

Adaptive Support Ventilation for Faster Weaning in COPD: A Randomized Controlled Trial

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Running head: ASV in the weaning of COPD

ABSTRACT

Objective: Adaptive support ventilation (ASV) is a closed loop ventilation mode that can act both as pressure support (PSV) and pressure controlled (PCV) ventilation. Weaning with ASV shows promising results mainly in post-cardiac surgery patients. The aim of this randomized controlled study was to test the hypothesis that weaning with ASV could reduce the weaning duration in patients with chronic obstructive pulmonary disease (COPD) when compared with PSV.

Patients and Methods: From among 435 COPD patients admitted in the ICU during a 20-month period, 97 were enrolled. Patients were assigned at random to either ASV or PSV as a weaning mode.

Measurements and Main Results: Compared with PSV, ASV provided shorter weaning times (median [IQR]: 24 hours [20-62] vs. 72 hours [24-144], p=0,041) with similar weaning success rates (34/49 for ASV and 32/48 for PSV). Length of stay in the ICU also seemed shorter with ASV but the difference was not statistically significant.

Conclusions: This study suggests that ASV may be used in the weaning of COPD patients with the advantage of shorter weaning times. Further studies are needed to investigate the role and potential advantages of ASV in the weaning period of different patient groups.

Keywords: Weaning; COPD; ICU; mechanical ventilation.

INTRODUCTION

Patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) often require either non-invasive (NIV) or invasive (IMV) mechanical ventilation and prolonged weaning times [1]. Although rapid weaning is preferable, there is still debate on the best weaning procedure [2]. Spontaneous breathing trials (SBT) with T-piece or pressure support ventilation (PSV) are common methods of weaning, but both require close patient observation for indicators of possible failure. Moreover, intensive care unit (ICU) staff experience with PSV is necessary to set the appropriate level of pressures [2-4]. Closed loop modes and automated weaning procedures aim to set the most appropriate supporting pressure levels for the patient and promote early extubation, with conflicting results [5-8].

Adaptive support ventilation (ASV) is an improved closed-loop ventilation mode that provides both pressure controlled ventilation (PCV) and PSV according to the patient's needs [9-12]. Some studies have evaluated ASV in weaning cardiac surgery patients and have shown a reduction in weaning time, a reduced need for arterial blood gas (ABG) analyses, and fewer ventilator adjustments [9, 10, 13, 14]. The use of ASV in patients with COPD has been described [12, 15], but only one study reported the use of ASV as a weaning mode for chronically ventilated patients, some of whom had COPD [16]. The present study was therefore designed to compare ASV with PSV in the weaning of COPD patients.

MATERIALS AND METHODS

Patients:

This prospective, randomized, controlled single blinded study was conducted during a 20-month period in the respiratory ICU of a hospital specialized in pulmonary diseases and thoracic surgery. The hospital is the largest regional education and research hospital in the western part of Turkey and has an ICU of 30 beds equipped with both invasive and non-invasive ventilation facilities. The study was approved by the local institutional review board, and written informed consent was obtained from the patient and/or next of kin.

COPD patients with a confirmed diagnosis according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were included in the study [17]. They were orally intubated or replaced with an endotracheal tube of at least 8 mm internal diameter in the ICU to minimize the negative effect of tube resistance and ventilated with a microprocessor controlled mechanical ventilator (Galileo GOLD, Hamilton Medical AG, Switzerland) using an assisted volume controlled ventilation mode. Initial settings were as follows: tidal volume (V_T) = 8ml/kg, back-up respiratory rate (RR) =12 to 15 breaths/min, and positive end-expiratory pressure (PEEP) = 3 to 5 cmH₂O. FiO₂ was titrated to obtain a SaO₂ > 90%. All the patients were under standard medical therapy with nebulised bronchodilators (ipratropium bromide+salbutamol), corticosteroids, theophylline and antibiotics if needed. Sedation was achieved with midazolam and/or fentanyl. If the arterial blood gas analysis showed improvement in respiratory parameters (pH ≥ 7.32, PaO₂/FiO₂ > 150 with a FiO₂ ≤ 40%), sedation was stopped and the patients were re-evaluated for potential weaning [18]. Randomization was performed when patients were in stable condition (normal mental status; no signs of anxiety, somnolence, or dyspnea; and no severe respiratory acidosis and/or hypoxemia in ABG) and able to trigger the ventilator effectively. Patients who had severe cardiac, neurologic disease or sepsis, IMV less than 24 hours and a tracheostomy were not

