Intensive Care Med (2011) 37:775–784
DOI 10.1007/s00134-011-2179-3

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Predictors of prolonged weaning and survival during ventilator weaning in a respiratory ICU

Received: 5 August 2010
Accepted: 13 December 2010
Published online: 4 March 2011

This article is discussed in the editorial available at:
doi:10.1007/s00134-011-2202-8.

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Abstract *Purpose:* An International Consensus Conference proposed classifying weaning into simple, difficult, and prolonged weaning. However, the usefulness of this classification in a respiratory intensive care unit (ICU) is unknown. The aims of the study were: (1) to compare the clinical characteristics and outcomes of patients from the three weaning groups in a respiratory ICU; and (2) to assess predictors for prolonged weaning and survival. *Methods:* We prospectively studied 181 mechanically ventilated patients (131, 72% with chronic respiratory disorders) in whom weaning had been initiated, divided into simple (78, 43%), difficult (70, 39%), and prolonged (33, 18%) weaning. We compared the characteristics and outcomes among the three groups and determined the factors associated with prolonged weaning and survival in multivariate analysis. *Results:* Patients with simple and difficult weaning had similar characteristics and outcomes. A higher proportion of patients with prolonged weaning had chronic obstructive pulmonary disease, and these patients also had more complications, a longer stay and lower survival. Increased heart rate ($\geq$105 min^{-1}, $p < 0.001$) and $PaCO_2$ ($\geq$54 mmHg, $p = 0.001$) during the spontaneous breathing trial independently predicted prolonged weaning. In addition, the need for reintubation ($p < 0.001$) and hypercapnia during the spontaneous breathing trial ($p = 0.003$) independently predicted a decreased 90-day survival. *Conclusion:* Because of the similar characteristics and outcomes, the differentiation between simple and difficult weaning had no relevant clinical consequences in a respiratory ICU. Patients with prolonged weaning had the worst outcomes. For the overall population, hypercapnia at the end of spontaneous breathing predicts prolonged weaning and a worse survival, and clinicians should implement measures aimed at improving weaning outcome.

Keywords Hypercapnia · Prolonged weaning · Respiratory intensive care unit · Weaning from mechanical ventilation

Introduction

Weaning from mechanical ventilation (MV) is a challenging period that represents 40–50% of the duration of MV [1–4], and furthermore there is an increasing burden on the health-care system related to prolonged MV [5]. Different approaches have been proposed to optimize the weaning process [6, 7], including weaning protocols [3, 8, 9], automated systems [10], daily spontaneous breathing trials (SBT) [11], and pressure-support ventilation [12]. In spite of this, it is estimated that 20–30% of patients cannot be extubated at the first weaning attempt [2, 6].

An International Consensus Conference (ICC) on weaning from MV [6] proposed a new classification based on the difficulty and duration of the weaning period: simple, difficult, and prolonged weaning. Although it is considered that prolonged weaning is associated with the lowest survival [13, 14], this classification was based solely on expert opinion. Moreover, previous studies have analysed the factors associated with prolonged MV [15] and reintubation [16], but the factors involved in prolonged weaning have not yet been assessed. The identification of these factors could be important in influencing the survival of ventilated patients in whom weaning has been initiated. The ICC recommended further research on the basis of careful testing and scrutiny of groups of patients who undergo weaning, and stressed the need for studies assessing the outcome of patients with difficult and prolonged weaning [6].

A recent study in medical and surgical intensive care units (ICU) has shown that prolonged weaning is associated with increased mortality and morbidity [17]. However, the proportion of difficult and prolonged weaning is low in the general ICU population [2, 6]. Moreover, factors associated with prolonged weaning were not assessed in that study [17]. Applying this classification in specific settings with higher proportions of difficult and prolonged weaning would add valuable information regarding the factors associated with prolonged weaning. A large proportion of patients admitted to respiratory ICUs have chronic respiratory disorders, which are associated with a longer duration of weaning [6, 12]. Consequently, a respiratory ICU seems an optimal setting to assess the outcome of patients with difficult and prolonged weaning due to the expected higher proportion of such patients compared with the general ICU population [6]. In fact, chronic respiratory failure is more frequent in patients with prolonged weaning [17].

The aims of the present study were: (1) to compare the clinical characteristics and outcomes of patients with simple, difficult and prolonged weaning in a respiratory ICU; and (2) to determine predictive factors associated with prolonged weaning and its potential association with mortality, as this was expected in the group with worst outcomes [6].

