Evaluation of the weaning process in COPD patients with acute respiratory failure

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ÖZET

Akut solunum yetmezlikli KOAH olgularında ventilatörden ayırma sürecinin değerlendirilmesi

Akut solunum yetmezliği nedeniyle solunumsal yoğun bakım ünitesine kabul edilen kronik obstrüktif akciğer hastalığı (KOAH) olan olgularda invaziv mekanik ventilasyondan ayırma süresinin (AS) belirgin farklılıklar gösterdiği gözleminden hareketle retrospektif kohort çalışma planladık. Çalışmaya invaziv mekanik ventilasyon sonrası başarıyla ekstübe edilen 59 KOAH olgusu alındı. Ayırma modu olarak hastaların çoğunda SIMV + PSV kullanıldı. Çalışma popülasyonu AS'ye göre iki gruba ayrıldı: Grup 1: AS ≤ 24 saat (n= 32), grup 2: AS > 24 saat (n= 27). Gruplar demografik ve klinik özellikleri, vital bulguları, arter kan gazları, laboratuvar bulguları ve tedavi özellikleri açısından karşılaştırıldı. Ortalama AS grup 1'de 13 ± 8 saat, grup 2'de 58 ± 34 saat bulundu (p< 0.001). Lojistik regresyon analizinde AS'nin 24 saatten uzun olması için prediktif faktörler: Bazal kalp hızının yüksek olması, ayırma gününde pH'nın alkalotik olması, midazolam infüzyon süresi ve akciğer grafisinde amfizematöz bulguların baskın olması. Sonuç olarak, KOAH'ta mekanik ventilatörden ayırma süresinin hasta ve hastalığa ait özelliklerin yanı sıra tedavi özelliklerinden de etkilenebileceği kanısındayız.

Anahtar Kelimeler: *Akut solunum yetmezliği, kronik obstrüktif akciğer hastalığı, invaziv mekanik ventilasyon, mekanik ventilasyondan ayırma.*

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SUMMARY

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Based on our observations in chronic obstructive pulmonary disease (COPD) patients admitted to our respiratory intensive care unit due to acute respiratory failure suggesting a significant variation in weaning duration (WD), we conducted a retrospective cohort study in such patients. Fifty-nine patients successfully extubated following invasive mechanical ventilation were included. Syncronized intermittent mandatory ventilation plus pressure support ventilation was used as the weaning mode in mostly. Study population was divided into two groups. Group 1: patients with a WD ≤ 24 hours (n= 32), Group 2: patients with a WD > 24 hours (n= 27). Groups were compared with respect to demographics, vital signs, arterial blood gases, laboratory values, and the treatment characteristics. The average WD was 13 ± 8 and 58 ± 34 hours in group 1 and group 2, respectively (p< 0.001). In the logistic regression analysis, the following factors were found to have a predictive value for a WD > 24 hours: elevated baseline heart rate, alkaline pH at the day of weaning, duration of midazolam infusion, and emphysematous findings on chest X-ray. In conclusion, whether the WD in COPD patients is less or greater than 24 hours is not only determined by the medical treatment administered, but also by the patient and disease characteristics.

Key Words: *Acute respiratory failure, chronic obstructive pulmonary disease, invasive mechanical ventilation, weaning from, mechanical ventilation.*

Intensive care and mechanical ventilation are lifesaving in the treatment of acute respiratory failure (ARF). Invasive mechanical ventilation (MV) carries a significant risk of complications which may result in significant morbidity and mortality. Therefore, after the patient's clinical situation is stabilized, every effort should be made by the clinician to discontinuation of MV as soon as possible (1).