included (Figure 1). Patients who had NIV before intubation were also not enrolled because most of them received NIV support in the pulmonary ward or emergency room and they were managed by the non-intensivist pulmonary physicians. These factors may lead to delayed ICU admissions and late intubation, thus affect weaning period.

ASV Description:

ASV provides automatic ventilation in which minute volume (MV) is controlled through a V_T - RR combination based on respiratory mechanics. In patients unable to trigger a breath, the ventilator generates pressure-controlled breaths, automatically adjusting inspiratory pressure and timing to achieve the target V_T and RR. In patients able to trigger a breath, the ventilator generates pressure support breaths, automatically adjusting the level of support pressure to achieve the target V_T , and delivers additional pressure-controlled breaths if the patient's RR is below the target RR. The target V_T - RR combination is based on the Otis equation, which determines an RR that minimizes work of inspiration for a clinician-set MV, based on the time constant of the respiratory system [19]. The time constant is estimated on a breath-by-breath basis by the expiratory time constant (RCexp) obtained from the expiratory flow-volume curve [20, 21].

Weaning protocols:

The weaning protocols are summarized in Figure 2. After the randomization, assisted volume controlled mode was stopped and the two weaning modes (ASV and PSV) were allocated randomly using sealed envelopes according to a list of random numbers. Weaning and extubation was performed by the pulmonary and critical care physicians who were not aware of the study. In both modes of weaning, inspiratory trigger sensitivity was set at -1 cmH₂O. Pressure triggering was used to measure airway occlusion pressure (P_{0.1}). High pressure alarm limit was set to 45 cmH₂O for ASV.

The initial level of pressure support (PS, above PEEP) was set at 15 cmH₂O in the PSV group as in the study of Lellouche and coworkers [22]. The PS level was then evaluated at least every 30 minutes and titrated to keep the RR ≤ 35 breaths/min and if possible gradually decreased to 7 cmH₂O by 2 cmH₂O intervals. Patient in whom 7 cmH₂O PS level could be achieved, a 2 hours trial of spontaneous breathing with this PS level was performed before extubation [23].

In the ASV group, after the randomization, MV was set at 100 mL/kg IBW. As tolerated (hemodynamically stable; normal mental status; no signs of anxiety, somnolence, or dyspnea), the MV was decreased to 50 ml/kg IBW at the end of one hour and then to 30 mL/kg IBW at the end of two hours, which would be predicted to be associated with an inspiratory pressure level below 10 cmH₂O, similar to that with PSV. Patients underwent a spontaneous breathing trial with 30mL/kg IBW MV support for 2 hours before extubation similarly as in PSV.

If the patients showed good tolerance with an acceptable arterial blood gas analysis (pH ≥ 7.35, PaO₂/FiO₂ > 150 with a FiO₂ ≤ 40%, RR ≤ 35), they were ventilated with the above final settings for two hours and then extubated. Otherwise, the trial was stopped and patients were ventilated with assisted volume controlled ventilation (A/C) mode during the night. They were evaluated for weaning again the following day.

Post-extubation failure occurring within the first 48 hours was defined as follows: pH ≤ 7.35, increase in PaCO₂ ≥ 15 mmHg from the value just prior to extubation, RR > 24 breaths/min, and accessory muscle use. NIV trial with a full face mask was performed in these patients using the same ventilator in NIV mode to avert re-intubation.[1, 24, 25] Patients who could not tolerate NIV or showed impairment in their clinical status (unable to protect airway, inability to remove secretions, cardiac instability, loss of consciousness) or blood gas analysis

(pH ≤ 7.25 and PaO₂ < 60 mmHg while receiving NIV) were re-intubated. These patients were considered as having failed weaning irrespective of their outcomes using NIV.

