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Chronic Obstructive Pulmonary Disease and Weaning of Difficult-to-Wean Patients from Mechanical Ventilation: Randomized Prospective Study

Ivo Matić[1], Davorin Đanić[2], Višnja Majerić-Kogler[3], Matija Jurjević[1], Ivan Mirković[1], Natalija Mrzljak Vučinić[1]

[1]Department of Anesthesiology and Intensive Care, Dr Josip Benčević General Hospital, Slavonski Brod, Croatia
[2]Department of Ear, Nose, and Throat and Cervicofacial Surgery, Dr Josip Benčević General Hospital, Slavonski Brod, Croatia
[3]Department of Anesthesiology and Intensive Care, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia

> **Correspondence to:**

Ivo Matić
Department of Anaesthesiology and Intensive Care
Dr Josip Benčević General Hospital
Andrije Štampara 42
35 000 Slavonski Brod, Croatia
ivo.matic@bolnicasb.hr

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Aim To compare T-tube and pressure support ventilation (PSV) as two methods of mechanical ventilation weaning of patients with chronic obstructive pulmonary disease (COPD) after failed extubation.

Methods A prospective randomized trial carried out at the multidisciplinary intensive care unit (ICU) over 2 years included 136 patients with COPD who required mechanical ventilation longer than 24 hours. The patients who could be weaned from mechanical ventilation were randomized to either a T-tube or PSV 2-hour spontaneous breathing trial. The patients in whom 2-hour trial was successful were extubated and excluded from further research. Patients in whom 2-hour trial failed had mechanical ventilation reinstated and underwent the same weaning procedure after 24 hours in case they fulfilled the weaning criteria. The weaning outcome was assessed according to the following parameters: extubation success, mechanical ventilation duration, time spent in ICU, reintubation rate, and mortality rate.

Results Two-hour trial failed in 31 patients in T-tube and 32 patients in PSV group, of whom 17 and 23, respectively, were successfully extubated ($P<0.001$, χ^2 test). Mechanical ventilation lasted significantly longer in T-tube than in PSV group (187 hours vs 163 hours, respectively, $P<0.001$, Mann-Whitney test). Also, patients in T-tube group spent significantly more time in ICU than patients in PVS group (241 hours [interquartile range 211-268] vs 210 hours [211-268], respectively, $P<0.001$, Mann-Whitney test). Reintubation was required in 8 and 6 patients in T-tube and PVS group, respectively, and death occurred in 4 and 2 patients, respectively, during ICU stay.

Conclusion Patients with COPD who failed the 2-hour spontaneous breathing trial had more favorable outcome when PVS rather than T-tube method was used for weaning from mechanical ventilation.

Clinical Trial Registration ClinicalTrials.gov Identifier: **NCT00355732**

Chronic obstructive pulmonary disease (COPD) is a disease with an increasing prevalence and mortality worldwide (1). Acute respiratory failure (ARF) due to COPD is becoming an ever-larger medical and economic problem not only in developed, but also in developing countries (2). The main characteristic of COPD is an airflow limitation that is not fully reversible, but usually progressive and associated with an abnormal bronchoalveolar inflammatory response to noxious particles or gases (3). COPD encompasses chronic bronchitis and emphysema. Severe form of the disease usually causes a state of chronic respiratory muscle compromise because of the incomplete alveolar emptying at the end of expiration leading to dynamic hyperinflation, intrinsic positive end-expiratory pressure, flattened diaphragm, recruitment of accessory respiratory muscles, and changes in the shape of the rib cage (4). Therapeutic management of COPD includes administration of antibiotics for those with infection, systemic corticosteroids, β_2 agonists, oxygen, physiotherapy, mechanical ventilation (MV), and lung transplant (5).

Mechanical ventilation is often life-saving when patients with COPD experience acute respiratory compromise (6,7), but it also has its risks. There are adverse effects caused by PEEPi, which need to be kept in mind, including barotrauma risk, hemodynamic compromise, overload of inspiratory muscles, and weaning failure (8).