Weaning is problematic and difficult in 20 to 30% of patients undergoing prolonged periods of MV, and in 35 to 67% of patients with chronic obstructive pulmonary disease (COPD) (2,3). It has been reported that weaning is responsible for 41% of the total duration of MV in patients receiving MV due to medical reasons, and while this ratio is 19% for patients with myocardial infarction, it rises to nearly 60% in COPD patients (4). In studies about the weaning process, the factors influencing the success of weaning have usually been investigated and different weaning techniques and ventilation modes have been compared (2,5). In recent years, using of the weaning protocols in the intensive care units have been reported to result in an improvement of weaning and mortality rates and in reduced costs for the treatment (6,7). Most of the studies on weaning are multi-center trials that include different patient populations (medical, surgical, trauma etc.) which may possibly result in an inadequate evaluation of the effect of certain factors on weaning process such as the expertise level and medical approach of the clinician implementing ventilation or the patient and/or disease characteristics.

Based on our observations in COPD patients admitted to our respiratory intensive care unit (RICU), which were about 70% of total admissions during a four-year period, suggesting a significant variation in weaning duration, we aimed to compare COPD patients with a weaning duration less than or equal to 24 hours and greater than 24 hours following a switch to weaning mode with respect to demographic, clinical, radiological, laboratory and treatment characteristics.

MATERIALS and METHODS

This study was conducted in patients admitted to the RICU at a large teaching hospital in Istanbul. RICU, having 6-bed and the facility of mechanical ventilation invasively or noninvasively, provides care to the patients mostly respiratory based critically ill.

Study Design

Retrospective cohort study with prospectively collected data.

Patient Selection

Between April 2001 and December 2003, a total of 92 COPD patients ventilated invasively were evaluated. Out of 92, 59 patients received MV at least 24 hours and extubated successfully were included in the study. Patients with unsuccessful or self-extubation, patients received MV less than 24 hours, and patients who were referred to our center due to prolonged MV or difficult weaning were excluded. Study population was divided into two groups based on weaning duration (WD): Patients with a WD ≤ 24 hours (group 1, n= 32) and patients with a WD > 24 hours (group 2, n= 27). COPD was diagnosed on the basis of the clinical history, physical examination and the findings of the chest radiograph. Additional information was obtained from previous pulmonary function test (PFT)s when available within 12 months before patients admitted to RICU.

Ventilatory Management

In the presence of hemodynamic instability, severely altered mental status, severe respiratory distress and unsuccessfull noninvasive trial (progressive deterioration with increasing distress or physical exhaustion and/or worsening arterial blood gases), the patients underwent endotracheal intubation and received invasive mechanical ventilation (MV). In all patients, Puritan-Bennett 760 (Tyco Healthcare Company) model ventilators were used. Assist-control (A/C) ventilation was applied as the initial ventilator mode with the following settings: Respiratory rate of 10-12 breaths per minute, tidal volume (Vt) of 6-8 mL/kg and inspiratory flow rate of 40-100 L/min. As the patient's airway and plateau pressures increased above acceptable level (peak inspiratory pressure > 40 cmH_2O; plateau pressure > 35 cmH_2O), the ventilatory mode was immediately switched to the pressure-controlled ventilation (PCV). At last, 48 patients received MV with VCV, and 11 patients with PCV. Pre-weaning duration (PWD) was defined as the time (hours) from intubation to the beginning of weaning mode. The criteria for the initiation of weaning were as follows:

1. An improvement of the precipitating factors of ARF (infection, severe bronchospasm, eg),

2. Adequate gas exchange (PaO_2/FiO_2 > 200; PEEP ≤ 5-8 cmH_2O; FiO_2 ≤ 0.4 and pH ≥ 7.30),

3. Hemodynamic stability with no further need for vasoactive agent,

4. Regaining of consciousness, and presence of spontaneous breaths,

5. A core temperature below 38°C,

6. A hemoglobin level above 10 g/dL.

Weaning Protocol

Synchronized intermittent mandatory ventilation plus pressure support ventilation (SIMV + PSV) was used in all patients as the weaning mode, and subsequently it was switched to PSV mode in nine patients because of the patient-ventilator asynchrony was observed as shown on the Figure 1. During this trial, initial ventilator rate was set as 8-10 bpm (breaths per minute), and initial support pressure was set individually according to the target tidal volume. Ventilator rate was reduced 2 bpm hourly, evaluation according to goal (f ≤ 25/min, Vt: 6-8 mL/kg) was performed after each settings. When the patient tolerated a ventilator rate of 4 bpm with the achievement value, support pressure was reduced 2 cmH_2O per hour to achieve a Vt for spontaneous breaths equal to 6-8 mL/kg. Patients who tolerated a ventilator rate of 4 bpm and Psupp ≤ 10 cmH_2O evaluated according to the goal and the following extubation criteria (8):

