from Spain[27] showed a significantly higher rate of successful extubation in the PSV, compared with the T-piece (82.3% in the PSV group and 74% in the T-piece group, p=0.001) but showed the similar rates of reintubation (11.1% in the PSV group and 11.9% in the T-piece group, p=0.630). It might be explained that the heterogeneity of research protocols, including duration of SBT and the use of non-invasive ventilation (NIV) prophylaxis after extubation, led to the inconsistency of the results.

Generally, the rate of extubation failure after spontaneous breathing trial (SBT) is about 20-30%[20,27,28]. Noticeably, 60% of the patients with unsuccessful extubation had EFL[9,28]. Previous studies showed that positive end expiratory pressure (PEEP)[29,30], upright position[31], bronchodilator[32], and diuretics[33] possibly improved extubation outcomes in the patients with EFL.

Up to our knowledge, there were no studies of weaning methods focusing on the patients with EFL. We hypothesized that a SBT technique with PEEP might be non-inferior or superior to other SBT techniques in terms of successful extubation among the patients with EFL. Thus, we conducted the first study to evaluate effects of 2 SBT techniques on extubation outcomes, namely a rate of successful extubation, a SBT success rate, a reintubation rate within 7 days, and time to reintubation in the patients with EFL.

Methods

Study design:

We conducted a single-center non-inferiority randomized controlled trial, which enrolled ventilated patients with EFL between June 2020 and January 2021.

Patients:

Eligible patients were age of ≥ 18 years with EFL, who were assisted with mechanical ventilation for at least 24 hours and considered as readiness for liberation from mechanical ventilation. The criteria for readiness to wean were as followed: (1) improvement of the conditions leading to intubation; (2) stable hemodynamics, defined as systolic blood pressure of 90-160 mmHg and heart rate of 50-140 beats per minute (bpm) with or without low-dose vasopressors (Norepinephrine ≤ 0.1 mcg/kg/min or Adrenaline ≤ 0.1 mcg/kg/min or Dopamine ≤ 5 mcg/kg/min); (3) intact level of consciousness, defined as Glasgow Coma Scale score (GCS) of ≥ 13; (4) no respiratory distress, defined as oxygen saturation (SpO_2) of ≥ 90% with fraction of inspired oxygen (FiO_2) ≤ 0.4, respiratory rate of ≤ 35/min, spontaneous tidal volume of ≥ 5 mL/kg; and (5) no copious secretions, defined as no greater than 2 aspirations in last 2 hours. We excluded patients with upper airway obstruction, tracheostomy tube, and do-not-reintubate (DNR) status. The written informed consents were given to all eligible patients. This study was approved by the Chulalongkorn Medical Institutional Review Board. Trial registration: Thai Clinical Trial Registry TCTR20200604003. Registered 23 May 2020.

Protocol:

All mechanically ventilated patients were screened for EFL by a PEEP reduction maneuver[9]. The patients were considered to have EFL if expiratory flow did not increase when PEEP was decreased by 3 cmH_2O (from 3 cmH_2O to 0 cmH_2O [ZEEP]) as Figure 1 and 2.

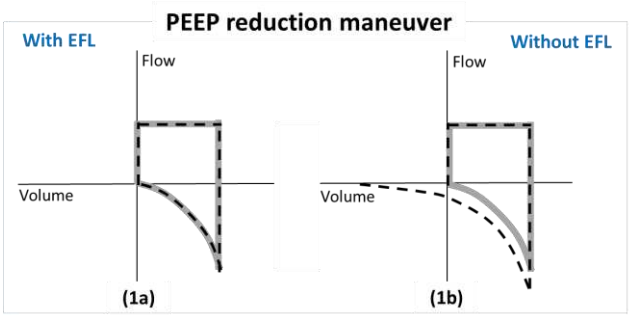

Figure 1 This figure demonstrated flow-volume loops of 2 consecutive breaths with 2 levels of PEEP in patients with EFL (1a) and without EFL (1b), who received volume control mode with square wave flow. Solid line (——) represented a flow-volume loop of PEEP 3 cmH_2O and dash line (- - -) represented a flow-volume loop of PEEP 0 cmH_2O [ZEEP].

(1a) Expiratory flow after PEEP reduction (dash line) overlapped with flow of previous consecutive breath (solid line), which represented EFL.

(1b) Expiratory flow after PEEP reduction (dash line) increased in its peak and separated apart from flow of the previous consecutive breath (solid line), which represented no EFL.

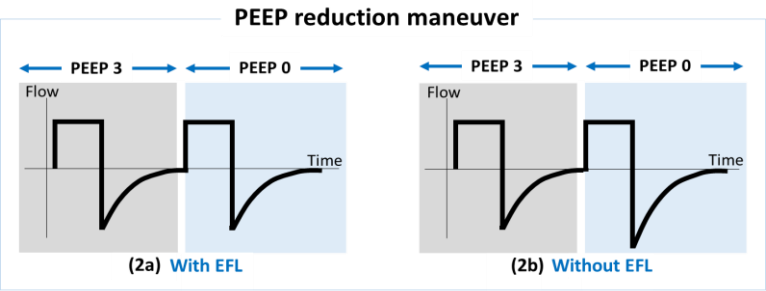

Figure 2 This figure demonstrated the flow-time waveform of 2 consecutive breaths with 2 levels of PEEP in patients with EFL (2a) and without EFL (2b), who received volume control mode with square wave flow.

(2a) Peak expiratory flow of the next consecutive breath after PEEP reduction from 3 cmH_2O to 0 cmH_2O [ZEEP] did not increased, which represented EFL.

(2b) Peak expiratory flow of the next consecutive breath after PEEP reduction from 3 cmH2O to 0 cmH_2O [ZEEP] increased, which represented no EFL.

The patients with EFL were recruited. We allocated the eligible patients by computer-generated random number in block of 4. The patients were randomly assigned into 2 groups with 1:1 ratio. The 30-minute SBT with T-piece, defined as T-piece with oxygen flow 10 liter per minutes (LPM) and FiO_2 between 0.3-0.4 to maintain SpO_2 of ≥ 90%, was provided for weaning in the control group, while the 30-minute SBT with PSV, defined as PSV mode: PS 5 cmH_2O, PEEP 5 cmH_2O, and FiO_2 between 0.3-0.4 to maintain SpO_2 of ≥ 90%, was provided in the intervention group.

All patients in both groups received the same standard care and monitoring during pre and post-extubation periods. The patients were considered as SBT failure if they met any of the following conditions: (1) respiratory distress: respiratory rate > 35/min and/or SpO_2 < 90% with FiO_2 > 0.5; (2) hemodynamic instability: heart rate > 140 bpm or ≥ 20% increase from baseline, systolic blood pressure < 90mmHg, or new onset of arrhythmia; (3) impaired consciousness (GCS score <13). The patients with SBT failure were reconnected to the ventilators.