Weaning from MV is a process where MV is gradually withdrawn and the patient resumes spontaneous breathing (9). The major factor in successful weaning is the resolution of precipitating illness and a stable low requirement for oxygen (10). However, neither laboratory nor clinical parameters have been defined on when to begin with the weaning procedure. If the weaning procedure is started early, it can often lead to cardiorespiratory failure. On the other hand, if it is started too late, it can be unsuccessful because of respiratory muscle weakness caused by deconditioning and disrupted breathing regulation (11).

Evaluation of the MV outcome and understanding of the weaning procedure and extubation have a significant clinical importance (12). It has been estimated that the weaning phase accounts for approximately 40% of the time that the patient spends on a mechanical ventilator. In patients with COPD this phase may account for as much as 59% of that time (13).

Overall, the weaning procedures are unsuccessful in around 20% of the cases (14), whereas the first weaning attempt in patients with COPD is unsuccessful in over 50% of the cases (15). Unsuccessful weaning of COPD patients from mechanical ventilator is predictive of poor outcome, including mortality, which is 2.6% only in patients successfully weaned from MV and as high as 27% in those who require reintubation (16).

The best weaning procedure has not yet been established. There are four basic techniques as follows: spontaneous breathing using T-piece, pressure support ventilation (PSV), synchronized intermittent mandatory ventilation (SIMV), and biphasic positive airway pressure (BiPAP). Different weaning procedures have different reintubation statistics. In patients with expiratory flow limitation, which is common in COPD, these modes may lead to an increased dynamic hyperinflation and PEEPi. The deterioration of respiratory mechanics increases the elastic work of breathing and may cause weaning failure (17).

Over the past decade, non-invasive positive pressure ventilation (NPPV) in cases of acute exacerbations of COPD has gained in popularity. However, in hospital settings, patients with milder COPD exacerbations have not been shown to benefit from the addition of NPPV to the conventional therapy (18). Moreover, NPPV had a high rate of failure in COPD patients with advanced hypercapnic acute respiratory failure, although it did provide some advantages in comparison with conventional MV (19). The choice

between NPPV and invasive MV depends upon the severity of illness, the rapidity of response, coexisting diseases, and capacity of the medical environment. NPPV is used in the treatment of mild or simple conditions, whereas invasive MV is usually required in case of a more complex or severe disease. MV settings should be adjusted so to ensure controlled hypoventilation, longer expiratory time, and titrated PEEP-e to avoid dynamic hyperinflation and its consequences (20).

None of the many clinical trails was able to establish whether T-tube or PSV method was superior in weaning patients with COPD from MV. Therefore, we decided to compare these two weaning methods of patients with COPD in whom extubation failed after a 2-hour spontaneous breathing trial.

Patients and methods

Patients

The study included 136 adult patients with COPD requiring MV longer than 24 hours who were admitted to a multidisciplinary intensive care unit (ICU) at Dr Josip Benčević General Hospital in Slavonski Brod between April 2004 and April 2006. The diagnosis of COPD was confirmed on the basis of medical history, physical examination, chest radiography, and recent pulmonary function tests (airflow obstruction, hyperinflation, and air trapping). Only patients with COPD who had exacerbation of dyspnea that lasted <2 weeks, alternating rhythm of respiration, and abdominal paradox as signs of respiratory muscle dysfunction were included in the study. Exclusion criteria were absence of COPD, age <18 years, tracheotomy, MV duration shorter than 24 hours, use of MV on admission to the ICU or transfer to some other ICU for treatment continuation, death or weaning from MV was discontinued because of another associated disorder, central nerve system disorders unrelated to hypercapnic encephalopathy or hypoxemia, cardiac arrest within 5 days, and being scheduled for organ donation.

