Respiratory weakness is associated with limb weakness and delayed weaning in critical illness*

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Objective: **Although critical illness neuromyopathy might interfere with weaning from mechanical ventilation, its respiratory component has not been investigated. We designed a study to assess the level of respiratory muscle weakness emerging during the intensive care unit stay in mechanically ventilated patients and to examine the correlation between respiratory and limb muscle strength and the specific contribution of respiratory weakness to delayed weaning.**

Design: **Prospective observational study.**

Setting: **Two medical, one surgical, and one medicosurgical intensive care units in two university hospitals and one university-affiliated hospital.**

Patients: **A total of 116 consecutive patients were enrolled after ≥7 days of mechanical ventilation.**

Interventions: **None.**

Measurements and Main Results: **Maximal inspiratory and expiratory pressures and vital capacity were measured via the tracheal tube on the first day of return to normal consciousness. Muscle strength was measured using the Medical Research Council score. After standardized weaning, successful extubation was defined as the day from which mechanical ventilatory support was no longer required within the next 15 days. The median value (interquartile range) of maximal inspiratory pressure was 30 (20–40) cm H_2O, maximal expiratory pressure was 30 (20–50) cm H_2O, and vital capacity was 11.1 (6.3–19.8) mL/kg. Maximal inspiratory pressure, maximal expiratory pressure, and vital capacity were significantly correlated with the Medical Research Council score. The median time (interquartile range) from awakening to successful extubation was 6 (1–17) days. Low maximal inspiratory pressure (hazard ratio, 1.86; 95% confidence interval, 1.07–3.23), maximal expiratory pressure (hazard ratio, 2.18; 95% confidence interval, 1.44–3.84), and Medical Research Council score (hazard ratio, 1.96; 95% confidence interval, 1.27–3.02) were independent predictors of delayed extubation. Septic shock before awakening was significantly associated with respiratory weakness (odds ratio, 3.17; 95% confidence interval, 1.17–8.58).**

Conclusions: **Respiratory and limb muscle strength are both altered after 1 wk of mechanical ventilation. Respiratory muscle weakness is associated with delayed extubation and prolonged ventilation. In our study, septic shock is a contributor to respiratory weakness. (Crit Care Med 2007; 35:2007–2015)**

KEY WORDS: neuromuscular diseases; respiration; artificial; sepsis; respiratory function tests

Critical illness neuromyopathy (CINM) has been increasingly recognized in patients with severe critical illness treated in the intensive care unit (ICU). The limb neuromuscular component of CINM has been particularly studied during the last decade. Because there is no gold standard for the diagnosis of CINM, two approaches are commonly used, electrophysiological or clinical detection. Electrophysiological investigation of the limbs reveal diffuse neuromuscular abnormalities in >50% of ICU patients after 5–7 days of mechanical ventilation (MV) (1–4). Limb weakness, the main clinical sign of CINM, can be identified at awakening after the acute phase of illness by using a simple bedside score such as the Medical Research Council (MRC) score (5). The MRC score has shown satisfactory reproducibility, internal consistency, and predictive value in various neuromuscular disorders requiring or not requiring MV (6–8), and it has been used in several retrospective (9) and prospective studies of CINM (2, 10, 11).

The respiratory neuromuscular component of CINM has been less studied. However, the respiratory neuromuscular involvement might contribute to difficulty in weaning from the ventilator and prolonged duration of MV. The involvement of respiratory muscles in patients with CINM has not been quantified to date. Furthermore, although a strong association has been established between

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MV duration and limb neuromuscular involvement (12, 13), with the limb involvement being considered a surrogate marker of the respiratory involvement, the relationship between limb and respiratory muscle strength abnormalities and the specific contribution of respiratory muscle involvement to delayed weaning have not been clearly established.

The objective of the present study was to assess the severity of respiratory neuromuscular function abnormalities using bedside measurements in ICU patients at the time they regain normal consciousness after ≥7 days of MV. Furthermore, this study aimed to investigate the correlation between respiratory and limb muscle strength and to determine the contribution of respiratory neuromuscular involvement to delayed weaning.

METHODS

The study was conducted prospectively between June 2003 and June 2005 in four ICUs (two medical, one surgical, and one medicosurgical) in two university hospitals and one university-affiliated hospital. All consecutive patients mechanically ventilated for ≥7 days were eligible. Patients were excluded if they had previously identified disease of the peripheral nervous system, bi-hemispheric or brainstem lesions, fewer than two limbs in which muscle strength could be tested, a language barrier that was expected to limit patient comprehension, or if they had been referred from another ICU. The study protocol was approved by the Ethics Committee of Saint-Germain-en-Laye, France. Informed consent was obtained from patients or relatives.

After 7 days of MV, patients were screened daily for awakening and comprehension, based on their response to five commands ("open/close your eyes," "look at me," "open your mouth and put out your tongue," "nod your head," and "raise your eyebrows when I have counted up to five") involving neck and face muscles, which are commonly spared in CINM. The first day that the patient responded to at least three of these orders on two consecutive evaluations at a 6-hr interval was referred to as "awakening." The day of awakening, muscle strength was measured in the four limbs using the MRC score, with values ranging from 0 (tetraplegia) to 60 (normal muscle strength) (6). On the same day, the maximal inspiratory (MIP) and expiratory (MEP) pressures and vital capacity (VC) were measured via the tracheal tube during a short disconnection from the ventilatory circuit in a semirecumbent position at 45 degrees. MIP was measured after a forced expiration against a manual occlusion of the respiratory circuit and held for ≥1 sec. Three maneuvers were performed, and the highest value was used for analysis. MEP was measured similarly, after a forced inspiration. VC capacity was measured using a Spirobank (MIR Laboratory, Rome, Italy). The highest of three values was used for analysis.