Methods

Patients

In this prospective observational study, patients intubated and mechanically ventilated for more than 48 h were considered eligible when the following criteria for initiating weaning were fulfilled [18–20]: (1) improvement or resolution of the underlying causes of acute respiratory failure; (2) no fever ($\geq$38°C) or hypothermia (<35°C); (3) blood haemoglobin concentration $\geq$70 g/l; (4) haemodynamic stability; (5) alertness and ability to communicate after discontinuing sedation; and (6) arterial O_2 tension >60 mmHg with fraction of inspired oxygen (FIO_2) $\leq$0.4 and positive end-expiratory pressure $\leq$5 cmH_2O. For the purposes of this study, patients with previous tracheostomy were not considered eligible, and patients were excluded on the basis of the following criteria: (1) scheduled use of non-invasive ventilation (NIV) to facilitate the weaning process; (2) lack of cooperation for reliable measurements during the SBT; and (3) a previous decision to limit life-sustaining treatments. The study was approved by the Ethics Committee of the institution, but informed consent was not required.

Setting

The study was conducted in the Respiratory ICU of Hospital Clinic, Barcelona. This six-bed ICU serves patients with severe acute respiratory failure needing either invasive ventilation or NIV, difficult weaning with either NIV or tracheostomy, and monitoring. Patients with other non-respiratory organ system failures are also attended.

Study protocol

A SBT was performed with a T-piece. Prior to the SBT, assisted-control or pressure-support ventilation was used depending on the patient's preference or tolerance. We defined SBT failure as the presence and persistence of one of the following criteria [18–20]: (1) respiratory frequency >35 min^{-1}; (2) arterial O_2 saturation by pulse oximetry <90% at FIO_2 $\geq$0.40; (3) heart rate >140 or <50 min^{-1}, or increases or decreases of more than 20% compared to MV; (4) systolic blood pressure >180 or <70 mmHg, or increases or decreases of more than 20% compared to MV; (5) decreased consciousness, agitation or diaphoresis; and (6) thoracic-abdominal paradoxical movement. If no signs of SBT failure appeared after 30–120 min [13, 18–20], the trial was considered successful. If the patient had adequate mental status, adequate cough, and ability to expectorate, extubation was performed. Alternatively, if signs of spontaneous breathing failure appeared during this period, the patient was reconnected to the ventilator, and other attempts were performed on subsequent days if the patient still fulfilled the inclusion criteria. If the patient could not be disconnected from MV after several attempts without positive evolution of the weaning process, a tracheostomy was considered [21].

Tracheostomy was also performed after reintubation if the patient was unable to clear or remove secretions.

Definitions

The weaning process included the period from the first SBT to extubation. If a tracheostomy was performed, the weaning period was considered finished at the point when the patient had bee breathing spontaneously for at least 48 h without ventilatory support. Patients were divided into three groups as previously described [6]: (1) simple weaning (patients who proceeded from initiation of weaning to extubation on the first attempt without difficulty); (2) difficult weaning (patients who failed initial weaning and required up to three SBT or as long as 7 days from the first SBT to achieve successful weaning); and (3) prolonged weaning (patients who failed at least three weaning attempts or required >7 days of weaning after the first SBT).

The patient was immediately reintubated if any of the following major events occurred: respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation inadequately controlled by sedation, massive aspiration, persistent inability to remove respiratory secretions, heart rate below 50 min^{-1} with loss of alertness, and severe haemodynamic instability without response to fluids and vasoactive drugs [18–20]. In addition to the immediate reintubation criteria, respiratory failure after extubation was also defined as the presence and persistence, within 48 h of extubation, of at least two of the following: (1) respiratory acidosis (arterial pH <7.35 plus $PaCO_2$ >45 mmHg); (2) arterial O_2 saturation by pulse oximetry <90% or PaO_2 <60 mmHg at inspired O_2 fraction ≥0.5; (3) respiratory frequency >35 min^{-1}; (4) decreased consciousness, agitation or diaphoresis; and (5) clinical signs suggestive of respiratory muscle fatigue and/or increased work of breathing, such as the use of respiratory accessory muscles, paradoxical abdominal motion, or retraction of the intercostal spaces [19, 20, 22]. NIV was used to avoid reintubation in the patents with respiratory failure after extubation if immediate reintubation was not necessary [19, 20].

Ventilator-associated pneumonia (VAP) was defined as pneumonia that arises more than 48 h after endotracheal intubation [23]. For this study, only VAP episodes occurring after the onset of weaning were registered.

Data collection

All relevant data from the medical records and bedside flow charts of patients were reviewed at admission, including the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score [24], and at the onset and the end of the weaning process. Patient follow-up was extended to 90 days. Physiological parameters were obtained on the day the weaning process was started.

