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NT-proBNP levels at spontaneous breathing trial help in the prediction of post-extubation respiratory distress

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Abstract *Purpose:* To evaluate and compare the performance of NT-proBNP levels, plasma protein concentration, hematocrit, and fluid balance for the preceding 24 h in predicting the outcome of the two steps of weaning: (1) spontaneous breathing trial (SBT), (2) extubation. *Methods:* This was a prospective observational study of 143 patients who were mechanically ventilated for more than 48 h (55 % COPD) and were ready to wean. They underwent an SBT and were extubated when they passed the trial. Immediately before the SBT, we measured the evaluated diagnosis tools. *Results:* Of 143 patients, 80 (56 %) passed the SBT and were extubated. Of these, two were reintubated for laryngeal dyspnea, 57 had no respiratory problem during the next 48 h, and 21 developed post-extubation respiratory distress (26 %). Rescue noninvasive ventilation (NIV) prevented reintubation in 15 (71 %). None of the tested diagnosis tools predicted the outcome of the SBT. Patients who developed post-extubation respiratory distress were older, had lower values of plasma protein concentration and higher values of NT-proBNP than those who did not. Only NT-proBNP was an independent predictor of the occurrence of post-extubation respiratory distress (OR 1.2; 95 % CI 1.09–1.4; $p = 0.003$); the area under the ROC curve for NT-proBNP to predict post-extubation respiratory distress was 0.78 (95 % CI 0.67–0.89; $p = 0.0001$). NT-proBNP was more accurate to rule out (negative likelihood ratio 0.09 for a cutoff of no greater than 1,000 pg/ml) than to rule in the risk of post-extubation respiratory distress (positive likelihood ratio 3.45 for a cutoff of at least 2,000 pg/ml). *Conclusion:* NT-proBNP levels at SBT help in the prediction of post-extubation respiratory distress and could identify the subgroup of extubated patients requiring close observation and/or prophylactic NIV.

Keywords Mechanical ventilation · Weaning · Non-invasive ventilation · Natriuretic peptides

Introduction

Weaning patients from mechanical ventilation (MV) remains a daily challenge for intensivists [1]. Time spent in the weaning process represents 40–50 % of the total duration of mechanical ventilation with evidence suggesting that weaning tends to be delayed, thus exposing patients to undue risk of additional morbidity and mortality [2]. Although most patients (69 %) will have a simple weaning from MV with a good prognosis and low ICU and hospital mortality, almost one-third of patients will have a difficult or prolonged weaning

process exposing them to the risk of a higher morbidity and mortality [3].

Weaning failure is usually defined as the failure of the spontaneous breathing trial (SBT), or the need for reintubation during the 48 h following extubation [4]. Weaning failure occurs in 26–42 % patients with increased rates (up to 62 %) in chronic obstructive pulmonary disease (COPD) patients [4–6]. Reintubation is associated with a high mortality rate because it usually occurs in high-risk patients and increases the risk of aspiration, and nosocomial pneumonia [7].

In addition to upper airway obstruction, reintubation is frequently due to post-extubation acute respiratory failure (ARF) either from respiratory or cardiac dysfunction. Respiratory failure is traditionally considered the main cause of weaning failure, but cardiac function and, more importantly, volume status may play a key role in this setting [8]. B-type natriuretic peptide (BNP) and NT-proBNP levels, which are increased in congestive heart failure (CHF) and hypervolemia, have been suggested as useful indicators of weaning failure [9–12]. Zapata et al. [9] recently demonstrated that either the natriuretic peptides levels measured immediately before the SBT, or their increase between the start and the end of the SBT, can accurately relate weaning failure to heart rather than to respiratory failure. Several other accessible markers (fluid balance, plasma protein concentration, echocardiographic Doppler indices) have been evaluated in the prediction of weaning outcome or for the diagnosis of weaning-induced pulmonary edema [13–16]. Head-to-head comparison of these indicators is lacking.

Prediction of weaning outcome might be clinically relevant because several studies have shown that early use of noninvasive ventilation (NIV) in extubated patients (mainly chronic hypercapnic patients) reduces the rate of post-extubation ARF and that of reintubation, and lowers the risk of mortality in these patients [17–19]. Conversely, NIV did not prove effective when used on a curative basis in patients experiencing post-extubation ARF [20, 21].