Data collection:

Demographic data, medical histories, APACHE II (Acute Physiology and Chronic Health Evaluation) scores and duration of mechanical ventilation before randomization were recorded. During the weaning period the ventilator was connected to a personal computer via RS232 serial port and data were recorded using data acquisition software (Hamilton Medical Ventilator Data Logger Version 3.27). Breath by breath V_T, MV, RCexp, airway occlusion pressure (P_{0.1}), inspiratory pressure support level (PS), and RR directly obtained from the digital readout of the ventilator and ABG measurements were recorded. Only the values at the last 15 minutes of the successful two-hour period before extubation were averaged and analyzed.

Outcomes and definitions:

The primary outcome was the *weaning duration* defined as the time from randomization to spontaneous breathing with or without a tracheostomy. *Weaning success* was defined as independence from mechanical ventilation (invasive or noninvasive) at least 48 hours after extubation or with a tracheostomy cannula at day 28. Secondary outcomes were weaning success rates, respiratory parameters at the end of the weaning period, duration of MV, and length of stay (LOS) in the ICU.

Duration of MV was defined as the time from the initiation of MV support until the permanent cessation of any form of ventilatory support (invasive or noninvasive). *Duration of IMV before* was defined as the time of IMV from intubation to the time of randomization. LOS in the ICU was defined as the time from admission to the ICU until discharge or death.

Statistical Analysis

The sample size of 45 in each group was chosen to give a power of 0.80 to detect a 6 hours reduction in mean weaning time, assuming a standard deviation of 10 hours with a two-sided test at the 0.05 level. Statistical analyses were done with Statistica 8.0 software (Statsoft, Inc. Tulsa, OK, USA). Data are expressed as median (IQR). Weaning durations were compared by log rank test. Other comparisons between groups were done by nonparametric Mann-Whitney U test. Differences of proportions between groups were evaluated by Fischer's exact test. A value of $p < 0.05$ was considered as significant.

RESULTS

During the study period, 4228 of 15099 hospitalized patients had a diagnosis of COPD, and 435 of them were admitted to the ICU because of acute respiratory failure. Of the 435 patients, 261 were treated with NIV as a first line treatment, and 72 of them subsequently required intubation (Figure 1).

The ASV and PSV groups were demographically similar at the time of randomization. Factors that could affect weaning such as the severity of patients assessed by APACHE II score, need of sedation and respiratory parameters were also comparable between the two groups (Table 1).

Seventy-nine patients were extubated after the weaning period. Respiratory data during the last 15 minutes of the weaning period before extubation are shown in Table 2. Fourteen patients in ASV (%28) and 15 patients in PSV (%31) were considered to be weaning failures ($p > 0.05$). Three in the ASV group and 4 in the PSV group could not tolerate extubation and underwent a percutaneous dilatational tracheostomy procedure. These patient could not also be weaned and discharged with a home ventilator. Two patients in ASV group and 3 in PSV group were also discharged from the ICU under noninvasive ventilation support. Weaning duration was significantly shorter with ASV vs. PSV (median [IQR]: 24 hours [20-62] vs. 72

hours [24-144], p=0,041). Weaning duration for the two groups expressed as Kaplan-Meier curves is also shown in figure 3. Length of stay (LOS) in the ICU seemed also shorter with ASV (median [IQR]: 11 days [6-15] vs. 13 days [8-14], p=0.5, Table 3) but this difference was not statistically significant.

DISCUSSION

The major finding of this study was that, when compared with PSV in the weaning process of COPD patients, ASV was associated with a shorter weaning duration.