1. Fully control of underlying cause of ARF,

2. Full consciousness and cooperation,

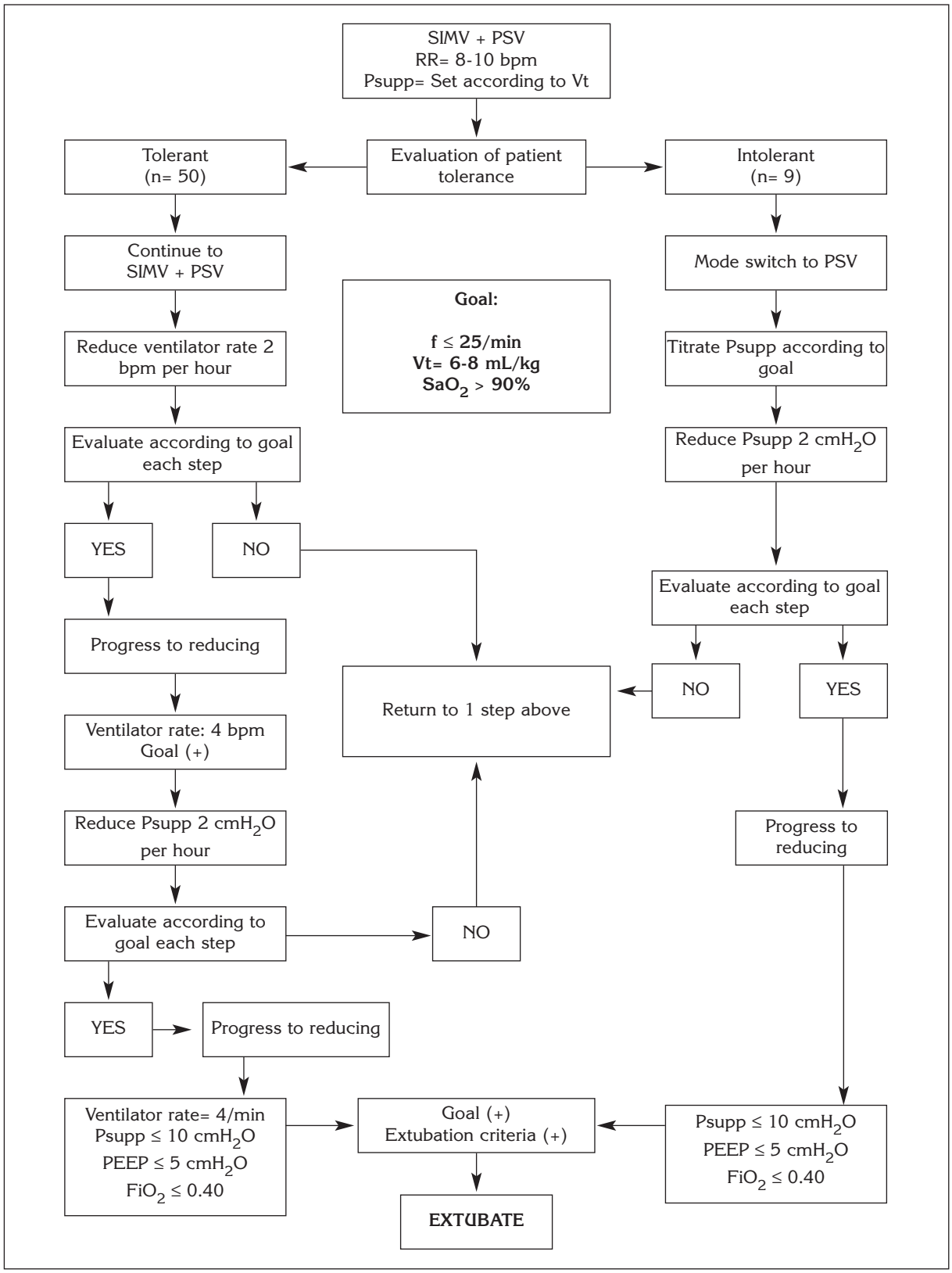

Figure 1. There was a weaning protocol written by the RICU staff physicians, and all the doctors involved in the treatment of study population act in the same way.