The aim of this prospective observational study was to compare the performance of the serum NT-proBNP, plasma protein concentration, hematocrit, and fluid balance in predicting the outcome of the two steps of weaning: (1) SBT, (2) extubation.

Patients and methods

We conducted a prospective cohort study between February 2006 and June 2009 in the Intensive Care Unit of University Hospital Fattouma Bourguiba, Monastir, Tunisia. This is a ten-bed medical ICU admitting 300–350 patients/year, of whom two-thirds are ventilated either noninvasively or conventionally.

Inclusion criteria

All patients mechanically ventilated for more than 48 h were considered for inclusion in the study. Patients deemed ready to wean from MV were included in the study. They had to meet all of the following criteria [1]: resolution or significant improvement in the cause of respiratory failure, cardiovascular stability, correction of metabolic disorders, recovery from the effects of sedation, effective cough, no significant respiratory acidosis, PaO_2 greater than 60 mmHg and/or SaO_2 greater than 90 % with FiO_2 less than 0.40, positive expiratory pressure (PEEP) less than 8 cmH_2O, respiratory rate (RR) less than 35 breaths/min, spontaneous tidal volume (Vt) greater than 5 ml/kg, minute ventilation (mV) greater than 15 l/min.

Exclusion criteria

Exclusion criteria were prolonged cardiac arrest with poor neurological prognosis, renal impairment defined by either plasma creatinine above 180 μmol/l, plasma urea greater than 25 mmol/l, creatinine clearance less than 30 ml/min, increase of more than 25 % of plasma creatinine in the previous 24 h; pregnancy or breast-feeding, tracheostomy at baseline, myasthenia gravis or acute polyradiculoneuropathy, end-stage chronic illness, or a decision to limit active treatment.

Protocol

The protocol was approved by our institutional ethics committee, and written informed consent was obtained from patients or their next of kin. All patients meeting the inclusion criteria of MV weaning had an SBT on a T-tube connected to a humidifier and an oxygen flow (FiO_2 of 0.4). SBT lasted 120 min. Patients were considered to have failed SBT if they developed any of the following signs during the 2 h SBT: agitation or anxiety; altered neurological status, sweating, cyanosis, contraction of accessory respiratory muscles, thoraco-abdominal dyssynchrony, dyspnea, tachypnea (RR greater than 35 breaths/min), heart rate (HR) greater than 140 beats/min, systolic blood pressure (SBP) greater than 180 mmHg or an increase of over 20 %, SBP less than 90 mmHg, and arrhythmia. Patients who had none of these features at the end of the SBT were subsequently extubated. After extubation, the patients were closely monitored for 48 h. Patients who developed signs of post-extubation respiratory distress first had rescue NIV and were eventually reintubated in the case of persisting respiratory failure. This group of patients, who formed the "weaning failure" group in previous studies, will be termed the "post-extubation distress" group in this study

regardless of the final outcome (reintubation or not) because reintubation was averted by NIV in some of these patients. Signs of post-extubation respiratory distress were the following: (1) hypoxemia (SaO_2 no greater than 90 % or PaO_2 no greater than 60 mmHg breathing at an FiO_2 greater than 0.50), (2) respiratory acidosis (pH no greater than 7.30 with $PaCO_2$ greater than 50 mmHg), and clinical signs of respiratory distress including at least one of the following: retraction of the intercostal spaces, use of accessory respiratory muscles, and paradoxic breathing. Patients who required reintubation due to upper airway obstruction were excluded from further data analysis.

Data collection and NT-proBNP measurement

Patients' baseline characteristics, including demographic data, disease severity, causes of respiratory failure, pre-existing comorbidity, were recorded at the ICU admission. Severity of the disease at the ICU admission was assessed by the Simplified Acute Physiology Score (SAPS) II score. The following were measured immediately before the start of the SBT: fluid balance of the day preceding SBT, biological variables, namely plasma protein concentration, hematocrit, and NT-proBNP.