Statistical analyses

Sample size estimation

The main outcome of our study was mortality. No previous studies had assessed mortality using the ICC classification when we started collecting patients. We estimated from a previous study [18] that 23% of the patients in our respiratory ICU required prolonged weaning. Assuming the ICU mortality rates estimated for the different weaning groups in the ICC report [6], we expected to include at least 178 patients to observe differences in the main outcome [confidence level $(1 - \alpha)$ 95%, power level $(1 - \beta)$ 80%].

Comparison between the three groups

Data were analysed with SPSS 16.0 and are presented as number (percentage) or mean ± SD unless otherwise stated. Quantitative continuous variables were compared among the three groups using one-way analysis of variance, with Tukey post hoc comparisons. Categorical variables were compared using the chi-squared test. The level of significance was set at 0.05.

Risk factors for prolonged weaning and mortality

To assess the risk factors for prolonged weaning, patients were divided in prolonged and non-prolonged (simple plus difficult) weaning. Univariate and multivariate analyses were performed with logistic regression. Receiver operating characteristics curves were made to determine the optimal cut-off values of quantitative variables. Univariate and multivariate analyses of 90-day survival were performed with Cox proportional hazard regression. A conditional stepwise forward model (p_{in} <0.10, p_{out} <0.05) was used to correct for colinearity, and adjusted odds ratios and 95% confidence intervals were computed for variables independently associated with these events in all multivariate analyses.

Results

Patient characteristics

We included 181 consecutive patients over a 5-year period: 78 (43%) with simple, 70 (39%) with difficult, and 33 (18%) with prolonged weaning (Fig. 1). The baseline

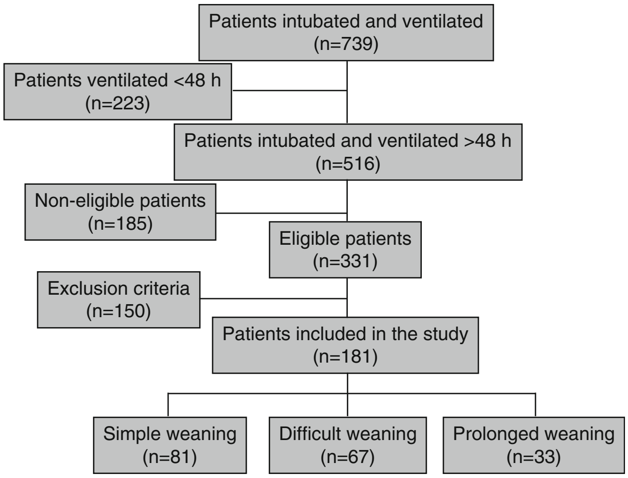

Fig. 1 Schematic representation of the studied population. Non-eligible patients were those who, prior to the start the weaning process, had died during the inclusion period, had been transferred to other units or hospitals, or had had a tracheostomy. The main reasons for excluding patients were scheduled use of NIV to facilitate the weaning process ($n = 105$), lack of cooperation that impeded reliable measurements during the SBT ($n = 25$), previous decision to limit life-sustaining treatments ($n = 18$). Two patients with relevant data missing were also excluded

characteristics of the patients are summarized in Table 1. Except for a higher proportion of patients with chronic obstructive pulmonary disease (COPD) or chronic bronchitis who required prolonged weaning ($p = 0.018$), the patient characteristics were similar between the three groups. Pulmonary function tests were available in 70 patients with chronic respiratory disorders (53%), without differences between the three groups.

The physiological parameters on the day of the first SBT are shown in Table 2. Patients with simple and difficult weaning were similar. Patients with prolonged weaning had a higher $PaCO_2$ ($p = 0.006$) and heart rate ($p = 0.044$), and a tendency to a lower arterial pH and oxygenation during MV prior to the SBT. Likewise, the frequency-to-tidal volume ratio at the beginning of the SBT was higher in this group ($p = 0.002$). At the end of the SBT in patients with prolonged weaning, $PaCO_2$ ($p = 0.001$), heart rate ($p < 0.001$) and systolic blood pressure ($p = 0.013$) were also higher, and arterial pH lower ($p = 0.001$), with a tendency to lower oxygenation.

Length of stay and complications

Patients with prolonged weaning had longer duration of ventilation and stay, as well as a higher rate of subsequent VAP. These data are presented in (Table 3).