The patients were randomly assigned to one of the two weaning methods by use of two closed, non-transparent, identically looking envelops, each containing information on one of the weaning methods investigated. After a patient was included in the study, a third party not involved in the study was asked to choose one of the envelopes. Depending on the information in the chosen envelope, the patient was allocated to undergo weaning either by T-piece or by PSV. The following data were collected: Acute Physiologic And Chronic Health Evaluation (APACHE II) score (21), sex, age, and parameters of weaning from MV, including ventilation time before the first spontaneous breathing trial and failure time during the first spontaneous breathing trial.

The study was carried out in line with ethical principles and approved by the Hospital Ethics Committee.

Weaning from mechanical ventilation procedure

The procedure of weaning from MV began by an assessment and objective measurement of the following respiratory mechanical and biochemical parameters: improvement of the underlying cause of respiratory failure (assessed by APACHE II scoring), spontaneous respiratory rate (RR)<25/min, spontaneous respiratory volume (Vt)>0.005 L/kg of body weight, maximal spontaneous inspiratory effort (PI_{max})≤25 cm H_2O, heart rate <140/min, body temperature <38.5°C, hemoglobin >100 g/L, partial arterial oxygen pressure (PaO_2)>60 mm Hg with inspired oxygen fraction (FiO_2)≤0.4, extrinsic positive end-expiratory pressure (PEEP)<5 cm H_2O, no need for vasoactive and/or inotropic support, PaO_2/FiO_2 ratio >200, and RR/Vt ratio <100.

In patients who met these criteria the weaning procedure started by a 5-minute spontaneous breathing trial. If this trial was successful, a 2-hour spontaneous breathing trial was performed. An initial 5-minute trial was considered success-

ful if RR was between 8 and 25 breaths/min, Vt >5 mL/kg, and RR/Vt ratio <100.

The 2-hour spontaneous breathing trial was performed with either T-tube or PSV, with initial positive pressure of 18 cm H_2O. Criteria for a successful 2-hour trial were the same as for the 5-minute trial. Patients in whom the 2-hour spontaneous breathing trial was successful were then extubated and excluded from further research.

If one or more signs of poor procedure tolerance were observed during the 2-hour trial, the patient was considered difficult-to-wean and returned to the MV. The ventilator settings were adjusted to provide full support of ventilation and allow muscle rest. In such patients, the same procedure of weaning was repeated after 24 hours, if permitted by the patient's clinical condition, following the same protocol. Signs of a low 2-hour trial tolerance, which were used as the criteria for termination of the trial, included spontaneous respiratory rate >25/min, $SatO_2$<90%, FiO_2≤0.4, heart rate >140/min (or more than 20% change from the initial heart rate), systolic blood pressure >200 mm Hg or <80 mm Hg, PaO_2≤60 mm Hg, pH≤7.30, and restlessness.

For patients who were weaned by means of PSV, initial positive pressure support was 18 cm H_2O. This support was then lowered by 2-4 cm H_2O based on the parameters of pulmonary mechanics, biochemistry, and circulation. Patients were extubated at pressure support of 5 cm H_2O, which was necessary to overcome increased airway resistance (reduced airway diameter due to an endotracheal tube).

Weaning procedure was considered successful when the unassisted spontaneous breathing was sustained for 48 consecutive hours without respiratory distress, with pH>7.35 and PaO_2>60 mm Hg in a patient breathing through a mask at FiO_2≤0.4. The weaning outcome was considered a failure when the patient needed continuing mechanical ventilator support for >7 days after weaning assessment or when death occurred before the ICU discharge. Initiation of MV support within 48 hours of liberation from MV was also considered to be a failure. Criteria for reintubation were a lack of improvement in arterial blood gases within 2 hours after MV discontinuation, worsening of respiratory distress, deterioration of the neurological status, including psychomotor agitation requiring sedation, and life-threatening cardiovascular alterations.

