

Serum Creatinine and Weaning in Patients with Chronic Obstructive Pulmonary Disease: Multicenter Pilot Study

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Abstract

Background: Serum creatinine can provide indirect information on body muscle mass. The role of respiratory muscle is very important during the weaning process in patients with chronic obstructive pulmonary disease (COPD). We aimed to assess whether low creatinine levels are a predictor of unsuccessful weaning or prolonged ventilation in COPD patients receiving mechanical ventilation (MV) in the intensive care unit (ICU).

Methods: A multicenter, retrospective cohort study was conducted in three ICUs between July 1st, 2007 and June 30th, 2008. All consecutive COPD patients receiving MV were enrolled. Patients with acute or chronic renal failure were excluded. Patient demographics, ICU severity score (APACHE II), body mass index (BMI), and serum creatinine and blood urea nitrogen (BUN) levels, were recorded on the first day in ICU, and the first and seventh day of weaning. Successful weaning was defined as successful extubation after the first T-piece trial. Unsuccessful weaning was failed extubation after more than one T-piece trial. Prolonged ventilation was MV duration more than seven days. The chi-square, Fischer's exact test, or t-test (where appropriate) were used to compare the simple weaning group, (SWG, successful weaning) and the prolonged weaning group (PWG, unsuccessful weaning or prolonged ventilation).

Results: Eighty-five patients were enrolled (SWG, 36 PWG, 49). No significant difference was found between the groups with respect to age, gender, APACHE II score, and BMI. Patients with low creatinine (less than 0.5 mg/dL) on the first day of ICU, and first day of the weaning trial in SWG and PWG were 4/36, 12/49, and 4/36, 19/49, respectively ($p > 0.16$ and $p < 0.006$). Mortality was detected in only PWG ($n = 7$, 8.2%).

Conclusion: Low creatinine levels at the start of weaning trial appear to be a predictor of unsuccessful weaning or prolonged ventilation in COPD patients in the ICU.

Keywords: Creatinine; Weaning; Mechanical Ventilation; Chronic Obstructive Pulmonary Disease

Introduction

Non-invasive mechanical ventilation (NIV) is a gold standard for acute respiratory failure (ARF) in patients with chronic obstructive pulmonary disease (COPD) [1]. When NIV fails, invasive mechanical ventilation (IMV) is required in COPD.

During the International Consensus Conference Brochard proposed a new weaning classification of patients into three groups according to the difficulty and length of the weaning process [2]. Although the NIV success rate is very high in COPD, when NIV fails or is contra-indicated, weaning from mechanical ventilation can be a problem [3]. Therefore, taking potentially prolonged ventilation and weaning difficulties into account, intensivists hesitate to intubate COPD patients. Successful weaning has been attributed to a number of factors, as stated in guidelines, including nutritional status and muscle strength [2-5]. The role of respiratory muscle is very important in COPD patients during the weaning process [3].

Serum creatinine can provide indirect information on body muscle mass. Oterdoom et al. report that low creatinine excretion in the urine is an indirect measure of low muscle mass (with normal renal function) and is associated with major adverse cardiovascular events [6].

An acute increase in serum creatinine originates from muscle destruction due to drug-induced muscle atrophy [7]. Serum creatinine is low in patients with whole body muscle wasting or atrophies [8]. Thus, we can speculate that invasively ventilated patients with low serum creatinine, especially during the weaning period, may have muscle wasting and atrophy. In addition, blood urea nitrogen (BUN)

levels are elevated by the catabolism of lean body mass [5], and lower levels of BUN may be a marker of the cessation of catabolism, which is necessary for respiratory muscle recovery and a good predictor of weaning [9].

We hypothesized that COPD patients with low serum creatinine levels on the first day of weaning would most likely not be successfully weaned because of inadequate muscle strength.

Methods

Design and settings

This multicenter, retrospective cohort pilot study was conducted in three centers. One center, a 14-bed respiratory intensive care unit (ICU) in a big government respiratory training and research hospital, was in İstanbul, while the others were medical faculties in Ankara; one was a six-bed ICU for patients with respiratory failure, the other was a

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ten-bed medical ICU. The study was conducted from June 1st, 2007 to June 30th, 2008.

The study was approved by our local ethical committee.

Patient recruitment

All consecutive, previously diagnosed, COPD [1] patients with ARF who, either failed a first attempt of NIV, or who had contraindications for NIV [10], and were intubated for IMV for more than 24 h, were enrolled into the study. We excluded patients with chronic renal disease or acute renal failure requiring hemodialysis, or those who had a tracheostomy (Figure 1).