Weaning Duration :

Most of the few studies evaluating ASV in weaning were performed in post-cardiac surgery patients, where the mean extubation time is under 6 hours. No systematic data were collected in COPD patients, where the duration of the weaning process is usually much longer and the weaning process is much more complicated. Sulzer et al. reported shorter duration of intubation and mechanical ventilation with ASV than synchronized intermittent mandatory ventilation (SIMV) in postoperative coronary bypass patients [9]. Cassina et al. used ASV in weaning 155 cardiac surgery patients; with 86% extubated within 6 hours. Mean time to extubation was 3.6 hours [5]. In a randomized controlled trial, Petter et al. compared ASV with SIMV+PSV in weaning 45 cardiac surgery patients and found that the duration of mechanical ventilation and the need for changing the ventilator settings were less with ASV [10]. These findings suggest that ASV could be used for fast and early extubation after post-cardiac surgery. However, none of these studies included COPD patients.

The median weaning duration in ASV and PSV in our study were 24 and 72 hours respectively, whereas in a similar population Matic et al. reported a weaning time of 54 hours with PSV [26]. Weaning times with PSV have been reported up to 115 hours [27]. In a recent study, weaning times with ASV and PSV were comparable (16.4 hours and 16.3 hours respectively); however, the study was performed in cardiothoracic surgery patients with

normal lungs [13]. The shorter weaning times with ASV in the present study might be due to the automation of inspiratory pressure levels and less manipulation and time spent to adjust the ventilator (manually in PSV versus automatic in ASV). There are some data suggesting that the automation of inspiratory pressures with a computer-driven system may lead the patients to spend much more time in the comfort zone of ventilation [28]. Increased patients ventilator interaction and decreased impact of the ICU staff on the setting of appropriate PS level for each individual patient in ASV may be the potential reason for faster weaning.

It is obvious that shorter duration of intubation will result in shorter LOS in the ICU. NIV seems to be an effective way for early extubation and reducing the LOS in ICU recently, especially in COPD patients [29]. ICU stay seemed also shorter in the ASV group but the effect of this closed loop mode as a weaning technique on ICU stay still remains uncertain. Automated closed-loop ventilation modes may be promising alternatives for conventional weaning techniques.

Weaning protocols and settings:

Randomized controlled studies and subsequent meta-analysis agreed that SBT with T-piece or PSV are equally effective and both superior to SIMV, mostly depending on the experience of the staff with a particular method [30-33]. Tassaux et al. compared ASV and SIMV+PSV patient-ventilator interactions in 10 patients, three of whom had acute exacerbations of COPD and concluded that ASV could provide the same minute ventilation with less muscle load and patient-ventilator dis-synchrony when compared with SIMV+PSV [12]. In addition, similar levels of minute ventilation and V_T/kg ratios were achieved with ASV.

PS levels were set between 5 and 10 cmH₂O in studies of weaning with PSV; such levels were suggested to be effective to overcome the resistance and workload of endotracheal tube and respiratory circuits [26, 34-37]. Sulzer et al. decreased MV% to 25% of baseline

value in cardiac surgery patients and achieved extubation with this level of support [9]. Linton et al. decreased MV% to 60% before extubation in chronically ventilated patients [16]. In our study we decreased MV% to 30% in ASV mode to achieve lower PS levels as in PSV and prepare the patient for extubation. However, after the analysis of the data we detected that some patients had PS levels greater than 7 cmH₂O in the ASV group, although the median PS levels of PSV and ASV were comparable. The ICU staff who were in charge of the weaning process made the extubation decision according to the ACCP-ACCCM weaning and extubation criteria without taking into account of the PS levels in ASV group. This might have caused the inappropriate extubation of some patients in ASV group. Bedside monitoring of the PS levels during weaning with ASV may lead to better prediction of weaning outcome.

Predictors and Success Rates of ASV and PSV Weaning:

The threshold values of different weaning indices and measured respiratory parameters obtained in COPD patients could differ from those in nonhomogeneous populations. Alvisi et al. found threshold values for MV, V_T, and V_T/kg for weaning success in COPD patients to be 8.6 L/min, 340 ml, and 5.0 ml/kg, respectively [38]. In the present study, median values for all these parameters in both groups were found to be in appropriate ranges for successful weaning, and there was no significant difference between ASV and PSV when these data were compared. Also P_{0.1}, another index of respiratory drive, showed no significant difference between ASV and PSV and was found to be below 6 cmH₂O, which Manthous et al. suggested as the successful weaning threshold value for COPD patients [39].