To measure plasma NT-proBNP levels, venous blood samples were drawn into tubes containing EDTA immediately before the beginning of the 2 h SBT. The plasma was stored at −80 °C and analyzed by the end of the study. The investigator responsible for the measurements was unaware of the patients' baseline parameters and clinical course. NT-proBNP was determined with the use of a quantitative electrochemiluminescence assay (Elecsys proBNP, Roche Diagnostics, Indianapolis) on an Elecsys 2010 analyzer (Roche Diagnostics) according to established methods.

Statistics

Statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, USA). Continuous data are presented as medians (interquartile range, IQR). The association of categorical variables with the two steps of weaning we evaluated (SBT and extubation outcome) was assessed using the c^2 test. Differences in continuous data between groups were analyzed using the Mann–Whitney U test. Two-sided p value no greater than 0.05 was considered statistically significant. The predictive value of NT-proBNP was determined using the receiver operator characteristic (ROC) curve. To evaluate independent risk factors for post-extubation respiratory distress, a logistic regression analysis was performed including significant univariate risk factors.

Results

During the study period 523 patients received ventilatory support. NIV was applied to 173 patients, whereas 350 were intubated, mechanically ventilated, and considered for inclusion in the study. Of these, 207 were excluded for the reasons detailed in Fig. 1. The remaining 143 patients were included in the study.

Patients' characteristics and weaning outcome

The included population had a median age of 65 years, the majority of patients were male (sex ratio 2.25). The median duration of MV before the spontaneous breathing test was 6 days (IQR 2–11). The causes of ventilation were dominated by respiratory causes (70 %, where COPD exacerbation represented 55 %), cardiovascular causes (15 %), and neurologic diseases (8 %). Median SAPS II was 38 (IQR 25–50).

Figure 1 displays weaning outcomes in the study population. Of the 143 patients who underwent the SBT, 63 failed the SBT (44 %, SBT failure) and 80 passed (56 %, SBT success).

Table 1 displays clinical and biological parameters before SBT in the SBT success and SBT failure groups. Both groups were fairly comparable regarding demographic characteristics, and causes of ARF which was dominated by COPD exacerbation. Significant differences were revealed regarding acute disease severity as measured by SAPS II at admission, and duration of ventilation prior to SBT which was longer in patients who failed SBT. Regarding variables measured shortly before the performance of SBT, namely fluid balance for the preceding 24 h, plasma protein concentration, hematocrit, and NT-proBNP, none was significantly different between patients who succeeded and those who failed SBT. Two out of 80 patients who passed the SBT and were extubated then rapidly developed laryngeal dyspnea (stridor) imposing reintubation (excluded from further analysis), 57 had no respiratory problem during the next 48 h, and 21 developed post-extubation respiratory distress. Rescue NIV which was applied in these 21 patients, prevented reintubation in 15 patients, whereas the remaining six were eventually intubated.

As compared to patients who were extubated without subsequent incident, patients who developed post-extubation respiratory distress were older, had lower values of plasma protein concentration and higher values of NT-proBNP (Table 2). However, there was no difference in the rates of history of COPD (55 and 45 % in patients who developed post-extubation respiratory distress and those who did not, respectively), or heart disease (16 and 18 %, respectively). Multivariate analysis revealed that only NT-proBNP levels were an independent predictor of