Weaning process

The following criteria had to be met before weaning was attempted: 1) An improvement in the precipitating factors of ARF, 2) hemodynamic stability (heart rate [HR] less than 140 beats·min⁻¹, systolic blood pressure [BP] between 90-160 mmHg, no or minimal vasopressors), 3) stable metabolic status, 4) adequate oxygenation (oxygen saturation rate [SatO₂] more than 90% on ≤ fractionated inspired oxygen [FiO₂] of 0.40 or PaO₂/FiO₂ more than 150), 5) positive expiratory end pressure (PEEP) ≤ 8 cm H₂O, 6) adequate pulmonary function (breath per minute [fR] less than 35, tidal volume [VT] 0.5 mL·kg⁻¹, rapid shallow breathing index [fR/VT] less and equal to 105 breaths·min⁻¹·L⁻¹), 7) no significant respiratory acidosis, and 8) adequate mentation without sedation or adequate mentation on sedation (i.e., stable neurological patient). All three institutions followed the same weaning protocol. All weaning was conducted by experienced ICU physicians and initiated in the morning. When patients met the criteria for weaning the pressure support ventilation (PSV) was gradually decreased (1-2 cm H₂O every 1-2 hours). When the PS reached 8-10 cm H₂O and PEEP was 0 or less than 5 cm H₂O, the patient progressed to spontaneous breathing trials (SBT) by T-piece with oxygen support [4]. Duration of the T-piece trial was 30 minutes. During this period the patient was observed directly by the ICU physicians and nurses.

The failure criteria for the T-piece trials were as follows: 1) Clinical assessment and subjective indices, i.e., agitation and anxiety, depressed mental status, diaphoresis, cyanosis, evidence of increasing effort, increased accessory muscle activity, facial signs of distress, and

dyspnea. 2) Measurements such as arterial blood gases (ABGs); PaO₂ ≤ 50–60 mmHg on FiO₂ ≥ 0.5 or SaO₂ less than 90%, PaCO₂>50 mmHg or an increase in PaCO₂ more than 8 mmHg, fR/VT>105 breaths min⁻¹ L⁻¹, fR>35 breaths min⁻¹ or increased by ≥ 50%, HR>140 beats min⁻¹ or increased by ≥ 20%, systolic BP>180 mmHg or increased by ≥ 20%, systolic BP<90 mmHg, and cardiac arrhythmias. Patients were extubated after 30 min of a successful T-piece trial. After extubation, NIMV was applied in cases of moderate respiratory distress if no contra-indication existed [4].

Definitions of weaning

Pre-weaning period: the time (hours) from intubation to the beginning of weaning.

Successful weaning (simple weaning): successful extubation after the first T-piece trial.

Unsuccessful weaning: failed extubation after more than one T-piece trial.

Prolonged ventilation: mechanical ventilation for more than seven days, or three or more T-piece trials.

Patients were divided into two groups based on their weaning success.

Simple weaning group (SWG): weaning was successful at the first weaning attempt.

Prolonged weaning group (PWG): weaning failed at the first attempt of the weaning trial, or death under IMV. We further divided patients according to their serum creatinine levels on the first day in ICU and the first day of the weaning trial. These were classified as low serum creatinine and normal to high creatinine according to the normal limits for females and males.

Data records

All records were collected retrospectively. Age, gender, smoking habits, co-morbidities (e.g. diabetes, cardiac disease), body mass index (BMI, kg/m²), arterial blood gas analysis on admission to the ICU, recent/current medications including bronchodilators, steroids (systemic/inhaler), and sedatives, were recorded. The cause of ARF was defined as hypercapnic respiratory failure (PaCO₂ more than 45 mmHg) without hypoxemia; hypoxemic and hypercapnic respiratory failure were defined as PaCO₂>45 mmHg and PaO₂/FiO₂<300. As an ICU severity score, the acute physiological and chronic health evaluation (APACHE) II was recorded on admission to the ICU [11]. Serum creatinine and BUN were recorded on the first day of ICU, and the first and seventh day of the weaning trial. The BUN/creatinine ratio was calculated to compare weaning groups with respect to hypercatabolic state, as described previously [9]. Blood glucose, sodium, potassium, hematocrit, and C-reactive protein levels on admission to the ICU were recorded from the patient's file. The duration of mechanical ventilation, ICU length of stay, and ICU outcome (mortality), were also recorded from the data.