Esteban et al. reported weaning success rates of 70% for PSV and 63% for SBT [23]. That study was performed on a heterogeneous population, but 20% of the patients enrolled had COPD. The present study found weaning success rates of 69% for each group, similar to those in the literature.

Limitations of Study:

Some limitations of the study are worth noting. Concerning the study design, in the PSV group, the absolute PS level patients were receiving was 7 cm H₂O which is accepted to be as effective as a SBT with T-piece [2]. However, in the ASV group, some patients who had weaning failure had PS levels greater than 10 cmH₂O, even up to 18 cmH₂O although the median PS levels were comparable. Taking into account of the PS levels during the weaning period while using ASV as a weaning mode might be a good predictor of weaning outcome especially in COPD patients.

We randomly allocated the patients into two modes when they were ready for weaning. Some studies concerning the weaning procedures suggested that SBT's with T-piece were superior to SIMV and PSV [32] while others showed that gradual reduction of PS was superior in patients who failed a 2 hours SBT with T-piece [30]. Further studies are needed to assess the feasibility of ASV in difficult to wean patients who fail SBT's with T-piece. Another interesting area may be the use of closed loop modes from the beginning of intubation and mechanical ventilation until the end of weaning and compare the total duration of ventilation and LOS in ICU with the conventional modes and weaning techniques. We used A/C mode until the randomization and on night shifts during weaning period in order to avoid fatigue and prepare the patient for the weaning trial the other day. This might have caused a bias and underestimation of the potential benefits of ASV on total ventilation time and ICU stay because the total time patients spent on A/C was not evaluated.

Patients with previous use of NIV were not included in the study. The reason of this was to evaluate the effects of these modes in a more homogenous group. But in the real world most of the patients with COPD are intubated after failure of NIV. This limits the generalization of the results to all intubated patients with COPD.

This single-center study reflects the skills and experience of a single unit. With 49 patients in ASV and 48 in PSV groups to detect a reduction of 2 days in the weaning time assuming a standard deviation of 4 days, the present study seemed to have a power of 0.68. Multicentric, more powered studies with large sample sizes could more accurately assess the generalizability of these results to different centers and patient populations. The lack of ICU staff prevented us from recording the number of interventions and ABG sampling needed for each group. Another potential interesting area might be the comparison of patient comfort and respiratory mechanics, such as work of breathing and pressure time product in ASV with different weaning modes. Further studies are needed to determine the advantages of this closed loop automated ventilation mode.

CONCLUSIONS

This study suggested that ASV may be used as a weaning mode in the weaning period of severe COPD patients with the advantage of shorter weaning duration. Further studies with large sample sizes are needed to investigate the role and potential advantages of this closed loop ventilation mode in the weaning period and ICU stay of different patient groups.

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Table 1: Demographic and respiratory data before randomization

	ASV (n:49)	PSV (n:48)	P
Age (years)	64 (54-70)	65 (56-70)	0,95
Gender: male, N (%)	44 (90)	45 (93)	0,36
BMI (kg/cm²)	25 (21-27)	25 (22-29)	0,23
APACHE II	16 (14-19)	16 (14-19)	0,74
pH	7,40 (7,37-7,43)	7,41 (7,38-7,46)	0,21
PaCO₂(mmHg)	55 (47-66)	51 (46-64)	0,4
HCO₃(mmol/L)	36 (31-39)	36 (29-40)	0,88
PaO₂/FiO₂	182 (170-198)	176 (168-184)	0,23
Duration of IMV before (hours)	48 (48-96)	67 (48-96)	0,82
Patients needed sedation before randomization, N (%)	16 (32)	15 (31)	0,52

Definition of abbreviations: PSV: pressure support ventilation; ASV: adaptive support ventilation; BMI: body mass index; PaCO₂: partial pressure of carbon dioxide in arterial blood; HCO₃: arterial bicarbonate concentration; PaO₂/FiO₂: partial pressure of oxygen in arterial blood/fractional inspired oxygen concentration; IMV: mechanical ventilation. Values are expressed as median (IQR) or number of patients (%).