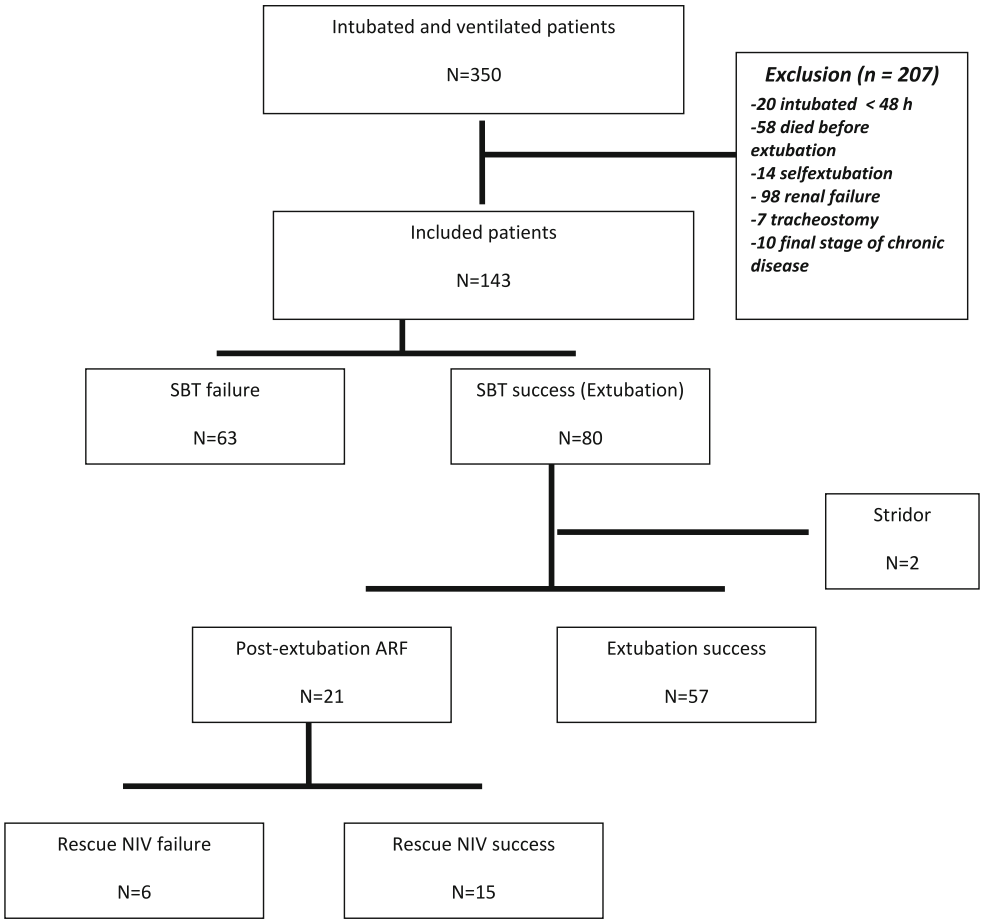

Fig. 1 Flow chart of weaning outcomes in the study population

Table 1 Clinical characteristics of patients

	SBT+ ($n = 80$)	SBT− ($n = 63$)	p
Age, years med (IQR)	64 (52–76)	65 (58–72.5)	NS
Male gender (%)	52 (65)	47 (74)	NS
SAPS II at admission	33 (25–41)	36 (26–46)	0.02
Cause of RF (%)			
COPD	40 (50)	38 (60)	NS
ARF de novo	23 (29)	13 (21)	NS
Coma	1 (1)	2 (3)	NS
Other	16 (20)	10 (16)	NS
MV duration before SBT, days med (IQR)	4 (1.5–7.5)	6 (2–12)	0.001
Fluid balance day 1 med (IQR)	+200 (140–350)	+300 (250–350)	NS
Plasma protein concentration (g/l)	59 (53–65)	59 (54–64)	NS
Hematocrit (%)	33 (29–37)	35 (31–39)	NS
NT-proBNP pg/ml med (IQR)	1,280 (600–2,050)	923 (200–1,600)	NS

SBT+ successful spontaneous breathing trial, *SBT−* failure of spontaneous breathing trial, *med* median, *NS* not significant

the occurrence of post-extubation respiratory distress (OR 1.2; 95 % CI 1.09–1.4; $p = 0.003$). The area under the ROC curve for plasma NT-proBNP to predict post-extubation respiratory distress was 0.78 (95 % CI 0.67–0.89; $p = 0.0001$; Fig. 2). Overall NT-proBNP dosage was more accurate to rule out than to rule in the occurrence of post-extubation respiratory distress. A cutoff value of no greater than 1,000 pg/ml had a high sensitivity (95 %) and a negative likelihood ratio of 0.09, providing strong evidence supporting its use in ruling out post-extubation respiratory distress. On the other hand, the best cutoff value to rule in the risk of post-extubation respiratory

Table 2 Clinical characteristics of extubated patients distributed according to the occurrence of respiratory distress