The rate of respiratory failure after extubation was higher in patients with prolonged weaning ($p = 0.031$), with a trend to a higher rate among patients with difficult weaning compared with simple weaning. The proportion of patients who needed reintubation, including those with immediate criteria and those who failed treatment with NIV, tended to be higher in the prolonged weaning group. Tracheostomy during the course of weaning or after reintubation was more frequently performed among patients with prolonged weaning ($p < 0.001$). There were no significant differences between the simple and difficult weaning groups for any of these outcomes. When comparing patients with difficult weaning who failed one or more than one SBT, we did not find significant differences in any outcome variable.

Factors predicting prolonged weaning

Several variables were associated with prolonged weaning in the univariate analysis (Table 4). In the multivariate analysis, higher values of heart rate ($p < 0.001$) and $PaCO_2$ at the end of the first SBT ($p = 0.001$) were independent predictors of prolonged weaning. Heart rate ≥ 105 min^{-1} and $PaCO_2$ ≥ 54 mmHg had the best discriminative capacity to predict prolonged weaning. Figure 2 shows the individual values of $PaCO_2$ at the end of the SBT for the three groups of patients.

Analysis of survival

The ICU, hospital and 90-day mortalities were higher in the prolonged weaning group (Table 3; Fig. 3). No differences were observed between the simple and the difficult weaning groups.

Among the variables associated with decreased 90-day survival in the univariate analysis (Table 5), reintubation ($p < 0.001$) and higher $PaCO_2$ at the end of the first SBT ($p = 003$) were independent predictors of decreased 90-day survival in the multivariate analysis. $PaCO_2$ ≥ 45 mmHg had the best discriminative capacity to predict decreased 90-day survival.

Relationship between hypercapnia and outcome variables in patients with non-prolonged weaning

Since higher levels of $PaCO_2$ were associated with both prolonged weaning and worse survival, we analysed separately patients with non-prolonged (simple plus difficult) weaning in order to compare those with and without hypercapnia during the SBT. Patients with hypercapnia had worse oxygenation during spontaneous breathing ($p < 0.001$), a higher rate of respiratory failure after extubation ($p = 0.007$, Fig. 4; although the reintubation rate was not significantly different), and a lower 90-day survival ($p = 0.033$), indicating that hypercapnia remained associated with worse clinical condition and outcomes even in the absence of prolonged weaning.

Table 1 Baseline characteristics of the patients

Variable	Simple weaning (n = 78)	Difficult weaning (n = 70)	Prolonged weaning (n = 33)	p value: Comparison between the three groups	p value: Comparison between simple and difficult weaning
Age (years)	70 ± 10	70 ± 10	71 ± 8	0.97	0.99
Gender (male/female)	55/23	50/20	28/5	0.26	>0.99
Underlying diseases, n (%)					
Chronic respiratory disorders[a]	55 (71%)	49 (70%)	27 (82%)	0.41	>0.99
COPD or chronic bronchitis	40 (51%)	30 (43%)	24 (73%)	0.018	0.99
FEV_1 (% predicted)[b]	39 ± 14	38 ± 15	32 ± 15	0.37	0.97
Chronic heart disorders[c]	10 (13%)	14 (20%)	9 (27%)	0.18	0.34
Diabetes mellitus	4 (6%)	2 (3%)	2 (6%)	0.70	0.78
Cancer	2 (3%)	4 (7%)	0 (0%)	0.29	0.58
Chronic liver disorder	3 (4%)	2 (3%)	0 (0%)	0.55	0.88
Chronic renal failure	4 (6%)	1 (2%)	0 (0%)	0.23	0.43
Causes for initiating MV, n (%)					
Acute-on-chronic respiratory failure	30 (39%)	19 (27%)	14 (42%)	0.21	0.20
Pneumonia	12 (15%)	15 (21%)	6 (18%)	0.64	0.46
Congestive heart failure	11 (14%)	8 (11%)	7 (21%)	0.42	0.81
Neurological disease	6 (8%)	8 (11%)	0 (0%)	0.13	0.62
Sepsis	8 (10%)	5 (7%)	1 (3%)	0.42	0.71
Postoperative respiratory failure	5 (6%)	6 (9%)	2 (6%)	0.85	0.85
Other	6 (8%)	9 (13%)	3 (9%)	–	–
Duration of MV before weaning, days	5 ± 4	5 ± 3	4 ± 3	0.44	0.79
APACHE-II score on admission	19 ± 6	20 ± 7	18 ± 5	0.33	0.62

The data are presented as number (%) or means ± SD as appropriate

COPD chronic obstructive pulmonary disease, *FEV₁* forced expiratory volume during the first second of the forced expiration manoeuvre, *MV* mechanical ventilation, *APACHE-II* Acute Physiology and Chronic Health Evaluation II