Table 2: Monitored respiratory data and arterial blood gases of extubated patients during the last 15 minutes of the weaning period

	ASV (n:40)	PSV (n: 39)	P
PS level	7 (6-8)	7 (7-7)	0,12
pH	7,41 (7,35-7,45)	7,39 (7,33-7,45)	0,54
PaCO₂ (mmHg)	56 (51-64)	57 (50-66)	0,62
HCO₃ (mmol/L)	36 (35-40)	36 (29-40)	0,6
PaO₂/FiO₂	288 (230-310)	267 (230-297)	0,46
MV (L/min)	8,3 (7,4-9,1)	8,4 (6,9-9,8)	0,87
MV/kg (ml/kg)	119 (101-148)	126 (103-133)	0,91
V_T (mL)	394 (333-489)	424 (326-474)	0,74
V_T/kg (ml/kg)	5,7 (5,3-6,3)	5,4 (4,9-6,9)	0,45
RR (breaths/min)	22 (17-26)	23 (20-27)	0,43
RCexp (sec)	0,9 (0,7-1,1)	0,8 (0,7-0,9)	0,37
t exp (sec)	1,9 (1,5-2,5)	1,7 (1,4-2)	0,16
t insp (sec)	0,8 (0,7-1,2)	0,9 (0,8-1)	0,81
P_{0,1} (cmH₂O)	2,8 (1,1-3,9)	2,3 (2-3,4)	0,57

Definition of abbreviations: PSV: pressure support ventilation; ASV: adaptive support ventilation; PS: pressure support; PaCO₂: partial pressure of carbon dioxide in arterial blood; HCO₃: arterial bicarbonate concentration; PaO₂/FiO₂: partial pressure of oxygen in arterial blood/fractional inspired oxygen concentration. MV: minute ventilation; V_T: tidal volume; RR: respiratory rate; RCexp: expiratory time constant; t exp: expiratory time; t insp: inspiratory time; P_{0,1}: airway occlusion pressure. Values are expressed as median (IQR).

Table 3: Comparison of two groups

Outcomes	ASV (n:49)	PSV (n:48)	p
Weaning duration (hours)	24 (20-62)	72 (24-169)	0,041
Weaning failure, N (%)	15 (31)	16 (33)	0,47
Duration of MV (hours)	120 (72-264)	156 (72-288)	0,56
LOS in ICU (days)	11 (6-15)	13 (8-14)	0,5
Mortality at day 28, N (%)	9 (18)	9 (18)	0,58

Definition of abbreviations: PSV: pressure support ventilation; ASV: adaptive support ventilation; MV:mechanical ventilation; LOS: length of stay; ICU: intensive care unit. Values are expressed as median (IQR) or number of patients (%).

FIGURE LEGENDS

Figure 1. Flowchart of patients through the study.

Definition of abbreviations: COPD: chronic obstructive pulmonary disease, ASV: adaptive support ventilation, PSV: pressure support ventilation, PDT: percutaneus dilatational tracheostomy, NIV: noninvasive ventilation.

(*except cor pulmonale due to COPD)