	Post-extubation respiratory distress (+) ($n = 21$)	Post-extubation respiratory distress (−) ($n = 57$)	p
Age, years med (IQR)	68 (61–75)	60 (48–72)	0.05
Male sex	15 (71 %)	36 (63 %)	NS
SAPS II med (IQR)	33 (20–46)	32 (24–40)	NS
MV duration med (IQR)	4 (2–6)	4 (2–5.5)	NS
Fluid balance day 1 (ml) med (IQR)	200 (35–340)	200 (150–350)	NS
Plasma protein concentration (g/l) med (IQR)	54 (49–59)	60 (55–65)	0.02
Hematocrit (%)	34 (28–40)	32 (26–38)	NS
NT-proBNP (pg/ml) med (IQR)	1,860 (1,800–1,920)	975 (910–1,040)	0.0001

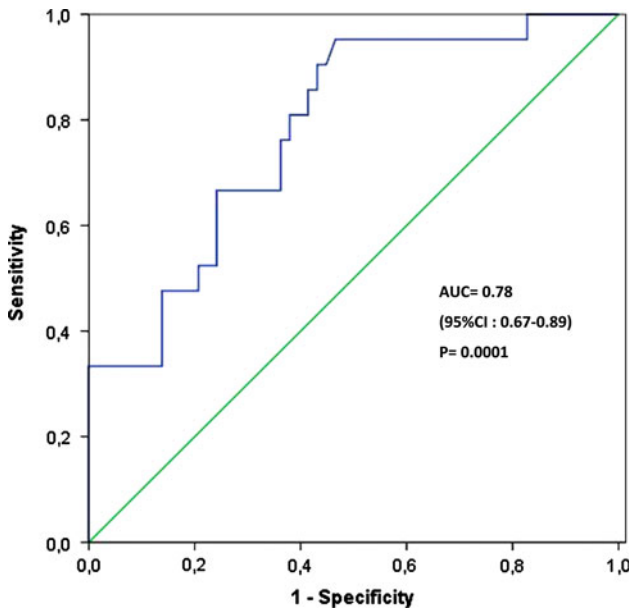

Fig. 2 Area under ROC curve (AUC) for NT-proBNP levels at SBT for predicting post-extubation acute respiratory distress (AUC 0.78)

distress was at least 2,000 pg/ml whose operative characteristics are considered moderate from a Bayesian perspective (positive likelihood ratio 3.45, specificity 0.86). Of note, the cutoff value of no greater than 1,000 pg/ml was present in 42 % of patients with a history of cardiac disease and in 62 % (nonsignificant difference) of patients without cardiac disease history.

Discussion

The current study, which included 143 ready-to-wean patients who underwent an SBT, showed that none of the tested diagnosis tools (fluid balance of the preceding 24 h, plasma protein concentration, hematocrit, and NT-proBNP) accurately identified the outcome of the SBT. Among the 80 patients who were extubated following a successful SBT, 21 (27 %) experienced an episode of post-extubation respiratory distress. In these patients, rescue NIV averted reintubation in 15 (71 %). Only NT-proBNP levels measured immediately before the SBT were independently associated with the occurrence of post-extubation respiratory distress. NT-proBNP levels were more helpful in ruling out than ruling in the risk of post-extubation ARF. A cutoff value of no greater than 1,000 pg/ml had a negative likelihood ratio (0.09) making the occurrence of post-extubation respiratory distress very unlikely in a patient fulfilling the diagnosis test. From a Bayesian perspective, the application of these figures to a general ICU population at risk of developing post-extubation respiratory distress (in whom the incidence of the event was 25 % in the multicenter study by Esteban et al. [20], a rate that was similar to the 26 % recorded in our study) means that a negative test (NT-proBNP no greater than 1,000 pg/ml) would reduce the pretest probability of developing post-extubation ARF from 25 % to a post-test probability between 2 and 3 %. The clinical implications could be very useful by focusing close post-extubation observation and monitoring merely those patients who do not meet the exclusion test.