3. Hemodynamic stability,

4. Reduction in the amount and purulence of tracheal secretions,

5. Presence of cough reflex during endotracheal aspiration,

6. An arterial oxygen saturation > 90% at a FiO_2 ≤ 0.40,

7. A hemoglobin level > 10 g/dL,

8. A core temperature < 38°C,

9. The spontaneous rapid shallow breathing index [f/Vt, measured according to the method of Yang and Tobin (9)] < 105. Weaning duration (WD) was defined as the time (hours) from the start of weaning mode to extubation. NIPPV was administered if a patient had signs of poor tolerance (respiratory distress, decrease in oxygen saturation or a tendency for acidosis in blood gases despite of the optimum medical treatment) at any time following extubation.

Sedation Protocol

Continuous midazolam infusion (0.15-0.3 mg/kg/hour) to increase the patient tolerance and to allow the presence of endotracheal tube was given. The lower and upper dose limits for midazolam was calculated on an individual basis, and the infusion was initially given at a rate of 0.15 mg/kg/hour. The infusion rate was titrated to obtain deep sedation adequate to suppress spontaneous breathing in the beginning of ventilation. After than, the dose was reduced in 2 mg steps per hour to achieve the lowest midazolam dose providing comfort and cooperation for the patient, and facilitating invasive procedures, nursing care, and patient interaction with the ventilator. Fentanyl citrate (bolus or infusion) was given in 14 subjects for whom breathing effort was not suppressed despite the highest dose of midazolam, and neuromuscular blocking agent (NMBA), vecuronium bromide with bolus dose, was performed at a dose of 0.05 to 0.1 mg/kg in 7 subjects with patient-ventilator asynchrony or uncontrolled airway pressure.

Medical Management

The standard treatment for an acute COPD exacerbation including bronchodilators, systemic steroids, antibiotics and diuretics (if cor pulmonale was present) was administered. Inhaled β_2-agonists as salbutamol was used with metered-dose inhaler (MDI) with a chamber device placed into the ventilator circuit. Dose and intervals of salbutamol was adjusted according to the patient's airway pressures and auscultation findings. The first dose of salbutamol was at least 4-8 puff (400-800 µg), then followed with 4 puff (400 µg) by 1-4 hours intervals (10,11). Intravenous methylprednisolone (1-2 mg/kg/day) was administered to all patients at the first three days, than it was tapered gradually. Theophylline was administered intravenously 5-6 mg/kg over 20-30 min, followed by a continuous infusion of 0.6 mg/kg/hour. Antimicrobial therapy was initiated empirically after obtaning an endotracheal aspiration material for the bacteriological investigation.

Recorded Data

Patients' demographics, presence of comorbidities, cor pulmonale or congestive heart failure, vital signs at entry and at the start of weaning, routine laboratory tests, arterial blood gases (ABG), PaO_2/FiO_2 ratio, radiological and bacteriological characteristics, Glasgow coma scala (GCS) score at entry, and the acute physiology and chronic health evaluation (APACHE) II score in the first 24 hours were recorded prospectively (12,13). Medical treatment and the total dose and durations of midazolam, systemic steroids, fentanyl citrate and NMBA were determined. Chest X-ray was defined emphysematous when the following findings were seen: Marked and persistent overdistention, a low and flat diaphragm, and a heart shadow tends to be long and narrow.