Statistical analyses

Data for continuous variables (i.e., age, body mass index, BUN, creatinine, BUN/creatinine, arterial blood gas values, APACHE II scores, and length of ICU stay) are presented as the mean ± standard deviation (SD) for normal distribution, and the median (inter quartile ratio, 25%-75%) for non-normal distribution. We used the student t-test to compare groups if the values were well distributed, and if not the Mann-Whitney-U test was performed. To compare data of

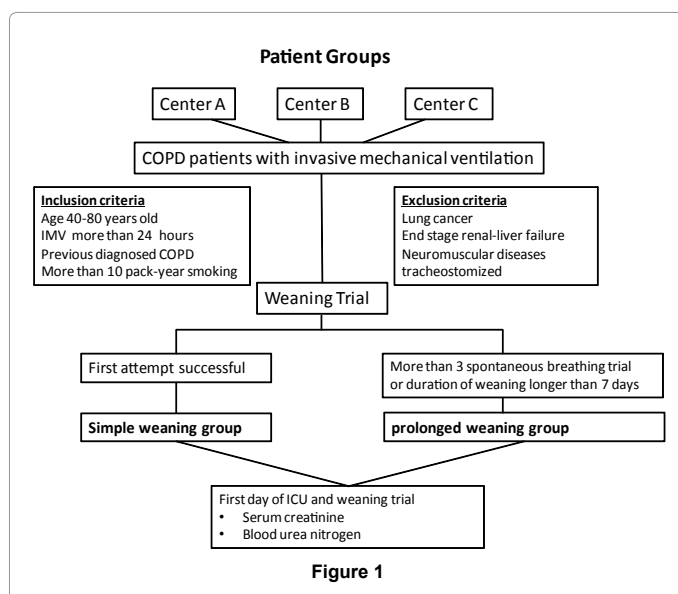


Figure 1

categorical variables (i.e., gender, presence of tracheostomy), the chi-square test was used. A p value < 0.05 was accepted as significant.

Results

In the study period 85 of 96 COPD patients (19 female) were enrolled from three centers. Patients were divided into two groups according to the weaning trials, as described in the Methods. Patient demographics and ICU data are summarized in table 1.

Table 2 shows the relationship between the patient groups and ICU data (IMV, sedation, tracheostomy, need for home MV, length of ICU stay, and mortality). The pre-weaning period and length of ICU stay were longer in the PWG group compared with the SWG group (p<0.004 and p<0.001, respectively). Mortality rate was similar but there were more patients discharged to home with a tracheostomy and home ventilators in the PWG than the SWG group (p<0.004 and p<0.020, respectively).

The relationship between the patient groups and BUN, creatinine, and BUN/creatinine ratio on first day of ICU, and the first and seventh day of the weaning trial are summarized in table 3. Serum creatinine on the first and seventh day of the weaning trial was significantly lower in the PWG group compared with the SWG group (p<0.003 and p<0.012, respectively).

Table 4 shows patient's BMI, ICU severity score, C-reactive protein on admission to the ICU, BUN/creatinine, pre-weaning duration, and length of ICU stay in the two patient groups relative to serum creatinine on the first day of ICU and the first day of the weaning trial. The percentage of patients in the low and normal creatinine groups on the first day of ICU and the first day of weaning are shown in figure 2. There were significantly more patients with lower creatinine levels in the PWG compared with the SWG (p<0.006).

Discussion

In the present study our hypothesis that low serum creatinine may

	SWG	PWG	p values
Patient demographics			
Gender, Female/male	7/29	12/37	0.58
Age, years, mean (SD)	67 (11)	68 (9)	0.76
Body mass index* kg/m ² , mean (SD)	25.1 (5.5)	24.6 (7.6)	0.76
Reasons of acute respiratory failure			
Hypercapnia and hypoxemia, n(%)	28 (77.8)	40 (81.6)	0.66
Hypercapnia, n(%)	8 (22.2)	9 (18.4)	
Co-morbid diseases,			
Diabetes mellitus, n(%)	6 (16.7)	11 (22.4)	0.51
Heart diseases, n(%)	27 (75.0)	34 (69.4)	0.57
Bronchiectasis, n(%)	5 (13.9)	7 (14.3)	0.95
Arterial blood gases on admission			
pH, median (IQR)	7.28 (7.20-7.32)	7.28 (7.19-7.34)	0.95
PaCO ₂ , mmHg, mean (SD)	77.0 (22.5)	85.0 (28.3)	0.16
PaO ₂ /FiO ₂ mmHg, median (IQR)	218 (167-284)	221 (161-268)	0.87
Biochemistry			
Hematocrit %, mean (SD)	42.9 (7.0)	42.8 (7.1)	0.96
Glucose mg/dL, mean (SD)	136 (39)	139 (64)	0.84
Sodium mmol/L, mean (SD)	138 (6)	139 (6)	0.37
Potassium mmol/L, mean (SD)	4.4 (0.6)	4.5 (0.9)	0.84
C-reactive protein# mg/dL, median (IQR)	42.3 (10.2-100.0)	35.4 (18.4-99.0)	0.81
APACHE II mean (SD)	22.6 (5.7)	23.0 (7.1)	0.79