[a] Chronic respiratory disorders include COPD, chronic bronchitis associated with dyspnoea and current or former history of smoking in the absence of pulmonary function testing, *sequelae* of pulmonary tuberculosis, chest wall deformity or obesity associated with a restrictive ventilatory disorder, and bronchiectasis

[b] The reported pulmonary function tests had been obtained during stable clinical condition within 1 year of the current hospital admission

[c] Chronic heart disorders include coronary artery disease, hypertensive or valvular heart diseases, and dilated myocardial disease of any cause

Discussion

Summary of results

Patients with prolonged weaning had more complications, longer stay and higher mortality than those with simple and difficult weaning. However, patients with simple and difficult weaning had similar outcomes. An increased cardiorespiratory stress (higher heart rate and $PaCO_2$) during the first SBT were independently associated with prolonged weaning. Likewise, hypercapnia when breathing spontaneously and reintubation were independently associated with decreased 90-day survival.

Duration of the weaning process

The ICC has estimated that around 69% patients can be extubated at the first weaning attempt (simple weaning), while around 31% need more than one SBT (difficult plus prolonged weaning) [6]. In a recent prospective study in medical and surgical ICUs, 59% of patients were classified as simple, 26% as difficult, and 14% as prolonged weaning [17].

We prospectively evaluated for the first time the new classification into three groups proposed by the ICC [6] in a respiratory ICU. As expected, the rate of simple weaning in our study was lower (43%) than in previous studies [2, 6, 17]. This is explained by the higher proportion of patients with chronic respiratory disorders (72%), and particularly COPD or chronic bronchitis (52%) in our study, compared with 16% with chronic respiratory failure in the study by Funk et al. [17]. Patients in our respiratory ICU also have worse outcomes than medical and surgical ICU patients [17], with higher mortality rates for each of the three weaning categories. One potential explanation for this finding is the higher proportion of reintubated patients observed in all the groups in our study. In fact, reintubation was independently associated with higher mortality, as has been reported previously [25, 26].

As previously shown in medical and surgical ICU patients [17], no differences in mortality between simple

Table 2 Physiological parameters of patients at the start of the weaning process

Variable	Simple weaning ($n = 78$)	Difficult weaning ($n = 70$)	Prolonged weaning ($n = 33$)	*p* value	
				Comparison between the three groups	Comparison between simple and difficult weaning
During MV, before the SBT					
Respiratory frequency (min^{-1})	16 ± 3	17 ± 5	17 ± 5	0.27	0.26
Heart rate (min^{-1})	81 ± 20	78 ± 19	88 ± 19	0.044	0.52
Systolic blood pressure (mmHg)	132 ± 22	130 ± 22	142 ± 33	0.28	0.85
Arterial pH	7.44 ± 0.05	7.44 ± 0.05	7.42 ± 0.05	0.087	0.85
$PaCO_2$ (mmHg)	42 ± 7	44 ± 8	47 ± 8	0.006	0.25
PaO_2 (mmHg)	101 ± 25	95 ± 21	93 ± 31	0.23	0.39
PaO_2/FIO_2	275 ± 81	258 ± 74	241 ± 83	0.099	0.41
At the beginning of the SBT					
f/V_t ratio	67 ± 33	79 ± 37	98 ± 55	0.002	0.18
At the end of the SBT					
Respiratory frequency (min^{-1})	23 ± 5	25 ± 7	27 ± 8	0.019	0.073
Heart rate (min^{-1})	92 ± 18	89 ± 15	105 ± 17	<0.001	0.54
Systolic blood pressure (mmHg)	148 ± 27	143 ± 25	167 ± 24	0.013	0.47
Arterial pH	7.42 ± 0.05	7.42 ± 0.06	7.37 ± 0.08	0.001	0.96
$PaCO_2$ (mmHg)	45 ± 9	46 ± 9	53 ± 13	0.001	0.74
PaO_2 (mmHg)	87 ± 23	87 ± 22	78 ± 23	0.12	0.99
PaO_2/FIO_2	228 ± 64	228 ± 68	198 ± 75	0.077	0.99
Delta changes from MV to the end of the SBT					
Respiratory frequency (min^{-1})	7 ± 7	8 ± 8	9 ± 9	0.19	0.43
Heart rate (min^{-1})	10 ± 15	12 ± 18	17 ± 17	0.22	0.83
Systolic blood pressure (mmHg)	17 ± 21	11 ± 18	24 ± 27	0.076	0.23
Arterial pH	−0.02 ± 0.04	−0.02 ± 0.05	−0.04 ± 0.07	0.060	0.69
$PaCO_2$ (mmHg)	3 ± 6	3 ± 6	6 ± 10	0.13	0.84
PaO_2 (mmHg)	−14 ± 24	−10 ± 23	−15 ± 29	0.46	0.50
PaO_2/FIO_2	−48 ± 67	−36 ± 57	42 ± 67	0.57	0.54