Extubation with 24-hour non-invasive ventilation (NIV) prophylaxis was performed in all patients who passed SBT. The NIV setting was PS 7 cmH_2O, PEEP 5 cmH_2O, and FiO_2 between 0.21-0.4 to maintain SpO_2 ≥ 90%. In case of NIV intolerance, NIV was replaced with high flow nasal cannula (HFNC) with a flow rate of 50 LPM, temperature of 34°c, and FiO_2 between 0.21-0.4 to maintain SpO_2 ≥ 90%. The patients were closely monitored and observed for respiratory failure, and intubation was performed in the patients with any of these conditions: respiratory rate of > 35/min, respiratory acidosis with pH < 7.32 or PaCO2 > 45mmHg, hypoxemia

with SpO_2 < 90% under FiO_2 ≥ 0.5, conscious deterioration with GCS score < 13, or severe unexplained agitation.

Outcomes:

The primary outcome was the success rate of extubation, defined as free of mechanical ventilation during the 72-hour post-extubation period. Secondary outcomes were the success rate of SBT, reintubation rate within 7 days, time to reintubation, and reasons for reintubation. Exploratory outcomes were changes of the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PF ratio), partial pressure of arterial carbon dioxide ($PaCO_2$), and SpO_2 at 2 hours after extubation, duration of NIV prophylaxis, and reasons for NIV intolerance.

Statistical analysis:

We calculated the sample size for the non-inferiority trial with the margin of -0.15, an α=0.05 and a power of 80%. According to Subira C. et al study[27], the successful extubation rates in the PSV group and the T-piece group were 82.3% and 74%, respectively, therefore 39 patients were required in each group. We estimated a drop-out rate of 10%, so the total number of patients in each group were 43.

Categorical variables were shown as numbers and percentages, and compared by Fisher's exact test. Continuous variables were shown as mean or median, and compared by independent t-test or Wilcoxon signed rank test, depending on the distribution of data. Intention-to-treat and per-protocol principles were used for the outcome analysis. A 1-sided α=.05 was considered statistically significant. Statistical analyses were performed by STATA version 16. Graphs for subgroup analysis were generated by R program.

Results

Study participants:

Approximately, 167 patients receiving mechanical ventilation for at least 24 hours were screened. Sixty-eight patients were excluded due to the absence of EFL. A total of 99 patients met the inclusion criteria and all were recruited into the study (Figure 3). The eligible patients were male (50.51%) with the median age of 70 [23] years, BMI of 22.04 ± 4.33 kg/m^2, Charlson comorbidity index score of 4.43 ± 2.39, and APACHE II score of 15.08 ± 3.52. Of recruited patients, 73.74% were non-smoker and 26.26% had underlying airway diseases, namely asthma, COPD, bronchiectasis, tracheobronchomalacia, and unspecified small airway disease. The most common cause of acute respiratory failure was intrapulmonary origin (68.69%). The

patients were randomized into the PSV group (50 patients) and the T-piece group (49 patients). The baseline characteristics were shown in Table 1. Except for hypertension, the demographic data between 2 groups were similar.

Table 1 Baseline Characteristics

Characteristic	30-minute SBT with PSV (N 50)	30-minute T-piece SBT (N 49)	p-value
Gender			
Male	27 (54.00%)	23 (46.94%)	0.549
Age (median [IQR])	70 [25]	69 [19]	0.872
BMI (kg/m²), mean ± SD	22.36 ± 4.78	21.71 ± 3.85	0.458
Underlying disease			
Hypertension	34 (68%)	23 (46.94%)	0.043
Diabetes mellitus	16 (32%)	13 (26.53%)	0.660
Congestive heart failure	13 (26%)	10 (20.41%)	0.635
Renal impairment	16 (32%)	8 (16.33%)	0.100
• Conservative treatment	6 (12%)	2 (4.08%)	0.269
• Renal replacement therapy	10 (20%)	6 (12.24%)	0.414
Cirrhosis	3 (6%)	6 (12.24%)	0.318
Airway disease	15 (30%)	11 (22.45%)	0.495
• COPD	10 (20%)	7 (14.29%)	0.595
• Asthma	3 (6%)	1 (2.04%)	0.617
• Small airway disease, unspecified	0 (0%)	1 (2.04%)	0.495
• Bronchiectasis	1 (2%)	2 (4.08%)	0.617
• Tracheobronchomalacia	1 (2%)	0 (0%)	1.000
Cancer	13 (26%)	19 (38.78%)	0.202
Disease status			
• Former	6 (12%)	8 (16.33%)	0.577
• Current	7 (14%)	11 (22.45%)	0.308
Type of malignancy			
Solid-organ malignancy	10 (20%)	17 (34.69%)	0.118
• Brain	1 (2%)	0 (0%)	1.000
• Head & Neck Cancer	1 (2%)	2 (4.08%)	0.617
• Lung cancer	3 (6%)	5 (10.20%)	0.487
• Gastrointestinal malignancy	2 (4%)	7 (14.29%)	0.092
• Gynecologic malignancy	2 (4%)	1 (2.04%)	1.000
• Breast cancer	1 (2%)	1 (2.04%)	1.000
Hematologic malignancy	3 (6%)	2 (4.08%)	1.000
Connective tissue disease	3 (6%)	2 (4.08%)	1.000
History of smoking			
• Non-smoker	36 (72%)	37 (75.51%)	0.820
• Quit smoking	11 (22%)	11 (22.45%)	1.000
• Current smoker	3 (6%)	1 (2.04%)	0.617
Amount (Pack-year, mean ± SD)	25.54 ± 15.26	21.80 ± 14.82	0.545
Severity of current disease and pre-existing comorbidities			
Charlson Comorbidity Index (mean ± SD)	4.74 ± 2.55	4.12 ± 2.20	0.200
APACHE II (mean ± SD)	15.42 ± 4.02	14.73 ± 2.94	0.336
Blood gas analysis			
PF ratio (median [IQR])	334.25 [70.75]	320.40 [78.33]	0.716
SaO_2 (median [IQR])	98 [2.40]	98.20 [2.10]	0.713
pCO_2 (median [IQR])	31.45 [11]	30.10 [6.90]	0.152
Lung mechanics			
Airway resistance (median [IQR])	10.65 [7.92]	9.60 [5.88]	0.785
Compliance of respiratory system (median [IQR])	35.07 [19.66]	32.40 [16.08]	0.552
iPEEP by expiratory hold maneuver at ZEEP* (median [IQR]) (mean ± SD)	0.40 [0.80] 0.53 ± 0.66	0.1 [0.90] 0.54 ± 0.74	0.523

* Total data analyzed n = 91 (Missing data n = 8, all of them were assisted with Hamilton-C2 ventilator which the expiratory occlusion maneuver could not be performed)

Table 1 Baseline Characteristics (continue)