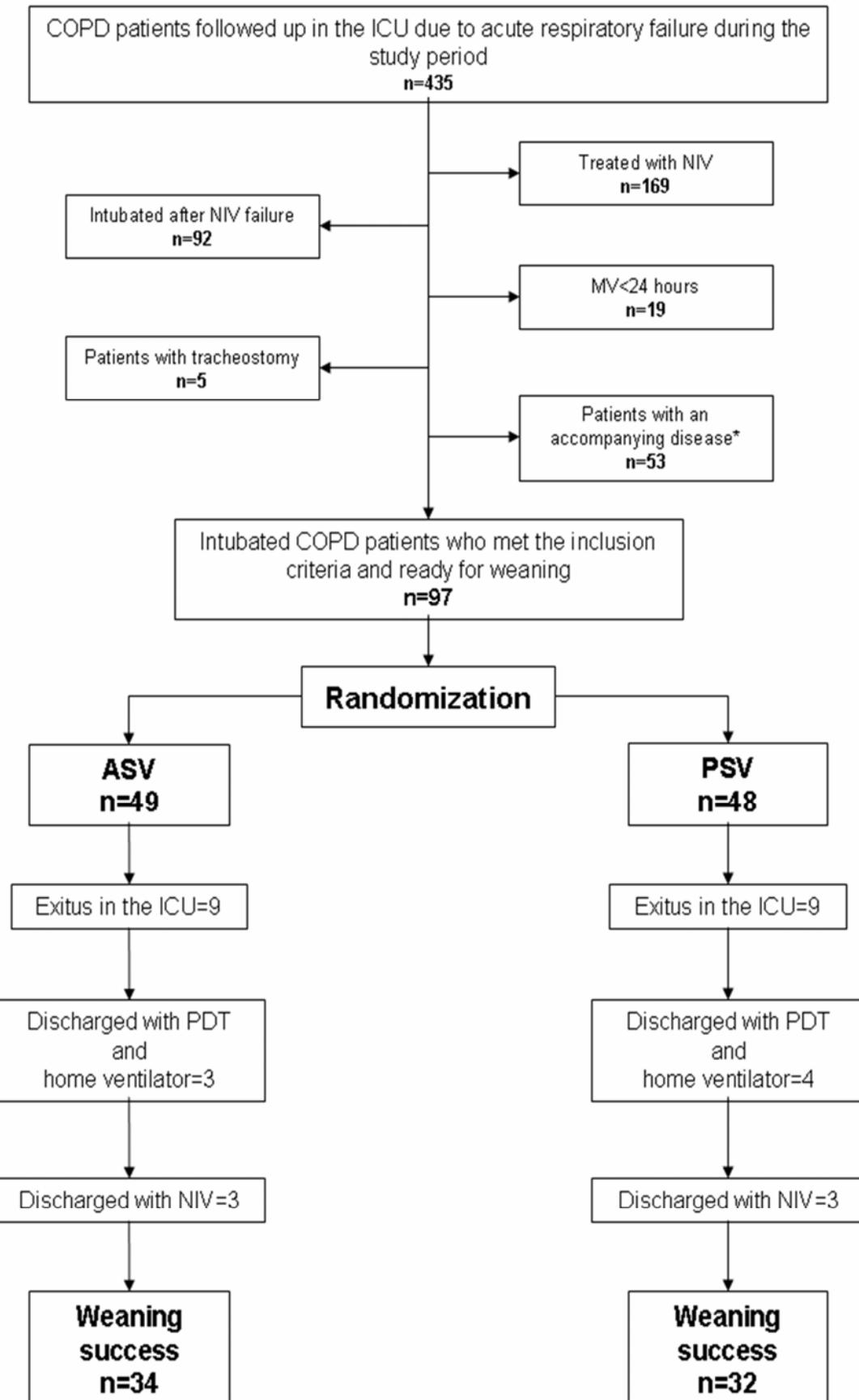


Figure 2. Weaning protocols for adaptive support ventilation group (ASV; left) and pressure support ventilation group (PSV; right).

*Good tolerance criteria are clinical stability (hemodynamically stable; normal mental status; no signs of anxiety, somnolence, or dyspnea), with an acceptable arterial blood gas analysis ($\text{pH} \geq 7.35$, $\text{PaO}_2/\text{FiO}_2 > 150$ with a $\text{FiO}_2 \leq 40\%$, $\text{RR} \leq 35$) .

Definition of abbreviations: ASV: adaptive support ventilation; PSV: pressure support ventilation; MV: minute ventilation; IBW: ideal body weight; PS: pressure support; PEEP: positive end-expiratory pressure; ETS: expiratory trigger sensitivity; FiO_2 : fractional inspired oxygen concentration.