Non-parametric continuous values are shown as median (interquartile ratio= IQR). The Mann Whitney U test was used and parametric continuous values are shown as mean (SD). The student-t test was also used. P<0.05 was accepted as statistically significant. SWG: simple weaning group, PWG: prolonged weaning group, PaCO₂: arterial partial carbon dioxide pressure, PaO₂/FiO₂: arterial partial oxygen pressure over inspired fractionated oxygen, *body mass index available for 27 patients in the SWG, 34 in the PWG, #C-reactive protein available for 31 patients in the SWG, and 37 in the PWG. APACHE II: Acute physiologic and chronic health evaluation (11)

Table 1: Patient demographics and arterial blood gases and biochemistry on admission to the intensive care unit.

Variables	SWG, n=36	PWG, n=49	p values
Mechanical ventilation, median (IQR)			
Pre-weaning MV duration, hours	71 (33-99)	103 (49-175)	0.004
Duration of midazolam, hours	29 (22-72)	51 (20-84)	0.40
Total midazolam doses, mg	60 (23-115)	57 (18-160)	0.75
ICU length of stay, day median (IQR)	9 (5-14)	15 (11-24)	0.001
Discharge from ICU			
Ward, n (%)	33 (91.7)	16 (32.7)	0.001
Home via non-invasive ventilators, n (%)	2 (5.6)	12 (24.5)	0.020
Tracheostomy, n (%)	0	10 (20.4)	0.004
Mortality %	2.8 (n=1)	12.2 (n=6)	0.23

Non-parametric continuous values are shown as median (IQR: interquartile ratio). The Mann Whitney U test was also used. P<0.05 was accepted as statistically significant. SWG: simple weaning group, PWG: prolonged weaning group, ICU: intensive care unit

Table 2: Patient ICU data and outcomes.

Variables	SWG, n=36	PWG, n=49	p values
Serum Creatinine			
First day of ICU, mean (SD)	1.08(0.36)	0.99 (0.51)	0.36
First day of weaning trial, mean (SD)	0.94 (0.29)	0.78 (0.0.37)	0.035
Seventh day of weaning trial* median (IQR)	0.80 (0.70-1.07)	0.58 (0.48-080)	0.012
Serum blood urea nitrogen (BUN)			
First day of ICU, median (IQR)	30 (21-37)	26 (18-42)	0.73
First day of weaning trial, median (IQR)	25 (19-35)	18 (11-31)	0.034
Seventh day of weaning trial*, median (IQR)	14 (11-23)	13 (10-21)	0.52
BUN/serum creatinine			
First day of ICU, median (IQR)	28 (19-38)	32 (20-48)	0.21
First day of weaning trial, mean (SD)	30.3 (12.7)	31.4 (17.2)	0.74
Seventh day of weaning trial*, mean (SD)	19.9 (7.9)	26.6 (15.7)	0.07

Non-parametric continuous values are shown as median (interquartile ratio=IQR) The Mann Whitney U test was used and parametric continuous values are shown as mean (SD). The student-t test was also used. P<0.05 was accepted as statistically significant. SWG: simple weaning group, PWG: prolonged weaning group, *n: 11 for SWG, n: 36 for PWG

Table 3: Patient serum creatinine and blood urea nitrogen levels.