Statistical Analysis

Data are expressed in mean ± SD. Comparisons of characteristics between groups were made with the Chi-squared test and/or Fisher's Exact test for categorical variables, and the independent samples t-test for continuous variables. The factors predicted for the weaning duration were explored with logistic regression analysis. A p value less than or equal to 0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of cases are summarized in Table 1.

In 41 (69.5%) patients, intubation was performed after an unsuccessful NIPPV intervention, while 18 patients with a contraindication for NIPPV were immediately intubated at the admission of RICU. The mean total duration of MV and WD for overall patients were 84 ± 49 hours (25-265 hours) and 33.8 ± 33 hours (1-169 hours), respectively. The WD to total MV duration ratio was 37 ± 22%.

Group 1 and group 2 were comparable with respect to age, gender, smoking status, PFTs, ABG findings at entry, and frequency of using NIPPV as a first-line intervention. In group 2, baseline APACHE II score was lower, heart rate was higher, magnesium level was lower and GCS was higher, compared to group 1; also patients in group 2 showed a tendency for alkalosis during the weaning day (Table 2).

In group 2, more patients had a positive result for the growth of pathogen bacteria in the endotracheal aspiration cultures and more patients had an emphysematous pattern in chest X-rays

Table 1. Demographic and clinical characteristics.

Age, years	62 ± 8 (41-80)
Sex, M/F	53/6
Smoking status, pack/years	52 ± 26
Current smoker, n	15
Pulmonary function tests	
FVC, mL	1598 ± 635
FVC, % predicted	51 ± 22
FEV_1, mL	887 ± 399
FEV_1, % predicted	32 ± 14
FEV_1/FVC	56 ± 10
Comorbidity, n (%)	26 (%44)
Causes of ARF	
COPD exacerbation	43 (73%)
Pneumonia	5 (8%)
CHF*	10 (17%)
Pulmonary embolism	1 (2%)
APACHE II, mean ± SD (range)	22 ± 5 (13-37)
PaO_2/FiO_2, mean ± SD (range)	196 ± 73 (60-375)
pH, mean ± SD (range)	7.23 ± 0.09 (7.02-7.44)
$PaCO_2$, mmHg	99 ± 25 (52-166)
PaO_2, mmHg	63 ± 37 (24-223)

* Congestive heart failure.

Table 2. Comparison of the groups with respect to clinical characteristics.

	Group 1 (WD ≤ 24 hour) (n= 32)	Group 2 (WD > 24 hour) (n= 27)	p
FEV_1, mL	896 ± 452	878 ± 346	NS
FEV_1, % predicted	34 ± 6	30 ± 8	NS
APACHE II score, on admission	23 ± 5	20 ± 4	0.03
GCS score, on admission	10 ± 3	12 ± 3	0.03
Heart rate, baseline	109 ± 20	125 ± 28	0.02
Magnesium, baseline	2.16 ± 0.6	1.85 ± 0.44	0.06
pH, just before intubation	7.22 ± 0.09	7.23 ± 0.08	NS
$PaCO_2$, just before intubation	100 ± 26	98 ± 25	NS
pH, on weaning day	7.41 ± 0.05	7.44 ± 0.05	0.068
$PaCO_2$, on weaning day	55 ± 8	52 ± 10	NS
HCO_3 , on weaning day	36.4 ± 6	36.5 ± 7	NS
Emphysematous findings on chest X-ray, %	6.3	33.3	0.03
Growing rate of pathogens in the culture of endotracheal aspiration, %	30.4	69.6	0.005
f/Vt, just before extubation	59 ± 23	54 ± 17	0.5

(Table 2). There were no significant differences between the two groups with regard to the presence of comorbidities, cor pulmonale or congestive heart failure, previous history of MV, using NIPPV initially, and complication rates.

In Table 3, the two groups are compared with regard to medical and ventilatory treatment characteristics. PWD was 46 ± 31 hours and 58 ± 37 hours in group 1 and 2 respectively, with no significant difference. Also there were no significant differences between the groups whether the weaning mode was SIMV/PSV or PSV alone.