The data are presented as means ± SD
MV mechanical ventilation, *SBT* spontaneous breathing trial, f/V_t frequency-to-tidal volume ratio, $PaCO_2$ arterial carbon dioxide tension, PaO_2 arterial oxygen tension, FIO_2 inspired fraction of oxygen

Table 3 Length of stay and outcome variables

Variable	Simple weaning ($n = 78$)	Difficult weaning ($n = 70$)	Prolonged weaning ($n = 33$)	*p* value	
				Comparison between the three groups	Comparison between simple and difficult weaning
Total duration of MV (days)	5 ± 4	6 ± 3	13 ± 11	<0.001	0.74
ICU stay (days)	11 ± 12	12 ± 8	21 ± 13	<0.001	0.97
Hospital stay (days)	25 ± 18	29 ± 18	36 ± 21	0.018	0.54
Respiratory failure after extubation, *n* (%)	21 (27)	29 (41)	17 (52)	0.031	0.062
Patients treated with NIV, *n* (%)	14 (67)	22 (76)	11 (65)	0.67	0.69
Reintubation, *n* (%)	12 (15)	13 (19)	11 (33)	0.090	0.77
Ventilator-associated pneumonia, *n* (%)	12 (15)	13 (19)	14 (42)	0.005	0.77
Tracheostomy, *n* (%)	6 (8)	6 (9)	13 (39)	<0.001	>0.99
ICU mortality, *n* (%)	10 (13)	8 (11)	14 (42)	<0.001	>0.99
Hospital mortality, *n* (%)	15 (19)	16 (23)	16 (49)	0.004	0.74

The data are presented as means ± SD
MV mechanical ventilation, *NIV* non-invasive ventilation, *ICU* intensive care unit

and difficult weaning patients were observed in our respiratory ICU. The average total duration of MV were 1 day longer in patients with difficult weaning from our population than in those with simple weaning, but the difference did not reach statistical significance. As mortality increases with the duration of MV [4], this may explain the similar outcomes observed in the two groups of patients. Therefore, an initial failure of the SBT has no

Table 4 Univariate and multivariate analysis of predictors of prolonged weaning

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	*p* value	Adjusted odds ratio	95% confidence interval	*p* value
COPD or chronic bronchitis	2.97	1.29–6.82	0.014	–	–	–
During MV, before the SBT						
Heart rate (min^{-1})	1.026	1.003–1.049	0.025	–	–	–
Arterial pH[a]	0.921	0.853–0.994	0.034	–	–	–
$PaCO_2$ (mmHg)	1.071	1.019–1.126	0.007	–	–	–
At the beginning of the SBT						
f/V_t ratio	1.014	1.004–1.023	0.004	–	–	–
At the end of the SBT						
Heart rate (min^{-1})	1.051	1.025–1.078	<0.001	1.060	1.029–1.091	<0.001
Systolic blood pressure (mmHg)[a]	1.032	1.007–1.057	0.011	–	–	–
PaO_2/FIO_2 (mmHg)	0.992	0.985–0.999	0.026	–	–	–
Arterial pH	0.889	0.830–0.952	0.001	–	–	–
$PaCO_2$ (mmHg)	1.067	1.027–1.109	0.001	1.071	1.027–1.118	0.001

The variables included in the model were those available when the SBT was performed: age, gender, underlying diseases (including COPD), cause for initiating MV, duration of MV prior to the start of weaning, APACHE-II score, and physiological parameters at the onset of weaning (see Table 2).