Characteristic	30-minute SBT with PSV (N 50)	30-minute T-piece SBT (N 49)	p-value
Volume status			
Negative I/O	14 (28%)	7 (14.29%)	0.140
Balanced I/O	31 (62%)	35 (71.43%)	0.395
Positive I/O	5 (10%)	7 (14.29%)	0.554
Net fluid (mL, median [IQR])	-10 [450]	10 [20]	0.125
Cause of respiratory failure			
Pulmonary cause	**33 (66%)**	**35 (71.43%)**	**0.666**
• Pneumonia	15 (30%)	17 (34.69%)	0.671
• Aspiration	2 (4%)	4 (8.16%)	0.436
• ARDS	2 (4%)	3 (6.12%)	0.678
• Secretion obstruction	0 (0%)	3 (6.12%)	0.117
• Bronchospasm	10 (20%)	7 (14.29%)	0.595
• DAH	1 (2%)	1 (2.04%)	1.000
• Pulmonary edema	8 (16%)	9 (18.37%)	0.795
• Massive pleural effusion	3 (6%)	1 (2.04%)	0.617
• Lymphangitic carcinomatosis	0 (0%)	1 (2.04%)	0.495
• Massive pulmonary embolism	0 (0%)	2 (4.08%)	0.242
• Post-intrathoracic operation	0 (0%)	1 (2.04%)	0.495
Extra-pulmonary cause	**17 (34%)**	**14 (28.57%)**	**0.666**
• Sepsis	9 (18%)	10 (20.41%)	0.803
• Metabolic acidosis from other cause	4 (8%)	1 (2.04%)	0.362
• Comatose status	3 (6%)	3 (6.12%)	1.000
• Hemorrhagic shock	2 (4%)	0 (0%)	0.495
• Post-extrathoracic operation	1 (2%)	0 (0%)	1.000
NIV before intubation	9 (18%)	6 (12.24%)	0.577
Days of mechanical ventilator before SBT (median [IQR])	3 [4]	4 [6]	0.351
Bronchodilator			
Bronchodilator use	13 (26%)	8 (16.33%)	0.326
Time after last dose of bronchodilator before SBT (hr, median [IQR])	2 [1.80]	1.50 [1]	0.827

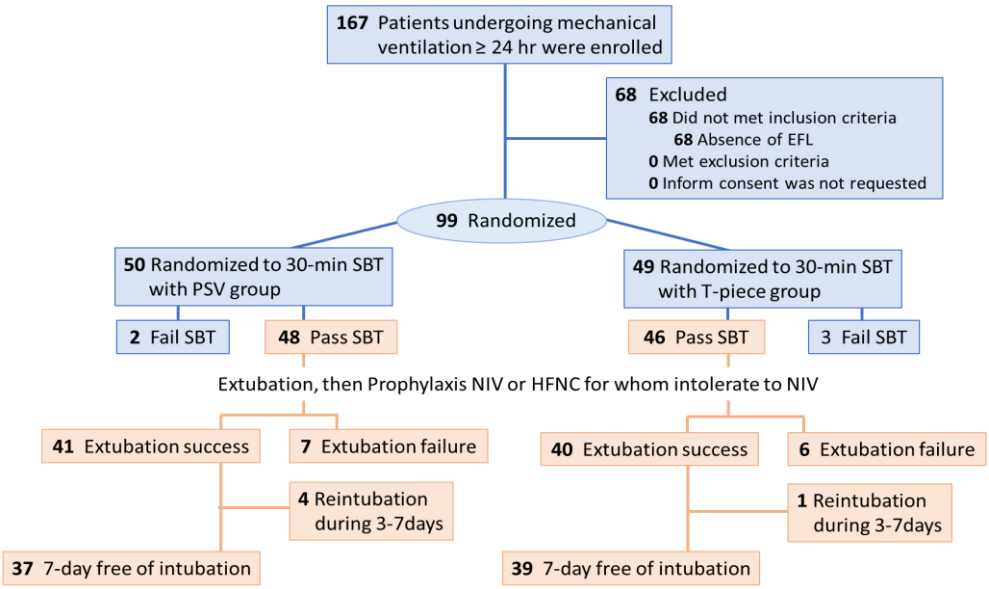

Figure 3 Flows of participants

Of 167 screened patients, 99 (59.28%) were recruited and randomized into 2 groups with a ratio of 1:1. No patients dropped out of the study. Data of all patients were used for analysis.

Primary outcome:

The success rate of extubation during the 72-hour period in the PSV group (41 out of 50, 82%) was non-inferior to the T-piece group (40 out of 49, 81.63%); 95%CI -0.148 to 0.156, p=0.0475 (Table 2 and Figure 3). However, for the patients who passed SBT, the rate of successful extubation was inconclusive: 41 out of 48 (85.42%) in the PSV group and 40 out of 46 (86.96%) in the T-piece group; 95%CI -0.155 to 0.124, p=0.0588 (Table 3 and Figure 5).

Table 2 Primary and Secondary Outcomes of All Patients (Intention-to-treat analysis)

Outcomes	30-min SBT with PSV (N 50)	30-min T-piece SBT (N 49)	95% Confidence interval	p-value*
Primary Outcome				
Extubation Success	41 (82%)	40 (81.63%)	-0.148 to 0.156	0.0475
Secondary Outcome				
SBT Success	48 (96%)	46 (93.88%)	-0.065 to 0.108	0.0001

* p-value for non-inferiority (one-sided p-value)

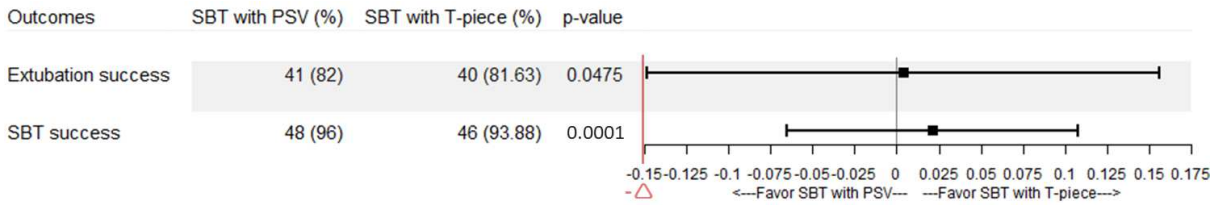

Figure 4 Forest plot showing respiratory outcomes comparing between SBT with PSV and SBT with T-piece (Intention-to-treat analysis)

Secondary outcomes:

The SBT success rate in the PSV group was non-inferior to the rate in T-piece group: 96% in the PSV group VS 93.9% in the T-piece group; 95%CI -0.065 to 0.108, p<0.001 (Table 2 and Figure 4). Similarly, the reintubation rate within 7 days in the PSV group was non-inferior to the rate in T-piece group: 11 out of 48 (22.92%) and 7 out of 46 (15.22%) respectively; 95%CI -0.081 to 0.235, p=0.005 (Table 3). Moreover, the median times to reintubation of the 2 groups were not significantly different: 54.5 [95.50] hours in PSV and 24.83 [48] hours in the T-piece group, p=0.683 (Table 4). According to Kaplan-Meier Survival Analysis, the hazard ratio (HR) of reintubation within 7 days in the PSV group was 1.55, p=0.363 (95%CI 0.602 to 4.005), compared with the T-piece group (Figure 6).

The main reason for reintubation in the PSV group was secretion obstruction (27.27%), while the main reason in the T-piece group was pneumonia (42.86%). Other reasons for reintubation in both groups were shown in Table 5.