In the logistic regression analysis, the following factors were found to have a predictive value for a WD greater than 24 hours: Elevated baseline heart rate, alkaline pH at the day of weaning, prolonged midazolam infusion, and presence of emphysematous pattern on the chest X-ray (Table 4).

DISCUSSION

In the present study, the mean total duration of MV was 84 hours (3.5 day) and the mean WD was 34 hours (1.5 day), with a weaning ratio of 37% in COPD patients extubated successfully. We chose SIMV + PSV as the weaning protocol mode because we had previously observed that most of COPD patients admitted to our RICU had favorable outcomes using this mode in the

Table 3. Comparison of groups with regard to treatment characteristics.

	Group 1 (n= 32) WD ≤ 24 hour	Group 2 (n= 27) WD > 24 hour	p
NIPPV, prior to intubation; n (%)	21 (65.6)	20 (74.1)	NS
Initial MV mode			
AC/PCV, %	27.3	72.7	0.049*
AC/VCV, %	60.4	39.6	
NIPPV following extubation, n (%)	18 (56)	13 (48)	NS
Pre-weaning duration, hour	46 ± 31	58 ± 37 hours	NS
Weaning duration, hour	13 ± 8	58 ± 34	< 0.001
Weaning ratio, %	24 ± 18	52 ± 16	< 0.001
MV-free RICU days	3.6 ± 2.8	5.8 ± 5.4	NS
Duration of midazolam infusion, hour	35 ± 25	63 ± 51	0.013
Total midazolam dose, mg	378 ± 334	713 ± 702	0.03
Daily midazolam requirement, mg	10 ± 3.6	10.5 ± 4	NS
Administering NMBA**, n	3	4	NS
Administering fentanyl sitrate, n	8	6	NS

* Fisher's Exact test.

** NMB: Neuromuscular blocking agents.

Table 4. Factors associated with a weaning duration greater than 24 hours.

	p	OR	CI, 95%
pH, at the day of weaning	0.026	30×10^8	$14.370\text{-}63 \times 10^{16}$
Baseline heart rate	0.006	1.049	1.014-1.086
Duration of midazolam infusion	0.017	1.031	1.006-1.058
Emphysematous pattern on the chest X-ray	0.042	10.224	1.091-95.845

weaning trial. PSV was used in nine patients who had significant intolerance with SIMV/PSV. We found that there were no significant differences between the groups whether the weaning mode was SIMV/PSV or PSV alone. However Esteban et al. showed a longer WD with SIMV + PSV than with PSV (4). In that study, weaning ratio in a heterogeneous group of patients who were mechanically ventilated due to ARF was 41%, and this figure was 59% for COPD patients (4). Nevins and Epstein reported that the mean WD was 5.2 ± 10.9 days and total duration of MV was 8.9 ± 13 days in COPD patients (14). In addition, mean WD was found 4.7 day for COPD patients in a large multicenter study (15). Of note, a lower weaning ratio (37%) and weaning duration (1.5 day) were found in our study compared to these reports, despite SIMV + PSV was used for most of our patients. This may be partly explained on the basis of a better patient-ventilator interaction afforded by modern ventilators which allow for a better evaluation of patient compliance and more effective documentation of data during patient monitoring. Also, in recent years there were collected more published studies, reviews and guidelines about ventilatory management of COPD patients in the literature (1,16). Furthermore, since most of the patients admitted to our RICU have obstructive airway diseases, the practice expertise in a specific patient population might have played an important role.

Although there was a significant difference with regard to several clinical, laboratory and medical parameters between the two groups, only 4 of these had a predictive value for the WD (Table 4): Higher baseline heart rate, a tendency for alkalosis at the weaning day, an emphysematous pattern in radiological examination, and the prolonged midazolam infusion. Age and PWD, which have been reported to influence the success of weaning, did not differ significantly between the two groups and did not show an effect on WD (2).