COPD chronic obstructive pulmonary disease, *MV* mechanical ventilation, *SBT* spontaneous breathing trial, *f/V_t* frequency-to-tidal volume ratio, *$PaCO_2$* arterial carbon dioxide tension, *PaO_2* arterial oxygen tension, *FIO_2* inspired fraction of oxygen

[a] Values are given for each unit of measure; in the case of pH, for centesimal units

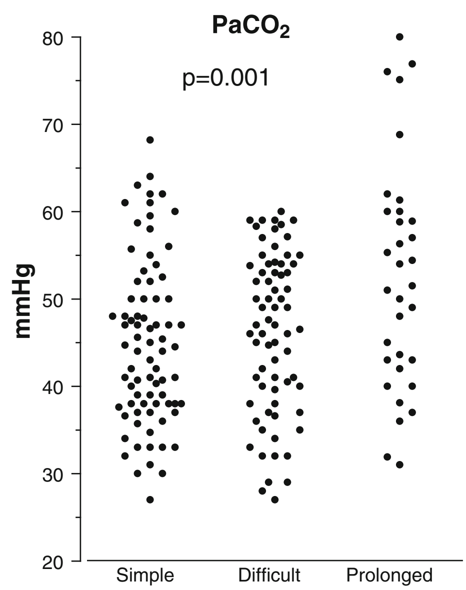

Fig. 2 Individual values of $PaCO_2$ at the end of the SBT in patients from the three weaning groups. $PaCO_2$ was significantly higher in the prolonged weaning group, compared with the simple and the difficult weaning groups ($p = 0.001$)

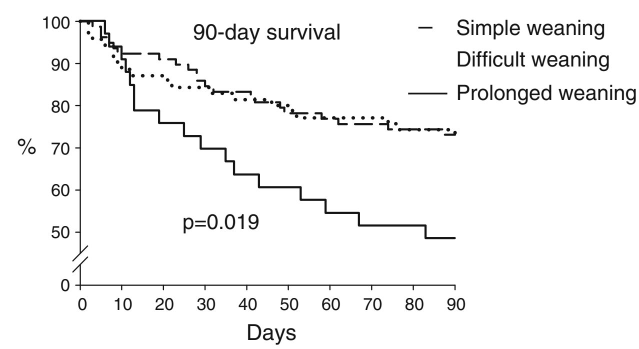

Fig. 3 Kaplan-Meier survival curves for patients over 90 days from entry into the study. The cumulative survival probability was significantly lower in the prolonged weaning group (log-rank test). No differences were observed between patients with simple and difficult weaning

impact in outcome if patients are extubated in the next following days. Conversely, patients with prolonged weaning had substantially longer duration of MV, thus explaining the higher rate of complications associated with prolonged ventilation and mortality.

Higher $PaCO_2$ and heart rate during the initial SBT were independently related to the prolongation of weaning. These findings are consistent with those of previous studies showing that patients develop increased cardiopulmonary stress during an unsuccessful SBT [27–31]. This is directly associated with the imbalance between ventilatory demands and capacity in patients who are not yet ready to be disconnected from the ventilator, which is influenced by many different factors [32]. However, the large overlap of $PaCO_2$ values between patients from the three groups, as shown in Fig. 2, limits the discriminative value of this individual variable. Heart rate and $PaCO_2$ during MV before the SBT were also higher in patients with prolonged weaning; this suggests that patients more likely to require prolonged weaning begin the weaning process in a worse condition than those less likely to.

Table 5 Multivariate analysis of predictors of decreased 90-day survival

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	*p* value	Adjusted odds ratio	95% confidence interval	*p* value
During MV, before the SBT						
Heart rate (min^{-1})[a]	1.015	1.001–1.030	0.042	–	–	–
$PaCO_2$ (mmHg)[a]	1.037	1.004–1.071	0.027	–	–	–
At the end of the SBT						
$PaCO_2$ (mmHg)[a]	1.040	1.016–1.064	0.001	1.033	1.011–1.055	0.003
Arterial pH[a]	0.959	0.924–0.997	0.033	–	–	–
Heart rate (min^{-1})[a]	1.018	1.003–1.033	0.017	–	–	–
Duration of weaning (days)[a]	1.034	1.005–1.063	0.020	–	–	–
Prolonged weaning	2.21	1.25–3.90	0.006	–	–	–
Respiratory failure after extubation	3.57	2.08–6.12	<0.001	–	–	–
Reintubation	5.74	3.39–9.72	<0.001	5.34	3.14–9.09	<0.001
Ventilator-associated pneumonia	3.74	2.21–6.35	<0.001	–	–	–
Tracheostomy	3.52	2.00–6.17	<0.001	–	–	–

The same variables entered in the multivariate analysis of risk factors of prolonged weaning (see Table 4) were included, and also the next variables: development of prolonged weaning, duration of mechanical ventilation and weaning, development of respiratory failure after extubation, reintubation in the first 48 h, and the need for tracheostomy

$PaCO_2$ arterial carbon dioxide tension, *MV* mechanical ventilation, *SBT* spontaneous breathing trial
[a] Values are given for each unit of measure; in the case of pH, for centesimal units