Table 3 Primary and Secondary Outcomes of Patients with SBT Success (Per-protocol analysis: from only the patients who passed SBT)

Outcomes	30-min SBT with PSV (N 48)	30-min T-piece SBT (N 46)	95% Confidence interval	p-value
Primary Outcome				
Extubation Success	41 (85.42%)	40 (86.96%)	-0.155 to 0.124	0.0588*
Secondary Outcome				
Reintubation within 72 hours	7 (14.58%)	6 (13.04%)	-0.124 to 0.155	0.0202*
Reintubation within 7 days	11 (22.92%)	7 (15.22%)	-0.081 to 0.235	0.0052*
Time to reintubation (hr, median [IQR]	54.5 [95.50]	24.83 [48]	-	0.6834†

* one-sided p-value (p-value for non-inferiority)
† two-sided p-value

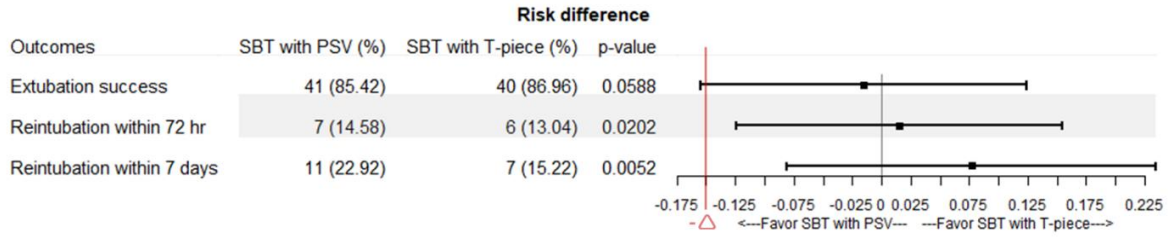

Figure 5 Forest plot showing respiratory outcomes comparing between SBT with PSV and SBT with T-piece (Per-protocol analysis)

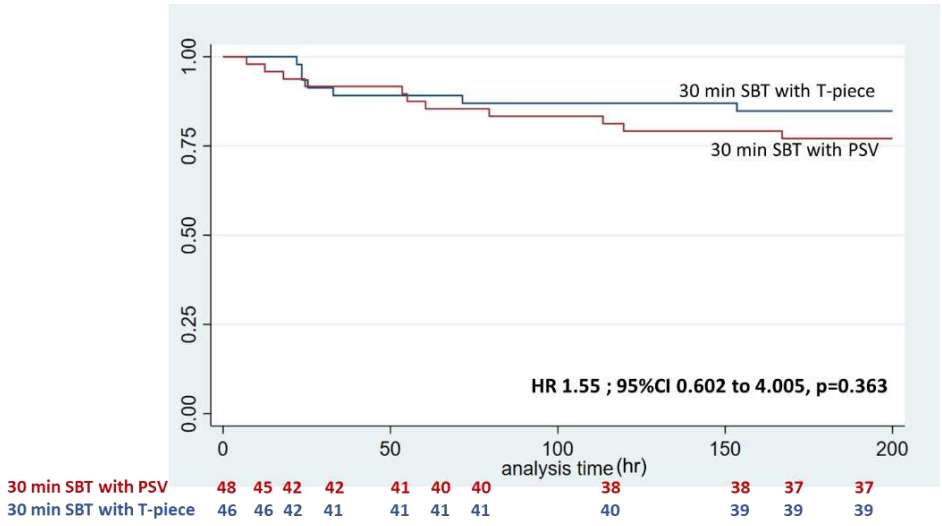

Figure 6 Kaplan-Meier Survival Analysis of reintubation within 7 days

Table 4 Exploratory Outcomes of Patients with SBT Success

Outcomes	30-minute SBT with PSV (N 48)	30-minute T-piece SBT (N 46)	p-value
Exploratory Outcome			
Blood gas analysis at 2 hours after extubation			
PF ratio (median [IQR])	328.17 [75.22]	329.67 [99.14]	0.922
SaO_2 (median [IQR])	97.90 [2.25]	97.85 [1.50]	0.895
pCO_2 (median [IQR])	30.30 [11.70]	30.15 [8]	0.391
Delta change (%, median [IQR])			
△ PF ratio	0.04 [0.16]	0 [0.21]	0.453
△ pCO_2	0 [0.05]	-0.01 [0.03]	0.150
△ SaO_2	0 [0.02]	0 [0.02]	0.976
Prophylactic NIV after extubation	32 (66.67%)	21 (45.65%)	0.061
Duration (hr, median [IQR])	18.50 [18]	23 [6]	0.476
Post-extubation HFNC after extubation	16 (33.33%)	25 (54.35%)	0.057
Duration (hr, median [IQR])	24 [27]	24 [30]	0.572
Cause leading to NIV intolerance / No NIV use (From Total N=41; 16 from the PSV group and 25 from the T-piece group)			
• Large leakage due to unfit mask	5 (31.25%)	4 (16%)	0.276
• Patient's discomfort	10 (62.50%)	17 (68%)	0.747
• Contraindication to NIV	1 (6.25%)	4 (16%)	0.632

Exploratory outcomes:

The number of patients receiving NIV prophylaxis tended to be higher in the PSV group (66.67% from the PSV group and 45.65% in the T-piece group, p=0.061). Nevertheless, the duration of NIV use tended to be shorter in the PSV group (18.5 [18] hours in the PSV group and 23 [6] hours in the T-piece group, p=0.476). HFNC was replaced in all patients unable to tolerate NIV. The durations of HFNC use in both groups were similar (24 [27] hours and 24 [30] hours in the PSV and T-piece group respectively, p=0.551). The major reason for NIV intolerance was patients' discomfort (62.5% and 68% in the PSV and the T-piece group, respectively). For the gas exchange at 2 hours after extubation, the changes of PF ratio, $PaCO_2$, and SpO_2 were not different. (Table 4)

Table 5 Reasons of reintubation within 7 days (Total N=18)

Characteristic	30-minute SBT with PSV (N 11)	30-minute T-piece SBT (N 7)	p-value
Reasons for reintubation within 7 days			
Pulmonary cause	**7 (63.64%)**	**4 (36.36%)**	**1.000**
• Pneumonia	1 (9.09%)	2 (28.57%)	0.528
• Aspiration	1 (9.09%)	1 (14.29%)	1.000
• Secretion obstruction	2 (18.18%)	1 (14.29%)	1.000
• Bronchospasm	1 (9.09%)	0 (0%)	1.000
• Pulmonary edema	1 (9.09%)	0 (0%)	1.000
• Massive pleural effusion	1 (9.09%)	0 (0%)	1.000
Extra-pulmonary cause	**4 (36.36%)**	**3 (42.86%)**	**1.000**
• Sepsis	2 (18.18%)	2 (28.57%)	1.000
• Comatose status	0 (0%)	1 (14.29%)	0.389
• Hemorrhagic shock	2 (18.18%)	0 (0%)	0.497

Subgroup analyses:

The subgroup analyses for successful extubation showed SBT with PSV was non-inferior to SBT with T-piece in the patients receiving mechanical ventilation for less than 4 days, patients without ARDS, and patients using NIV prophylaxis. However, the effect of these 2 SBT techniques was inconclusive in other subgroups (Figure 7).