Assessment methods

Mechanical ventilation was administered with Evita Drager dura 2 respirators (Dräger, Lubeck, Germany) or with Puritan Bennet 7200 respirators (Puritan Bennet, Carlsbad, CA, USA). Parameters of pulmonary mechanics were directly measured on the respirator. The tidal volume and respiratory rate of spontaneous breathing patients were measured with a spirometer (Ohmeda Biox, Louisville, CO, USA), and maximal inspiratory pressure was measured with manometer (Ohmeda Biox). Arterial blood gases analysis was performed on a Ciba Corning Blood Gas Machine (Ciba Corning, Halsted, UK). Cardio-respiratory functions including systolic and diastolic blood pressure, heart rate, and end-tidal CO_2 were continuously monitored on Datex monitors (Datex Ohmeda, Helsinki, Finland), and ventilation and oxygenation were monitored on Datex Engstrom AS3 and CS3 Compact Monitors (Datex Ohmeda).

Statistical analysis

Based on the power analysis, the study aimed to recruit 136 patients in order to have 70% power of detecting a clinically significant difference in the proportion of patients experiencing 2-hour trial failure at the 5% level of significance, with the assumption that 50% of the T-tube 2-hour trial failure group would fulfill the criteria for extubation failure and that a reduction to 20% in the PSV 2-hour trial failure group would be clinically relevant.

Qualitative and numerical data were presented as median, minimum, maximum, interquartile

range (IQR), and centile distribution. Frequency tables were used to present qualitative data. Two independent qualitative variables in contingency tables were compared with χ^2 test. Fisher exact test was used for small samples. Mann-Whitney test was used to compare two independent groups of numerical data. Normality of distribution was tested with the Kolmogorow-Smirnov test. $P<0.01$ was considered statistically significant. Statistical analysis was performed with Statistical Package for Social Sciences 9.0 for Windows (Standard version, SPSS Inc., Chicago, IL, USA).

Results

Out of 136 patients with COPD included in the trial, 66 were allocated for weaning from MV using 2-hour T-tube trial and 70 were allocated for 2-hour PSV trial (Figure 1). The weaning was unsuccessful in 31 (47%) patients from T-tube group and 32 (46%) from PSV group. Of patients in whom weaning failed, 17 (56%) in the T-tube group and 23 (72%) in the PSV group were successfully extubated.

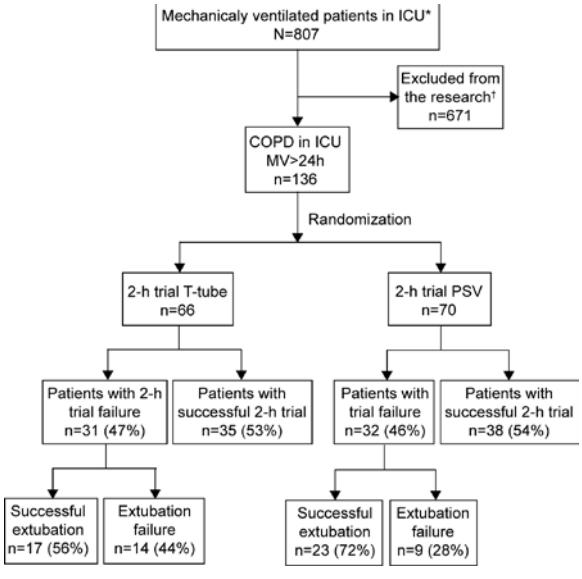

Figure 1. Flow of patients through the study. *Abbreviations: ICU – intensive care unit, MV – mechanical ventilation, COPD – chronic obstructive pulmonary disease, PSV – pressure support ventilation.†Patients excluded due to: non-COPD (n = 660), COPD with MV<24h (n = 10), COPD with tracheotomy (n = 1).

The two groups of patients did not significantly differ in age, sex distribution, APACHE II score, median ventilation time before spontaneous breathing trial, or median failure time during the first spontaneous breathing trial (Table 1).