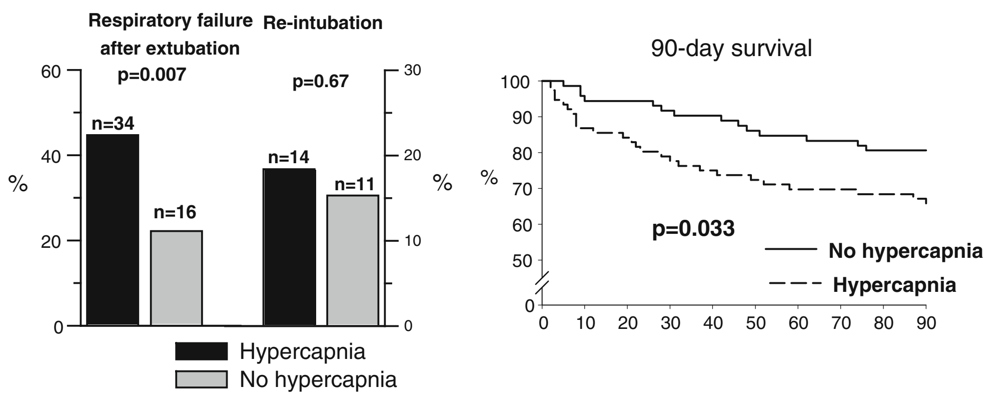

Fig. 4 Rate of respiratory failure after extubation, reintubation, and 90-day survival in patients with non-prolonged (simple plus difficult) weaning comparing patients with and without hypercapnia during the first SBT

Factors related to survival

Although prolonged weaning was associated with decreased 90-day survival, reintubation and hypercapnia during the SBT were the only independent predictors of 90-day mortality. Reintubation has already been described as an independent risk factor of hospital mortality [25]. The need for reintubation may serve as an additional independent marker of increased severity of illness, and may be aetiologically related to poor outcomes such as VAP [26]. The association of hypercapnia during a SBT with decreased survival has already been described in patients with persistent weaning failure [18]. In addition, patients with hypercapnia before extubation have poor outcomes when no ventilatory support is provided after extubation [19, 20, 33]. Increased $PaCO_2$ therefore appears to be an accurate indicator of clinical deterioration after recovery from an acute episode of respiratory failure. Alternatively, this may also reflect the presence of advanced chronic respiratory disease, since hypercapnic patients had worse lung function than non-hypercapnic patients (their FEV_1 was $34 \pm 11\%$ predicted and $48 \pm 19\%$ predicted, respectively, $p = 0.008$).

Potential clinical implications

If hypercapnia is detected while the patient is breathing spontaneously at onset of weaning, the clinician should implement measures such as the early application of NIV after extubation. This may help shorten the weaning period [18, 34] and prevent further respiratory deterioration [19, 20], resulting in improved survival in the respiratory ICU population. By contrast, using NIV to treat respiratory failure after extubation in mixed ICU populations is not efficient and may be harmful [22, 35].

Limitations

This study was conducted in a respiratory ICU of a single centre with a high proportion of patients with chronic respiratory disorders; this resulted in higher proportions of difficult and prolonged weaning than found in general ICU series [2, 17]. Although the most relevant findings of this study were also observed when patients with COPD and chronic bronchitis were excluded from the analysis, these results may not be extrapolated to other populations of critically ill patients. Moreover, the proposed $PaCO_2$ thresholds to predict prolonged weaning and worse survival deserve further prospective validation.

Conclusion

In a respiratory ICU, patients with simple and difficult weaning had similar characteristics and outcomes; this differentiation has therefore no relevant clinical implications in this population. Patients with prolonged weaning had the worst outcomes. For the overall population, increased CO_2 retention during spontaneous breathing strongly predicts prolonged weaning and worse survival. If high levels of $PaCO_2$ are detected in the patient at the onset of weaning, the clinician should implement measures aimed at improving the outcome of weaning from MV.

Acknowledgments The authors wish to thank Roger Marshall for his editing aid. The authors also thank the respiratory therapy and nursing staff, and the attending physicians of the respiratory ICU, for their cooperation in this study. The authors also acknowledge the support of the Centro de Investigación Biomédica En Red-Enfermedades Respiratorias (CibeRes, CB06/06/0028)-Instituto de Salud Carlos III (ISCiii), Suport a Grups de Recerca (2009 SGR 911), a European Respiratory Society (ERS) Fellowship, and the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS).

Conflicts of interest None of the authors have a financial relationship with the organizations that sponsored the research.

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