Variables	On the admission day to ICU			On the first day of the weaning trial		
	Serum creatinine level			Serum creatinine level		
	Low	Normal to higher	p	Low	Normal to higher	p
Body mass index, kg/m ²	19.2 (3.9)	26.1 (6.6)	0.002	24.2 (9.0)	25.2 (5.4)	0.66
APACHE II on admission*	19 (4)	24 (7)	0.011	20 (18-24)	23 (19-28)	0.025
APACHE II at discharge*	13 (5)	14 (4)	0.92	13 (4)	14 (5)	0.51
C-reactive protein on admission to ICU, mg/dL*	36 (9-80)	43 (14-106)	0.50	47 (26-99)	35 (10-100)	0.24
PaO ₂ /FiO ₂ on admission to the ICU*	248 (119)	230 (97)	0.50	238 (101)	231 (101)	0.78
BUN, mg/dL*	22 (12)	35 (22)	0.023	22 (10)	37 (23)	0.001
Serum creatinine mg/dl *	0.52 (0.08)	1.15 (0.43)	0.001	0.66 (0.02)	1.17 (0.45)	0.001
BUN/serum creatinine*	37.2 (14.2)	33.6 (14.4)	0.53	33.8 (17-33)	34.5 (21.5)	0.88
Assist/Control mod, preweaning hour#	77 (49-134)	82 (40-120)	0.88	98 (63-138)	72 (35-108)	0.07
Length of ICU stay, day#	15 (11-23)	12 (6-19)	0.18	15 (12-21)	11 (5-20)	0.031

*Parametric continuous values are shown as mean (SD). Analyses were done with the Mann Whitney U test and # nonparametric continuous values are shown as median (interquartile ratio). The student-t test was also used. P<0.05 was accepted as statistically significant. ICU: intensive care unit, APACHE II: Acute physiologic and chronic health evaluation (11), PaO₂/FiO₂: arterial partial oxygen pressure over inspired fractionated oxygen, BUN: blood urea nitrogen

Table 4: Patient characteristics, blood urea nitrogen (BUN), BUN/creatinine and ICU data in serum creatinine groups.

indicate a longer duration of ventilation weaning in COPD patients as a result of muscle wasting/atrophy, was supported. There were significantly more patients with low serum creatinine in the PWG compared with the SWG, even though they had similar APACHE II scores, and other factors (sedation doses and duration, co-morbidities, BMI), that might affect the success of a weaning trial.

COPD and weaning

The present study was performed in COPD patients to assess serum creatinine as an easy, quick, cheap, and reproducible test to predict weaning outcome. Non-invasive and invasive mechanical ventilation, and the weaning process are nearly standardized all over the world with consensus and guidelines [4,10]. Weaning from mechanical ventilation is complicated in intubated patients particularly those with COPD due to ARF [10]. In the present study, the majority of patients had both hypercapnic and hypoxemic respiratory failure. A previous study showed weaning success to be highest in post-operative patients (58%), and those with acute lung injury (57%), and lowest in patients with COPD or neuromuscular disease (22%) [2]. However the weaning success of our COPD patients was 42.4% in the first weaning trial. A longer duration of mechanical ventilation is an important risk factor for morbidity and mortality and the long-term survival rate after successful weaning is worse in patients with severe COPD compared with non-COPD patients [12]. Similarly, we found a longer duration of pre-weaning mechanical ventilation, and a five times higher mortality in the PWG compared with the SWG.

Creatinine, BUN, BUN/creatinine

In the present study COPD patients with a low creatinine level on admission to the ICU had a significantly lower body mass index. We showed a further decrease in the creatinine levels of patients with COPD as time passed in the ICU. This can be explained by the continuous catabolism and lesser amounts of muscle tissue to increase serum creatinine levels. We showed that on the day of the weaning trial, COPD patients with lower serum creatinine had higher levels of C-reactive protein than patients with normal serum creatinine. The group with lower serum creatinine spent longer in the ICU, although the ICU severity scores were similar in both groups. This can be attributed to muscle wasting/atrophy and muscle weakness in the patients with COPD due to the severity of inflammation. Muscle cells can be affected by C-reactive protein and other cytokines (IL-1, IL6, TNF) generated in response to systemic inflammation/infection, especially during COPD exacerbation [13-17]. In the present study, BUN levels gradually decreased during the ICU stay in both the SWG and the PWG, and a lower BUN level may be a marker of the cessation of catabolism. We showed that on the first day of weaning the BUN level in the SWG was significantly higher than in the PWG.