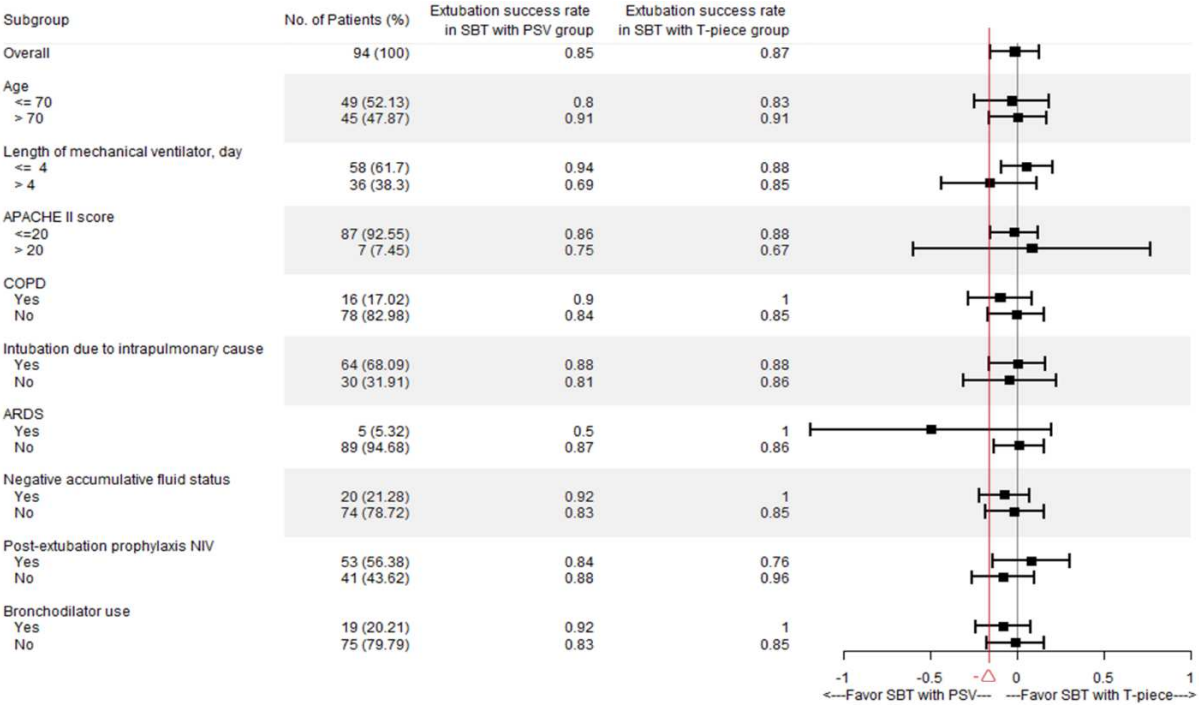

Figure 7 Forest plot showing subgroup analysis for extubation success rate comparing between SBT with PSV and SBT with T-piece

Discussion

Our study demonstrated that the SBT with PSV was non-inferior to the SBT with T-piece for the successful extubation during the 72-hour period, the success rate of SBT, the reintubation rate within 7 days, and the median time to reintubation in the patients with EFL. Nevertheless, SBT with PSV did not have the superior effect on the weaning outcomes in the patients with EFL than the T-piece.

Accordingly, EFL is the condition that some segments of peripheral airways collapse before alveolar emptying. The collapsing point is the flow-limiting site (so called the choke point) where the flow dose not increase in spite of the rising expiratory intraluminal pressure gradient. Consequently, air-trapping occurs and leads to the decrease in lung compliance and further diaphragmatic injury. To overcome air trapping, the patients have to increase their expiratory efforts, resulting in increased pleural pressure that worsens the dynamic airway compression.

Application of extrinsic PEEP might eliminate the EFL by counteracting the pleural pressure at the choke point, which improves air-trapping and reduces patient's work of breathing[29,30]. This concept is supported by Natalini et al[29] study, which demonstrated that the extrinsic PEEP could abolish the auto PEEP.

In our hypothesis, SBT with PSV including PEEP might alleviate the EFL and increase air emptying, possibly resulting in improvement of extubation outcomes. However, the study showed the non-inferiority of extubation outcomes between the PSV and T-piece, but PSV did not reach the superior margin. It might be explained that the patients in both groups had minimal intrinsic PEEP (iPEEP) despite EFL presence (iPEEP 0.40 [0.80] cmH2O in the PSV group VS 0.10 [0.90] cmH2O in the T-piece group), so PSV did not provide more benefit in alveolar emptying. We postulated that iPEEP did not increase in our patients due to the fact that the patients recovered from their active conditions, resulting in less work of breathing and less dynamic hyperinflation.

On the contrary, the reintubation rate within 7 days tended to be lower in the T-piece group. It was possible that the workload from T-piece was harder than PSV, so the patients who could tolerate this most demanding test might have more physiologic reserve. In other word, pressure support augmented spontaneous breathing and reduced the work and oxygen cost of breathing while PEEP maintained airway opening and prevented atelectasis, which masked the actual respiratory muscle function of the patients in the PSV group. Thus, after withdrawal of this support, the PSV group tended to have greater reintubation events. Additionally, the T-piece group received longer duration of NIV prophylaxis (18.50 [18] hours in the PSV group VS 23 [6] hours in the T-piece group), which minimized the risk of reintubation. Besides, sub analysis in the reintubated patients found the higher percentage of patients using NIV prophylaxis in the T-piece group (7 (63.64%) patients in the PSV group VS 5 (71.43%) patients in the T-piece group, p=0.061).

In addition, we compared our results with those from previous published studies (Table 6). Although EFL was one of the factors contributing to extubation failure, our findings showed the failure rate of extubation in the patients with EFL was comparable to other population. Furthermore, our study agreed with previous studies that PSV was not worse than T-piece in terms of the success rates of extubation and SBT.

Our study has several limitations. Firstly, the investigators and attending physicians could not be blinded due to the different devices used during the SBT, but the statisticians were blinded. Secondly, physicians' compliance to the NIV prophylaxis protocol was less in the PSV group (NIV duration < 24 hours), which confounded the reintubation outcome. Thirdly, some ventilators used in our study could not demonstrate the two different flow-volume loops on the same display, so the graphic comparison to determine the EFL had been made by manually taking 2 separated snapshots of the 2 consecutive flow-volume loops at

PEEP 3 and ~~at~~ 0 cmH_2O (ZEEP) with a mobile camera and then overlapping each other with an auto-align function in Adobe Photoshop (Adobe Inc., California, USA). However, this method had not been validated as the standard test to determine EFL, thus there might be a chance for misinterpretation of EFL. In addition, for intrinsic PEEP (iPEEP) measurement, we used a hyperventilation technique to abolish respiratory efforts before performing expiratory occlusion maneuver. As a result, the patient efforts might not be totally blunted, possibly leading to some errors of the measurement. Besides, the expiratory occlusion maneuver could not be performed in 8.1% of all patients because of no program for this maneuver available in some ventilators. Furthermore, our findings showed the non-inferiority effects of these 2 SBT techniques in the patients with EFL with nearly zero intrinsic PEEP, thus in the patients with EFL with increased intrinsic PEEP, the SBT technique with PEEP might result in different outcomes. Finally, this was a single-center study with limited numbers of the participants. Notwithstanding, our initial findings pointed out to a need for further study in a larger population.

Conclusions

Our study was the first study demonstrating the non-inferior effect of the 2 SBT techniques, namely PSV and T-piece, on the weaning outcomes in the patients with EFL. Further research is needed to confirm our results.