A higher baseline heart rate may be associated with multiple factors such as the severity of respiratory failure before admittance to RICU, high fever, infection, hypoxia, impaired baseline cardiac functions, or intensive bronchodilator treatment. Most of our patients had at least two of these factors. This suggests that the clinical picture resulting from the combination of these factors might have affected the weaning duration, although each did not have a significant effect on its own. Also, heart rate was shown as predictor factor in successful trial of extubation (17).

A tendency for alkalosis at the weaning day was also associated with a WD of greater than 24 hours. With regard to a respiratory or a metabolic cause, we observe that the mean HCO_3 levels were equal in the two groups, while $PaCO_2$ was lower in group 2, though not significantly (Table 2). Depressing the $PaCO_2$ below the chronically maintained level may reset chemical drives and the respiratory workload intensity so that the patient cannot maintain unassisted breathing without intolerable effort (18).

We found that an emphysematous pattern in chest X-ray was associated with a prolonged WD. Experimental studies show impaired diaphragmatic functions in mechanically ventilated animals after 12 hours of controlled ventilation, and this worsened with time spent on the ventilator (19). After three-days controlled mechanical ventilation, diaphragmatic myofibril injury ensues, resulting in reduced maximum diaphragmatic strength (19). This may prolong the total MV and WD even in patients without a primary lung disease. In emphysema, it is known that a higher transpulmonary pressure is required to obtain Vt due to the loss of normal curvature of the diaphragm, and the inspiratory pressure-forming capacity is reduced due to the shortening in diaphragmatic myofibrils (19). As such, a more prolonged course of MV and WD are inevitable in an emphysematous patient with a flattened diaphragm compared to a patient with a diaphragm with a normal curve. Also, hyperinflation in an emphysematous lung causes a mechanical disadvantage and inspiratory muscles need to overcome the mechanical difficulty posed by thoracic cage (20).

In the present study, the fourth factor associated with a WD greater than 24 hours was prolonged midazolam infusion. Although deep sedation is very helpful in the beginning of ventilatory insti-

tution, it may have detrimental effects when their use is prolonged unnecessarily. It is generally recommended, sedation and paralysis should not be continued for longer than 48-72 hours post-initiation (18). Studies have shown that the time to awakening and the time to extubation are longer in patients sedated with midazolam compared to propofol (21-23). In the study by Carrasco et al, time to extubation was shorter in patients who received midazolam for less than 24 hours compared to those who received medium-term (1-7 days) or long-term (> 7 days) midazolam (23). They reported that except for one patient, there was a cumulative effect in all participants who received midazolam for more than 24 hours (23). In our study, duration of midazolam infusion for overall patients was average 48 ± 41 hours, and 18 patients (30.5%) received midazolam longer than 72 hours. Interestingly, the mean GCS on entry was higher, and also the mean APACHE II score on admission was lower in group 2 than group 1 (Table 2). So we thought that, those patients might be required deeper sedation in achieving ventilatory and therapeutic objectives.

Critical illness myopathy, which is considered among the main causes of weaning difficulties, was present clinically in only one subject who also emphysematous and had the longest weaning (169 hours) and total MV (265 hours) durations. The principal causes of critical illness myopathy include high dose systemic steroids, paralytic agents, and particularly the combination of these two (23). Paralytic agents are associated with an increased risk of myopathy especially when they are administered with continuous infusion and for more than 24 hours (25-27). None of our patients received continuous paralytic agents, and only in seven patients it was administered with a bolus dose at the beginning of ventilation to assist in adaptation. The systemic dose of steroids was not different between the groups.

Because of the retrospective design, data about dynamic hyperinflation and/or PEEPi, which were important determinants of the weaning success, were lacking in most of the patients' files. So we couldn't compared the groups according to these parameters.

In conclusion, the average total WD was 34 hours and the weaning ratio was 37% in COPD patients mechanically ventilated due to ARF. Whether WD is less or greater than 24 hours is not only determined by the patient and disease characteristics, but also by the medical treatment administered. Although we also showed that SIMV + PSV mode could be associated shorter WD in COPD patients, because of the weaning protocol used in this study is not a commonly used weaning protocol, the results of this study are specific for this protocol and cannot be generalized.

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