Table 1. Demographic and clinical characteristics of patients with chronic obstructive pulmonary disease undergoing weaning from mechanical ventilation by use of either T-tube or pressure support ventilation*

	Median (IQR)		
Patient characteristics	T-tube (n = 31)	PSV (n = 32)	$P^{\dagger}$
No. (%) of men	17 (56.0)	19 (60.0)	0.411
Age (years)	59 (41-71)	57 (32-68)	0.529
APACHE II score	29 (23-31)	31 (23-34)	0.424
Ventilation time before spontaneous breathing trial (hours)	124 (94-151)	120 (88-139)	0.534
Failure time during first spontaneous breathing trial (minutes)	75 (50-98)	88 (64-112)	0.060

*Abbreviations: IQR – interquartile range, PSV – pressure support ventilation, APACHE – Acute Physiologic and Chronic Health Evaluation.
†Mann-Whitney test.

There was no significant difference in the median respiratory rate and median tidal volume during spontaneous breathing trial between the patients in the T-tube group and those in the PSV group (Table 2). However, median maximal spontaneous breathing effort was significantly higher in the T-tube group than in the PSV group, as opposed to median PaO_2/FiO_2 ratio, which was significantly lower in the T-tube than in PSV group (Table 2). Median RR/Vt ratio did not differ between the groups.

The outcome of weaning from MV was assessed on the basis of duration of weaning, total MV duration, time the patient spent in ICU,

Table 2. Parameters of T-tube or pressure support ventilation in weaning difficult-to-wean patients with chronic obstructive pulmonary disease from mechanical ventilation*

	Median (IQR)		
Parameter	T-tube (n = 31)	PSV (n = 32)	$P^{\dagger}$
Spontaneous respiratory rate (per min)	22 (19-25)	21 (14-25)	0.880
Spontaneous breathing volume (mL)	420 (390-478)	450 (410-515)	0.540
Maximal spontaneous breathing effort (cm H_2O)	-32 (-40 to -27)	-29 (-36 to -27)	0.003
Pao_2/FiO_2 ratio	220 (211-252)	230 (220-272)	0.070
RR/Vt ratio (L/breath/min)	74 (63-80)	72 (59-88)	0.810

*Abbreviations: IQR – interquartile range, PSV – pressure support ventilation, PaO_2 – partial arterial oxygen pressure, FiO_2 – inspiratory oxygen fraction, RR – spontaneous respiratory rate, Vt – spontaneous breathing volume.
†Mann-Whitney test.

number of successfully vs unsuccessfully extubated patients, number of patients requiring reintubation, and ICU mortality rate. Median weaning time from MV and median MV duration were both significantly longer in T-tube group than in PSV group (Table 3). Weaning time accounted for 43% of the total MV duration in T-tube group and for 36% in PSV group. Patients in T-tube group also spent significantly more time in ICU than did the patients in PSV group. Extubation was successful in 17 patients in T-tube and in 23 patients in PSV group, while it was unsuccessful in 14 patients in T-tube and in 9 patients in PSV group (Table 3). Eight patients in T-tube and 6 in PSV group needed reintubation. Four patients in T-tube group and 2 in PSV group died. Two patients in each group died of septic shock, one patient in T-tube group died of peritonitis and one of coagulopathy.

Table 3. Effects of T-tube and pressure support ventilation method for weaning difficult-to-wean patients with chronic obstructive pulmonary disease from mechanical ventilation on weaning outcomes

	No. (%) of patients		
Weaning outcomes	T-tube (n = 31)	PSV* (n = 32)	*P*
MV weaning duration (median, IQR, hours)	63 (51-69)	43 (35-49)	<0.001†
MV total duration (median, IQR, hours)	187 (143-222)	163 (113-203)	<0.001†
Time spent in ICU (median, IQR, hours)	241 (211-268)	210 (186-241)	<0.001†
Successful extubation	17 (56.0)	23 (72.0)	<0.001‡
Need for reintubation§	8 (24.0)	6 (16.0)	–
ICU mortality rate§	4 (12.0)	2 (8.0)	–

*Abbreviations: MV – mechanical ventilation, PSV – pressure support ventilation, IQR – interquartile range, ICU – intensive care unit.
†Mann-Whitney test.
‡χ^2 test.
§Not analyzed due to small number of patients.