List of Abbreviations:

EFL; Expiratory flow limitation, SBT; Spontaneous breathing trials, PSV; Pressure support ventilation, PEEP; Positive end expiratory pressure, iPEEP; Intrinsic positive end expiratory pressure, Bpm; Beats per minute, GCS; Glasgow Coma Scale score, SpO_2; Oxygen saturation, FiO_2; Fraction of inspired oxygen, DNR; Do-not-reintubate, PF ratio; Ratio of arterial oxygen partial pressure to fractional inspired oxygen, NIV; Non-invasive ventilation, HFNC; High flow nasal cannula

Table 6 Comparison of the success rates of extubation in previous published studies

Authors	Populations	Study designs	SBT techniques	Extubation success rate			NIV use#	Remarks
				Type of outcomes	Hr†	Extubation success rate		
Jones DP et al[19] 1991	106 patients ARDS N/A COPD 12.3%	Superiority trial	120min CPAP: PS 0 PEEP 5 120min T-piece	Secondary	N/A	CPAP 94% T-piece 96% p = 0.318	No	- Primary: Gas exchange analysis - SBT success rate: CPAP 100%/T-piece 100%
Esteban A et al[20] 1997	484 patients ARDS 2.3% COPD 20.7%	Superiority trial	120min PSV: PS 7 PEEP 0 120min T-piece	Primary	48	PSV 70% T-piece 63% p = 0.14	No	- SBT success rate: PSV 86%/ T-piece 78% (p 0.03)
Haberthur C et al[21] 2002	90 patients ARDS 78.9% COPD 8.9%	Superiority trial	120min ACT with PEEP 5 120min PSV: PS 5 PEEP 5 120min T-piece	Primary	48	ACT 83% PSV 60% T-piece 63%	No	- SBT success rate: ACT 96.7%/PSV 83.3%/T-piece 80% (NS) - ALI was included in ARDS - Post-extubation NIV was counted as extubation failure
Matic I et al[22] 2004	260 patients ARDS 6.5% COPD 10%	Superiority trial	120min PSV: PS 8 PEEP ≤ 5 120min T-piece	Primary	48	PSV 86.7% T-piece 70% p 0.117	No	- SBT success rate: PSV 80%/ T-piece 73% (p 0.61) - Subgroup analysis in APACHE II >20 : significant favor SBT with PSV
Santos Pellegrini JA et al[23] 2018	190 patients ARDS N/A COPD 100%	Superiority trial	30min PSV: PS 10 PEEP 5-7 30min T-piece	Exploratory	48	PSV 75.8% T-piece 70.5% p = 0.485	Yes	- Primary: MV duration before extubation (NS) - Extubation success rate = 100% (during a 48h period) - SBT success rate: PSV 78.7%/ T-piece 78.8% - NIV Prophylaxis duration (hr): PSV 28.32±38.16, T-piece 26.88±39.84
Chittawatanarat K et al[26] 2018	520 patients ARDS N/A COPD 7.88%	Superiority trial	120min PSV: PS 5-7 PEEP 5 120min T-piece	Primary	48	PSV (1st trial) 61.15% T-piece (1st trial) 81.54% p < 0.001 (superiority)	No	- 1st trial = First trial of SBT success & extubation - Confounded by prolonged ventilation - 48-hr reintubation rate: PSV 10%/T-piece 14.62% (p 0.109)
Subira C et al[27] 2019	1153 patients ARDS N/A COPD 19.8%	Superiority trial	30min PSV: PS 8 PEEP 0 120min T-piece	Primary	72	PSV 82.3% T-piece 74% p = 0.001 (superiority)	Yes	- SBT success rate: PSV 92.5%/ T-piece 84.1% (p <0.001) - Percentages of patients with NIV Prophylaxis: PSV 8.9%/T-piece 5.9%
Thille AW et al[34] 2020	641 patients ARDS N/A COPD 23.4%	Superiority trial	30-120min PSV: N/A 30-120min T-piece	Primary	72	PSV 67% T-piece 56% p = 0.0076 (superiority)	Yes	- Post hoc analysis from previous RCT - SBT success rate: PSV 77%/ T-piece 63% (p 0.002) - Percentages of patients with NIV Prophylaxis: PSV 53%/T-piece 53%
Our study 2021	99 EFL patients ARDS 6.1% COPD 17.2%	Noninferiority trial	30 min PSV: PS 5 PEEP 5 30min T-piece	Primary	72	PSV 82% T-piece 81.6% p = 0.0475 (noninferiority)	Yes	- SBT success rate: PSV 96%/ T-piece 93.88% (noninferior) - NIV Prophylaxis duration (hr): PSV 18.5 [18], T-piece 23 [6] (p=0.476)

N/A; not available (data of numbers or percentages of patients), NS; no statistical significance, ACT; automatic compensation tube, CPAP; continuous positive airway pressure, PSV; pressure support ventilation,
+ The observed duration after extubation (hours),
# Postextubation NIV prophylaxis

Declarations:

Ethical approval and Consent to participate:

This study was approved by ethical committee of Chulalongkorn Medical Institutional Review Board (IRB No. 209/63). Approved 16 June 2020. Written inform consents were given to all participants

Consent for publication: Yes

Availability of supporting data: Yes, additional data could be requested by e-mail

Competing interests: No conflict of interest

Funding: No funding was received

Authors' contributions:

Kongpolprom N. participated in the design of study and helped draft the manuscript. All authors read and approved the final manuscript.

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Figures

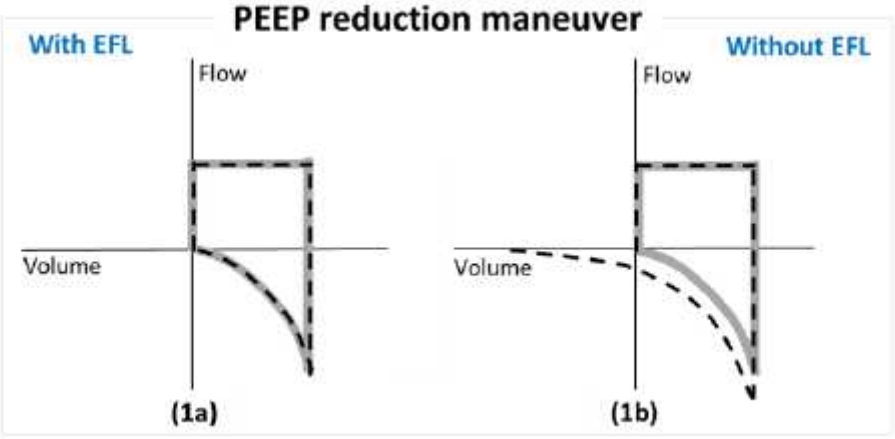

Figure 1

This figure demonstrated flow-volume loops of 2 consecutive breaths with 2 levels of PEEP in patients with EFL (1a) and without EFL (1b), who received volume control mode with square wave flow. Solid line (▯▯) represented a flow-volume loop of PEEP 3 cmH2O and dash line (- - -) represented a flow-volume loop of PEEP 0 cmH2O [ZEEP]. (1a) Expiratory flow after PEEP reduction (dash line) overlapped with flow of previous consecutive breath (solid line), which represented EFL. (1b) Expiratory flow after PEEP reduction (dash line) increased in its peak and separated apart from flow of the previous consecutive breath (solid line), which represented no EFL.