Weaning failure is defined as either the failure of SBT, or the need for reintubation within 48 h following extubation [4]. However, this definition has been challenged by the frequent use of NIV in the post-extubation period because prophylactic or curative NIV may avert intubation in a substantial proportion of patients who would have been otherwise reintubated. The consensus conference on weaning has slightly altered the definition of weaning success as an extubation that is not followed by ventilator support (either invasive or noninvasive) during 48 h following the extubation [1]. Because the resumption of any kind of ventilation defines weaning failure, we found it more clinically sound to predict a clinically relevant event (post-extubation respiratory distress) rather than the failure of extubation in its old definition based on the need for reintubation [1]. Nevertheless, the group "post-extubation distress" identified in our study actually corresponds to the "weaning failure" groups reported in previous studies where NIV was not used during the weaning process. Such a pragmatic approach has the

merit of identifying reliable indicators of a patient-centered major outcome for which close observation and/or prophylactic NIV, a therapy that proved effective, could be proposed.

None of the evaluated diagnosis tools proved accurate in the prediction of the outcome of SBT. Although predicting the SBT outcome may spare some patients from unnecessary testing, we do not usually need to predict in advance the outcome of a test (SBT); we only have to do this test. Conversely, among evaluated tools, plasma protein concentration and NT-proBNP were statistically different in patients with simple weaning and those who developed post-extubation respiratory distress. However, only NT-proBNP was independently linked to the occurrence of post-extubation respiratory distress. NT-proBNP baseline levels were more helpful in ruling out than ruling in the risk of post-extubation ARF. Likelihood ratios are considered as more useful than conventional statistics for summarizing the accuracy of a diagnostic or screening test [22]. Likelihood ratios above 10 and below 0.1 are considered to provide strong evidence to rule in or rule out diagnoses, respectively. In our study NT-proBNP dosage had a negative likelihood ratio (0.09) and a positive likelihood ratio (3.45) showing the greater benefit of this test in ruling out rather than ruling in the risk of post-extubation ARF. These findings are not surprising because most studies on the value of natriuretic peptides in the diagnosis of the cause of dyspnea showed the superiority of such tests to eliminate rather than to diagnose heart failure especially when the studied populations had a low cardiac risk [23]. In a meta-analysis summarizing the evidence on the accuracy of BNP tests in the diagnosis of CHF in the emergency department (ED), Battaglia et al. [23] found a pooled negative likelihood ratio of 0.18 and a positive likelihood ratio around 6. These findings suggested that for a typical ED population whose pretest probability could reasonably be considered around 20 %, a negative BNP result would give a post probability test between 3 and 5 %.

Several diagnostic tools have previously been evaluated in the diagnosis of cardiac dysfunction and hypervolemia that may impact the outcome of the weaning trial. Anguel et al. [14] showed that changes in plasma protein concentration during SBT are accurate in the diagnosis of weaning-induced pulmonary edema. The same investigators recently showed that variables that might be obtained noninvasively through transthoracic echocardiography (E/A and E/Ea ratios) accurately reflect acute changes of LV filling pressures after a SBT and can detect a weaning-induced pulmonary edema [15]. Upadya et al. [13] examined the relationship between fluid balance and weaning outcome and observed that positive fluid balance prior to weaning is significantly greater in weaning failures than successes. Natriuretic peptides are released into the bloodstream in response to ventricular increase of volume or pressure. Several studies have evaluated the utility of BNP and NT-proBNP measurements to predict weaning outcomes or ascribe weaning failure to cardiac dysfunction [9–12]. Baseline levels of natriuretic peptides and their change between the beginning and the end of SBT revealed accurate predictors of weaning failure of cardiac origin [9, 12]. A unique measurement of baseline levels of BNP prior to the start of the SBT, or the change of natriuretic peptides levels between the beginning of the SBT and its end (usually increased levels), accurately predicted weaning outcomes [10, 11].