Discussion

The major finding of our study was that both spontaneous breathing using T-tube and PSV are suitable methods for successful weaning of patients with COPD from MV, although PSV proved to be more successful according to the measured parameters. To be able to adequately analyze the data, we first had to standardize the weaning procedures, which was accomplished using a 5-minute and 2-hour spontaneous breathing trial. The failure time during first spontaneous breathing trial was not predictive of failure after T-tube or PSV weaning because the study insisted on the 2-hour trial. In patients who failed the 2-hour trial, the procedure was repeated after 24-hour if permitted by the patient's clinical condition, again following the same protocol. This was probably the reason why there was no difference between groups.

Kollef et al (22) compared the protocol method with the weaning procedure dictated by medical staff and concluded that the art and application of MV had influenced the weaning procedure more than the ventilation method itself. Furthermore, Smyrnios et al (23) found that MV weaning management protocol implemented as a hospital-wide quality improvement program lead to large reductions in the duration of MV, length of stay, and hospital costs. For this reason, we decided to apply and follow strictly defined protocols for both of the weaning methods investigated in our study. We also always avoided clinical experience-based weaning from MV and extubation.

There are different methods for weaning from MV. Esteban et al (17) compared 4 methods of weaning from MV, including intermittent mandatory ventilation, PSV, multiple, and single spontaneous breathing trial with T-tube. The median time of weaning with intermittent mandatory ventilation and PSV was 5 and 4 days, respectively. The single and multiple trials with T-tube proved to be most successful, with the median of 3 days. Brochard et al (24) compared synchronized intermittent mandatory ventilation, PSV, and T-tube weaning method, and found that PSV was superior to the other two methods of weaning from mechanical ventilation. Their finding is in accordance with our results, although we have to take into account the differences in the inclusion criteria, because there were patients with non-COPD conditions recruited in their study.

We compared the outcomes of T-tube and PSV weaning procedures and found that PSV produced more favorable results with respect to MV duration. Reduced total MV duration time with PVS weaning method also reduced the total time spent in ICU. The percentage of total MV time spent on weaning itself was lower in the PSV than T-tube group, and in both groups, it accounted for less than 50% of the total MV duration as opposed to 59% of total MV time reported by Kuhlen et al (13). In our study extubation was successful in more patients in the PSV than T-tube group. Petrof et al (15) reported extubation to be successful in half of the patients with COPD included in their study. These results suggest that weaning of patients with COPD from MV presents a significant problem. Taking into consideration the increasing costs of this treatment, further research should be conducted to find the ways to reduce the weaning time and total MV duration time, as well as to increase the extubation success rates. Reintubation was necessary in several patients in both groups, and a few patients died in both groups. We could not compare the reintubation and death rates in two groups, because the number of these patients was too small.

Our study had some limitations. Due to the small sample size, parameters such as ICU mortality and need for reintubation could not be statistically analyzed. Also, patients were monitored only during ICU stay, and no data were collected after patients were discharged from the ICU.

In conclusion, based on the shorter time needed for weaning from MV, total MV duration, median time spent in ICU, and lower proportion of successfully extubated patients, PSV was shown to be more suitable than T-tube weaning method for difficult-to-wean patients with COPD. Further research should collect data for such patients on a hospital, regional, or state level to ensure large sample size, which would allow drawing more reliable conclusions. The data on such patients should also be collected from the moment COPD was diagnosed, including when MV was first administered. Furthermore, 1-year and 3-year mortality rates should be determined to gain full insight into the problem of MV and weaning of patients with COPD from MV.

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