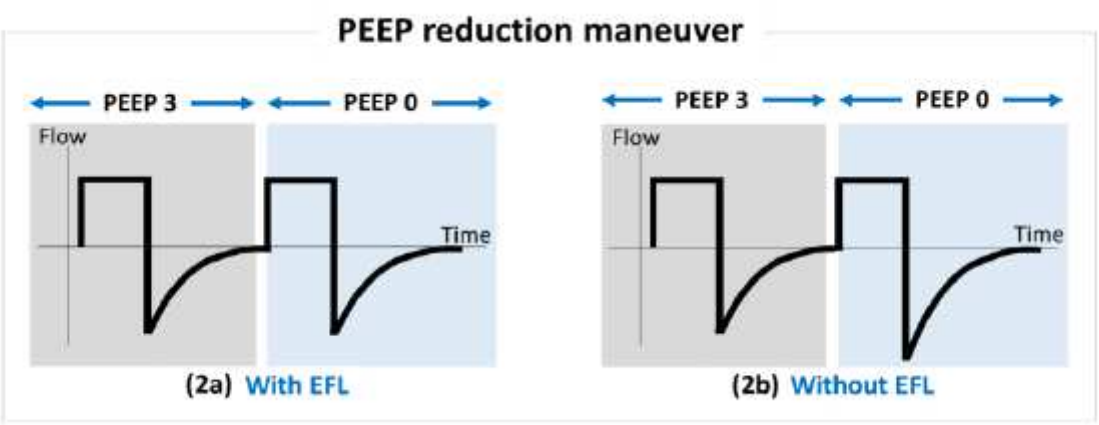

Figure 2

This figure demonstrated the flow-time waveform of 2 consecutive breaths with 2 levels of PEEP in patients with EFL (2a) and without EFL (2b), who received volume control mode with square wave flow. (2a) Peak expiratory flow of the next consecutive breath after PEEP reduction from 3 cmH2O to 0 cmH2O [ZEEP] did not increased, which represented EFL. (2b) Peak expiratory flow of the next consecutive breath after PEEP reduction from 3 cmH2O to 0 cmH2O [ZEEP] increased, which represented no EFL.

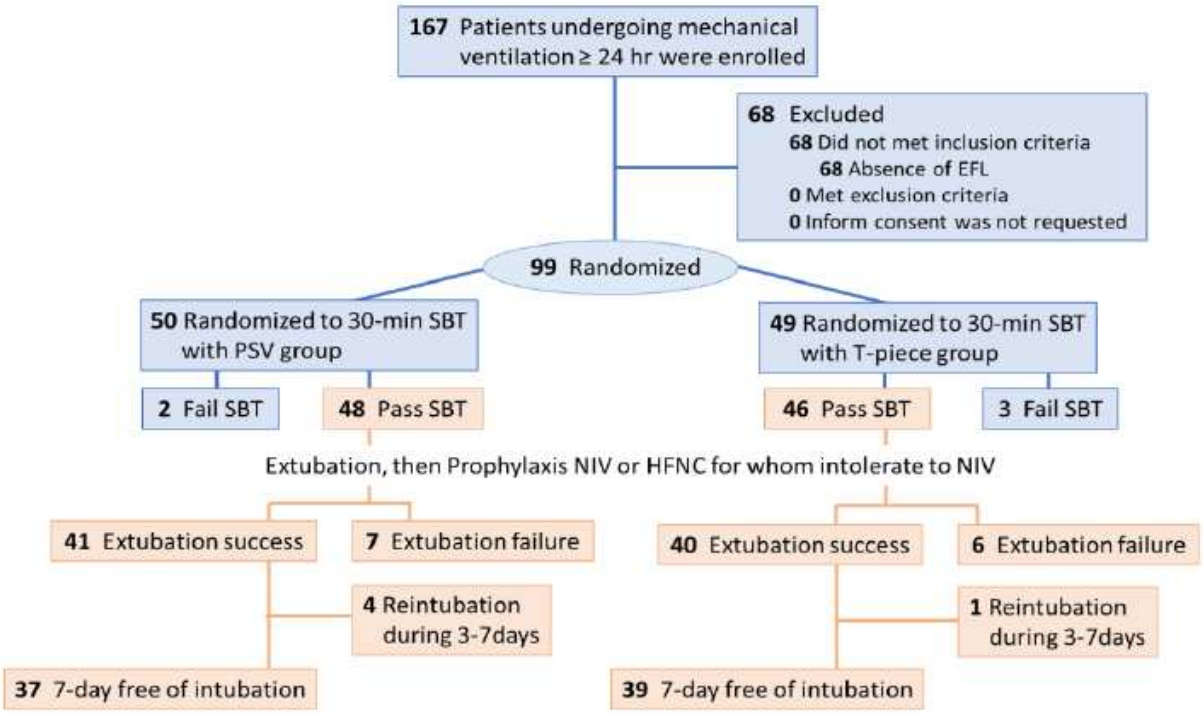

Figure 3

Flows of participants Of 167 screened patients, 99 (59.28%) were recruited and randomized into 2 groups with a ratio of 1:1. No patients dropped out of the study. Data of all patients were used for analysis.

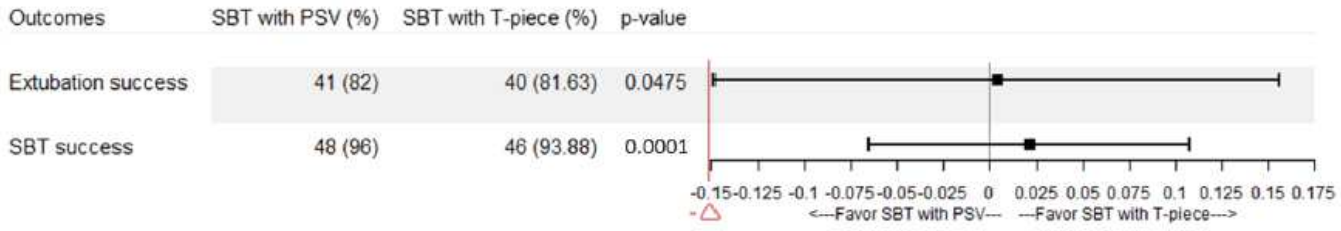

Figure 4

Forest plot showing respiratory outcomes comparing between SBT with PSV and SBT with T-piece (Intention-to-treat analysis)

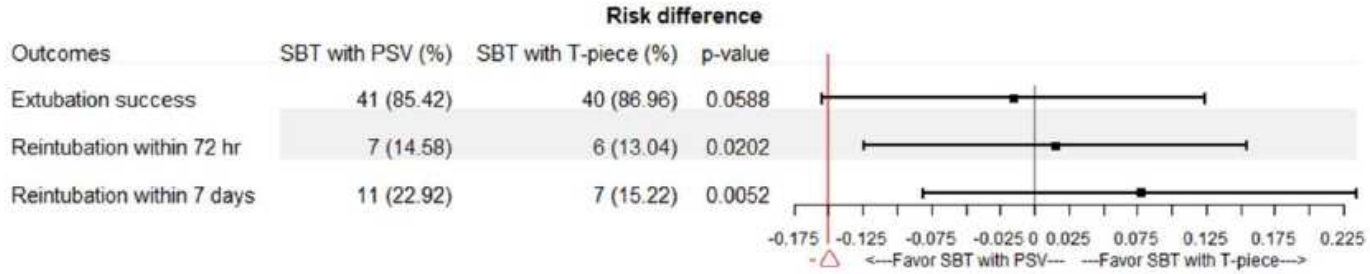

Figure 5

Forest plot showing respiratory outcomes comparing between SBT with PSV and SBT with T-piece (Per-protocol analysis)