Wu et al. found that BUN levels were higher in successfully weaned patients versus those that were unsuccessful (34 versus 50 mg/dL). Their values are a lot higher than presented in this study. In their study the length of ICU stay was longer and their underlying diagnoses were different to COPD [18]. A higher BUN level indicates a continuous

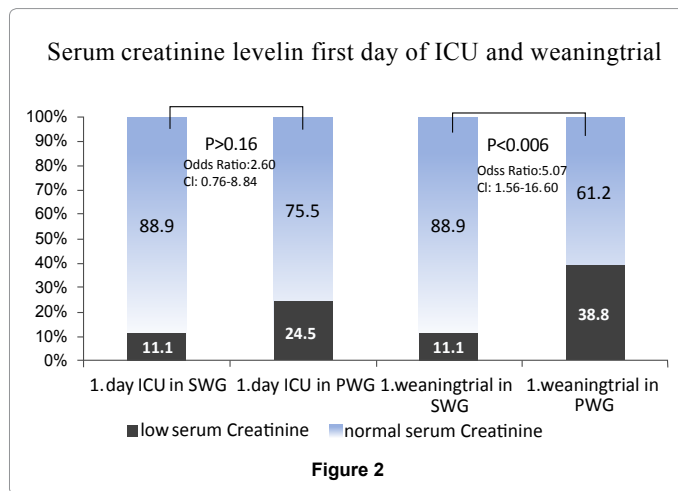


Figure 2

catabolic state [5]. In the Wu et al. study, due to the longer respiratory care stay, the patients' catabolic state was not ceased. Contrary to our results, they also found higher serum creatinine levels in the unsuccessfully weaned patients [18]. Some studies have shown that patients undergoing prolonged mechanical ventilation and with lower BUN and serum creatinine levels were well correlated with successful weaning [9,18]. In the present study, after the acute necessity for intubation was diminished or nearly controlled, we checked serum creatinine and BUN levels at the initiation of the weaning process. The BUN/Creatinine ratio is generally used as a conventional means to determine pre-renal azotemia, and a higher ratio correlates with a failure to wean due to fluid deficiency, after excluding other causes (upper gastrointestinal bleeding and overloaded protein). Scheinhorn et al. found that a BUN/serum creatinine of 35 was the crucial level for unsuccessful weaning [9]. However, we should consider that the ratio could be greater when the serum creatinine is lower or BUN is increased. In our study, COPD patients with a lower serum creatinine on admission to the ICU had a higher BUN/serum creatinine ratio than patients with a normal to high serum creatinine level.

One study showed a delta serum creatinine greater than 0.31 increased mortality in mechanically ventilated patients [19], however, this may reflect co-incident renal injury. Separating the effect of renal failure from endogenous creatinine generation in an ICU cohort is a very difficult task.

Although mortality was not a primary measurement in the present study, we did observe that mortality was mainly seen in the PWG. Interestingly, APACHE II scores on admission to the ICU were similar in the group with low serum creatinine and the normal to high creatinine groups. Besides a higher APACHE II score, prolonged mechanical ventilation increases mortality in the ICU [20]. We found that the serum creatinine decreased further during the ICU stay in the PWG and their mortality was higher than the SWG. A recent study showed that patients with normal creatinine levels on admission to hospital, and who suffered acute renal failure during their hospital stay, had higher mortality than patients who were admitted to hospital with acute renal failure [21]. However, in the present study we excluded patients with acute renal failure. Another new study concerning fluid overload and acute kidney injury in the ICU [22] defined an acute increase of serum creatinine > 0.5 mg/dL from baseline as acute kidney injury, and they defined volume related weight gain as the difference between initial weight and weight initiation of continuous renal replacement treatment [22]. They assessed statistically significant

associations with mortality in multivariate models that included sepsis and Apache II score, and they concluded that fluid overload is an important prognostic factor for survival in critically ill, acute kidney injury patients undergoing renal replacement treatment [22]. In the present study our patients did not have acute kidney injury and we did not measure the weight of patients.

There are some limitations to our study. Due to its retrospective design we did not check inflammatory markers such as IL1, IL6, and TNF (apart from C-reactive protein and urine creatinine levels) [6,13-17]. We also did not perform any measurements of muscle force or activity.

In conclusion, this study was performed in three training centers that followed their guidelines for weaning. We showed that low levels of serum creatinine on the first day of weaning indicated an unfavorable result for COPD patients during the weaning process, contrary to other studies. According to our data, a low serum creatinine on the first day of weaning had a 2.5 times higher risk for prolonged weaning. Although our study was done retrospectively in an homogenous group of COPD patients, the results may be significant in the weaning trials of other patient populations.

Key messages

1. Low serum creatinine and high a BUN/creatinine ratio indicates a hyper-catabolic state and muscle wasting/atrophy.
2. A hyper-catabolic state and muscle weakness/atrophy in COPD patients with low serum creatinine can indicate problems for the weaning process.

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Competing Interests

There was no financial research support and no conflict of interest for this study. All authors have no disclosure.

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