Some of our findings deserve further attention and comment. This concerns merely the rates of SBT failure and that of NIV success in post-extubation ARF. In studies that examined the role of natriuretic peptides in the prediction of weaning outcome the rate of SBT failure varied from 21 % in the study by Chien et al. [11] to 44 % in our series. One of the variables that could account for this variation is the type of patients who are being weaned and COPD patients are generally considered a more difficult-to-wean group [1]. Whereas COPD patients accounted for no more than 55 % of the included patients in our study, they represented 15, 8, and 33 % of the patients of Zapata, Chien, and Mekontso-Dessap, respectively [9, 11, 24]. Of note, an associated left heart dysfunction that could interfere with the weaning process was present in 31–45 % of the COPD patients who are usually admitted to our ICU [25]. The duration of the SBT procedure might also account for the recorded variation in the SBT failure rate. We and Chien elected to observe patients during 120 min [11], whereas the test lasted 30–120 min according to the physician's decision or patient's tolerance in Zapata's study [9], and 60 min in Mekontso-Dessap's study [10].

The success rate of NIV in post-extubation ARF was 71 % in our study, a rate that is higher than that reported by Esteban et al. [20] in their multicenter study on the efficacy of rescue NIV in post-extubation ARF (52 %). We cannot readily account for these discrepancies, but we could speculate that a key difference is that the majority of included patients had COPD in our study, whereas acute-on-chronic respiratory failure was present in only 10 % in multicenter Esteban's study. Acute-on-chronic respiratory failure is indeed considered an ideal indication for NIV which has become the first-choice ventilatory technique in these patients [26]. We could then speculate that the expertise we have acquired with acute-on-chronic respiratory failure even in the weaning context contributed to this performance [27].

Exclusion of patients with impaired renal function in our study relied on the fact that natriuretic peptides are usually removed from plasma by the kidney and can be markedly elevated in severe renal failure without association of heart dysfunction [28]. However, we have recently confirmed that NT-proBNP remains an accurate biomarker for the diagnosis of LV dysfunction associated with acute COPD exacerbation even in patients with

impaired renal function [29]. The thresholds revealed, however, are higher than those in patients with normal renal function.

In conclusion, although none of the evaluated diagnostic tools (fluid balance of the preceding 24 h, plasma protein concentration, hematocrit, and NT-proBNP) helped in the prediction of the outcome of the SBT, NT-proBNP levels at SBT proved helpful in the prediction of post-extubation acute respiratory distress. A cutoff value of no greater than 1,000 pg/ml had an accurate negative likelihood ratio making the occurrence of post-extubation respiratory distress very unlikely.