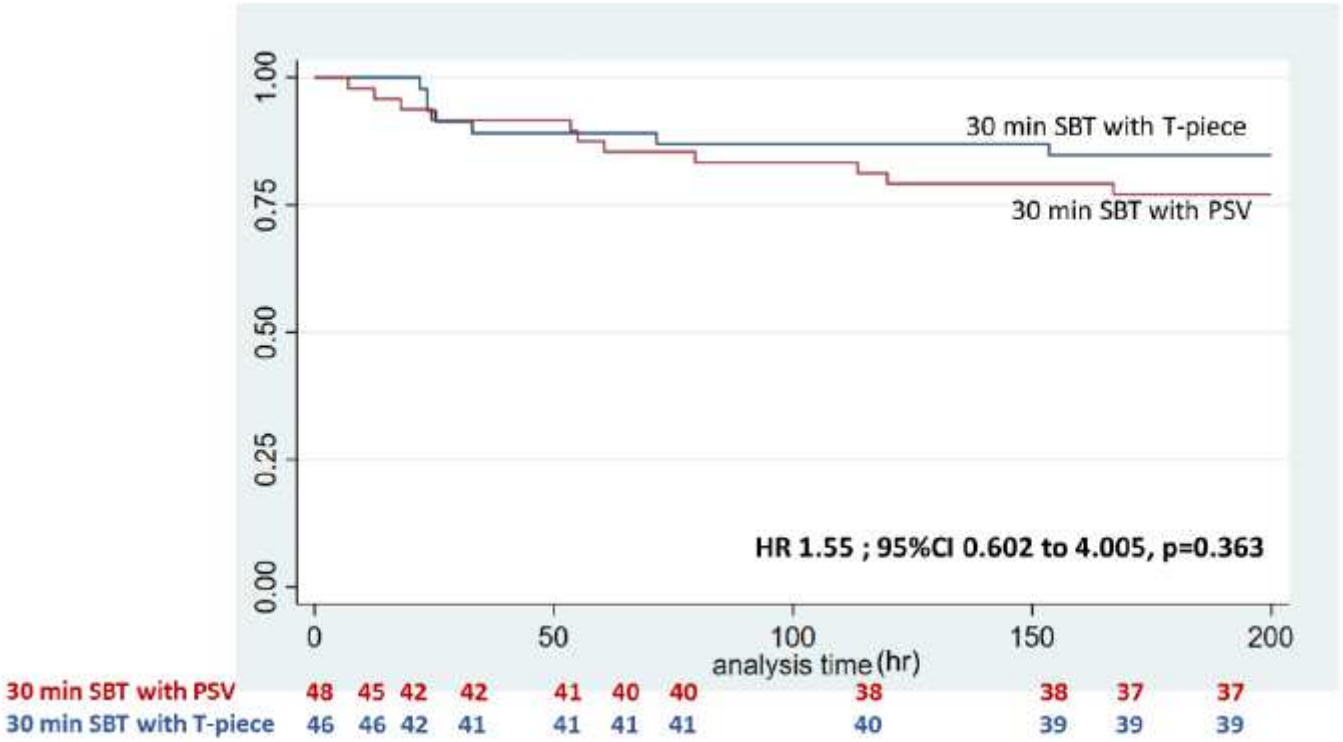

Figure 6

Kaplan-Meier Survival Analysis of reintubation within 7 days

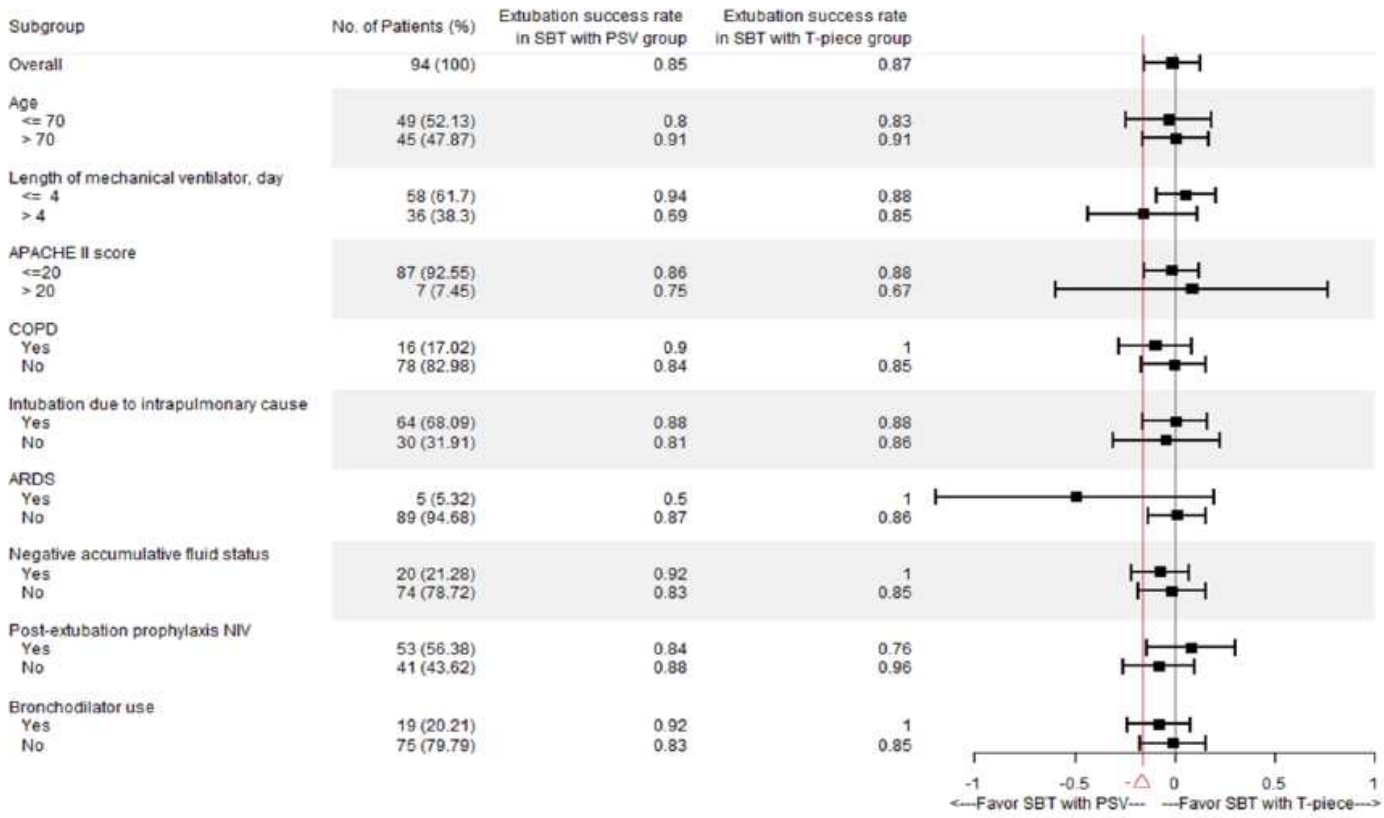

Figure 7

Forest plot showing subgroup analysis for extubation success rate comparing between SBT with PSV and SBT with T-piece