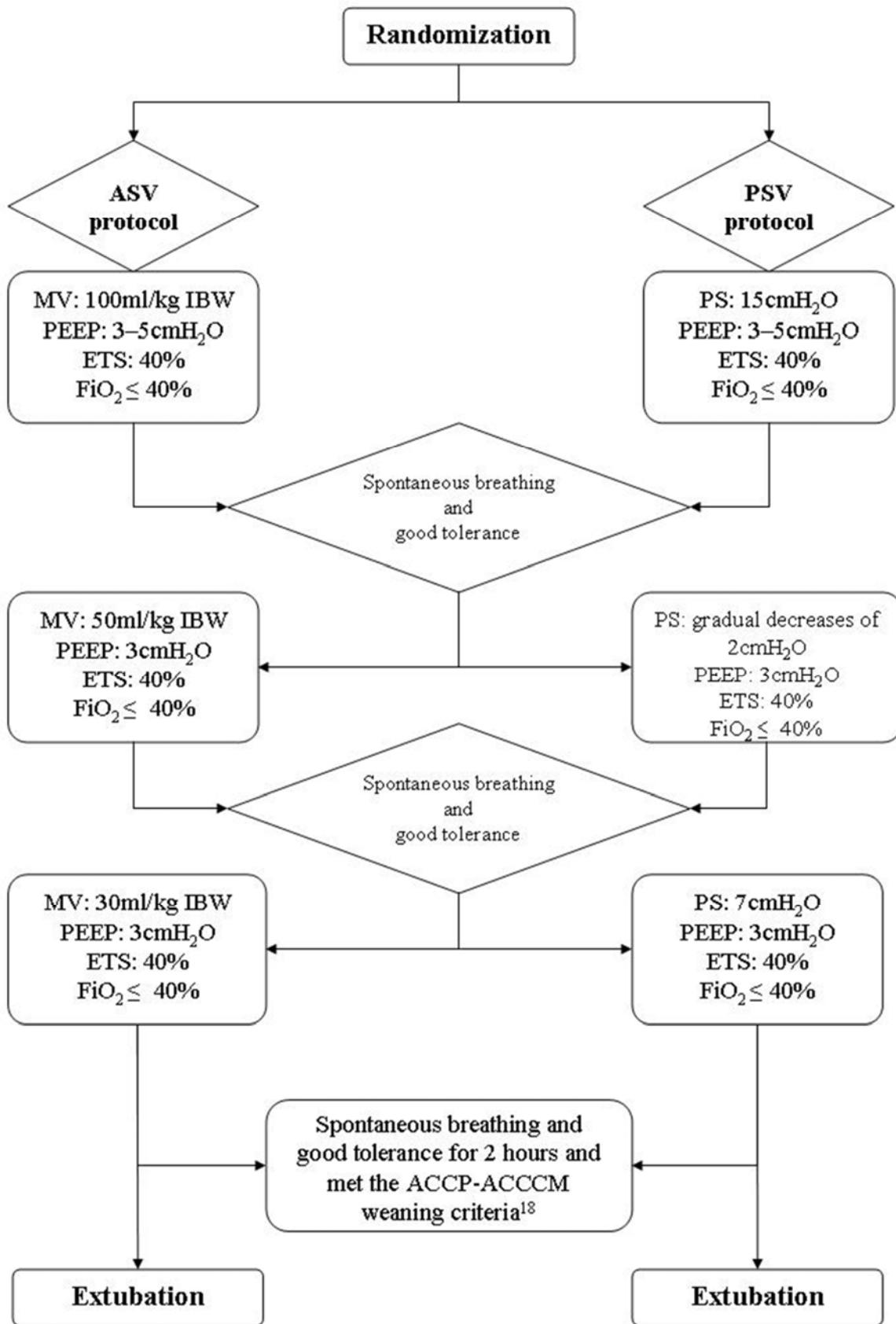


Figure 3. Duration of weaning (days) expressed as a Kaplan-Meier curve in the Adaptive Support Ventilation (ASV) and Pressure Support Ventilation (PSV) groups.