References

1. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H, Stanchina M, Vieillard-Baron A, Welte T (2007) Weaning from mechanical ventilation. Eur Respir J 29:1033–1056
2. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguia C, Nightingale P, Arroliga AC, Tobin MJ (2002) Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 287:345–355
3. Esteban A, Alia I, Tobin MJ, Gil A, Gordo F, Vallverdu I, Blanch L, Bonet A, Vazquez A, de Pablo R, Torres A, de La Cal MA, Macias S (1999) Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med 159:512–518
4. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, Fernandez R, de la Cal MA, Benito S, Tomas R et al (1995) A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 332:345–350
5. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, Gasparetto A, Lemaire F (1994) Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 150:896–903
6. Vallverdu I, Calaf N, Subirana M, Net A, Benito S, Mancebo J (1998) Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. Am J Respir Crit Care Med 158:1855–1862
7. Torres A, Gatell JM, Aznar E, el-Ebiary M, Puig de la Bellacasa J, Gonzalez J, Ferrer M, Rodriguez-Roisin R (1995) Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. Am J Respir Crit Care Med 152: 137–141
8. Jubran A, Tobin MJ (1997) Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med 155:906–915
9. Zapata L, Vera P, Roglan A, Gich I, Ordonez-Llanos J, Betbese AJ (2011) B-type natriuretic peptides for prediction and diagnosis of weaning failure from cardiac origin. Intensive Care Med 37:477–485
10. Mekontso-Dessap A, de Prost N, Girou E, Braconnier F, Lemaire F, Brun-Buisson C, Brochard L (2006) B-type natriuretic peptide and weaning from mechanical ventilation. Intensive Care Med 32:1529–1536
11. Chien JY, Lin MS, Huang YC, Chien YF, Yu CJ, Yang PC (2008) Changes in B-type natriuretic peptide improve weaning outcome predicted by spontaneous breathing trial. Crit Care Med 36:1421–1426
12. Grasso S, Leone A, De Michele M, Anaclerio R, Cafarelli A, Ancona G, Stripoli T, Bruno F, Pugliese P, Dambrosio M, Dalfino L, Di Serio F, Fiore T (2007) Use of N-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. Crit Care Med 35:96–105
13. Upadya A, Tilluckdharry L, Muralidharan V, Amoateng-Adjepong Y, Manthous CA (2005) Fluid balance and weaning outcomes. Intensive Care Med 31:1643–1647
14. Anguel N, Monnet X, Osman D, Castelain V, Richard C, Teboul JL (2008) Increase in plasma protein concentration for diagnosing weaning-induced pulmonary oedema. Intensive Care Med 34: 1231–1238
15. Lamia B, Maizel J, Ochagavia A, Chemla D, Osman D, Richard C, Teboul JL (2009) Echocardiographic diagnosis of pulmonary artery occlusion pressure elevation during weaning from mechanical ventilation. Crit Care Med 37:1696–1701
16. Frutos-Vivar F, Ferguson ND, Esteban A, Epstein SK, Arabi Y, Apezteguia C, Gonzalez M, Hill NS, Nava S, D'Empaire G, Anzueto A (2006) Risk factors for extubation failure in patients following a successful spontaneous breathing trial. Chest 130:1664–1671
17. Ferrer M, Esquinas A, Arancibia F, Bauer TT, Gonzalez G, Carrillo A, Rodriguez-Roisin R, Torres A (2003) Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. Am J Respir Crit Care Med 168: 70–76
18. Ferrer M, Sellares J, Valencia M, Carrillo A, Gonzalez G, Badia JR, Nicolas JM, Torres A (2009) Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet 374: 1082–1088
19. Burns KE, Adhikari NK, Keenan SP, Meade M (2009) Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review. BMJ 338: b1574
20. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguia C, Gonzalez M, Epstein SK, Hill NS, Nava S, Soares M-A, D'Empaire G, Alia I, Anzueto A (2004) Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 350:2452–2460
21. Keenan SP, Powers C, McCormack DG, Block G (2002) Noninvasive positive-pressure ventilation for postextubation respiratory distress: a randomized controlled trial. JAMA 287:3238–3244
22. Deeks JJ, Altman DG (2004) Diagnostic tests 4: likelihood ratios. BMJ 329:168–169
23. Battaglia M, Pewsner D, Juni P, Egger M, Bucher HC, Bachmann LM (2006) Accuracy of B-type natriuretic peptide tests to exclude congestive heart failure: systematic review of test accuracy studies. Arch Intern Med 166:1073–1080

24. Mekontso-Dessap A, Tual L, Kirsch M, D'Honneur G, Loisance D, Brochard L, Teboul JL (2006) B-type natriuretic peptide to assess haemodynamic status after cardiac surgery. Br J Anaesth 97:777–782
25. Abroug F, Ouanes-Besbes L, Nciri N, Sellami N, Addad F, Hamda KB, Amor AB, Najjar MF, Knani J (2006) Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. Am J Respir Crit Care Med 174:990–996
26. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS (2003) Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: cochrane systematic review and meta-analysis. BMJ 326:185
27. Girault C, Bubenheim M, Abroug F, Diehl JL, Elatrous S, Beuret P, Richecoeur J, L'Her E, Hilbert G, Capellier G, Rabbat A, Besbes M, Guerin C, Guiot P, Benichou J, Bonmarchand G (2011) Non-invasive ventilation and weaning in chronic hypercapnic respiratory failure patients: a randomized multicenter trial. Am J Respir Crit Care Med 184(6):672–679
28. Srisawasdi P, Vanavanan S, Charoenpanichkit C, Kroll MH (2010) The effect of renal dysfunction on BNP, NT-proBNP, and their ratio. Am J Clin Pathol 133:14–23
29. Ouanes I, Jalloul F, Ayed S, Dachraoui F, Ouanes-Besbes L, Fekih Hassen M, Elatrous S, Abroug F (2012) N-terminal proB-type natriuretic peptide levels aid the diagnosis of left ventricular dysfunction in patients with severe acute exacerbations of chronic obstructive pulmonary disease and dysfunction. Respirology. doi: 10.1111/j.1440-1843.2012.02153.x