So that the physician's awareness of the patient's neuromuscular status did not influence the conduction of weaning, ventilator weaning was standardized according to the French ICU Consensus Conference 2003 guidelines (14). Briefly, patients were screened daily after awakening for presence of prerequisite criteria for extubation, including F_{IO_2} of <50%, positive end-expiratory pressure of <5 cm H_2O, and absence of catecholamines infusion. From the day prerequisite criteria were met, patients underwent daily T-piece trials of 30–120 mins in duration. Satisfactory tolerance of the T-piece trial was followed by extubation, regardless of MIP, MEP, VC, or MRC values. Although weaning is commonly considered successful when there is no need for reconnection to the ventilator within 48 hrs after extubation, other investigations (15) and daily experience have shown that long-term mechanically ventilated patients, especially those with CINM, frequently require reintubation and further MV for >48 hrs after a first extubation. Therefore, to analyze the contribution of respiratory weakness to delayed weaning, we focused on the duration between awakening and successful extubation defined by absence of reintubation within 15 days after extubation.

Statistical Analysis. Categorical variables are presented as number (percentage) and compared using the chi-square or Fisher's exact test, as appropriate. Quantitative data are presented as median (interquartile range) and compared using the Mann-Whitney test, except when otherwise noted. Associations between MRC score and MIP, MEP, and VC were analyzed using Spearman's correlations and analysis of variance analyses.

To analyze the effect of MIP, MEP, and VC on MV, time from awakening to successful extubation in patients with high and low MIP, MEP, and VC (dichotomized on their median values) was estimated using the Kaplan-Meier method (16) and compared using log-rank analysis. Hazard ratios and their 95% confidence intervals (CIs) were estimated using Cox proportional hazards models (17). Other variables that could potentially influence time from awakening to successful extubation, including age, sex, presence of chronic obstructive pulmonary disease or cardiac insufficiency, duration of MV, number of days with two or more failed organs or presence of septic shock before awakening, and Simplified Acute Physiology Score II at awakening, were also analyzed. Proportional hazards assumption was graphically assessed, and the Schoenfeld residuals were used in the case of uncertainty. MIP, MEP, VC, and MRC were then each entered into separate multivariate Cox proportional hazards analyses of delayed successful extubation (17), along with other variables with a p value of ≤.20 in univariate analysis. Patients who did not reach the end point of successful extubation (i.e., those who died before or within the 15 days after extubation) were censored. Furthermore, patients who reached the end point of successful extubation were separated according to whether time from awakening to successful extubation was <7 or ≥7 days. The effects of MIP, MEP, VC, and MRC on the risk of further MV at ≥7 days after awakening were assessed in separate multivariate logistic regression analyses.

To analyze factors influencing respiratory muscle weakness, MIP and MEP at awakening (which were the two respiratory muscle strength variables found to be independent factors of delayed extubation) were combined into a single variable: MIP or MEP of ≤30 cm H_2O. Potential risk factors for MIP or MEP of ≤30 cm H_2O, including age, sex, admission Simplified Acute Physiology Score II (18), presence of chronic obstructive pulmonary disease, number of days of MV, number of days with two or more failed organs, use of corticosteroids or neuromuscular blockers, average daily morning blood glucose level, and occurrence of septic shock before awakening, were assessed in univariate analysis. Variables with a p value of ≤.20 in univariate analysis were entered into a multivariate logistic regression analysis.

Data were analyzed using the Stata Statistical Software (StataCorp 2003, Release 8.0, College Station, TX). Search for interaction and confounding was systematically performed before entering variables into multivariate models. Variables with a p value of ≥.10 were removed from the multivariate models according to a backward procedure. A p value of ≤.05 was considered significant.

RESULTS

Patient Characteristics. During the study period, 324 patients required MV for ≥7 days. Among these, 86 had exclusion criteria: 50 had preexisting neurologic disease (this large number is due to the recruitment of a large number of patients with peripheral neurologic disease at admission in one participating ICU), 24 had been transferred from another ICU, ten had no assessable limbs, and a language barrier was present in two patients. Among the 238 remaining patients, 71 died and 34 were transferred before awakening (as defined in the Methods section), 11 withheld consent, and six patients were overlooked. A total of 116 patients were included (Table 1) (18, 19). Among these, 58 (50.0%) had septic shock, 86 (74.1%) received vasopressors, and 73 (62.9%) received corti-

Table 1. Characteristics of the 116 study patients

Age, median (IQR)	64 (52–77)
Female sex, n (%)	41 (35.3)
Chronic obstructive pulmonary disease, n (%)[a]	44 (37.9)
Chronic cardiac insufficiency[a]	33 (28.4)
Medical/surgical/trauma, n (%)	81 (69.8)/28 (24.1)/7 (6.0)
SAPS II at ICU admission, median (IQR)	46 (38–58)
Main diagnosis, n (%)	
Pneumonia	28 (24.1)
COPD exacerbation	16 (13.8)
Intra-abdominal sepsis/pancreatitis	11 (9.5)
Soft-tissue infection	10 (8.6)
Cardiac failure	11 (9.5)
Complicated drug or smoke intoxication	10 (8.6)
Urinary tract infection	4 (3.4)
Trauma	7 (6.0)
Uncertain	1 (0.9)
Miscellaneous	18 (15.5)
Between admission and awakening, n (%)	
Septic shock[b]	58 (50.0)
ARDS	33 (28.4)
Renal failure[c]	38 (32.8)
Liver failure[c]	12 (10.3)
Hematological failure[c]	23 (19.8)
Use of catecholamines	86 (74.1)
Use of corticosteroids[d]	73 (62.9)
Use of neuromuscular blockers[e]	45 (38.8)
Time from intubation to awakening, median (IQR)	10 (8–14)
Time from awakening to first extubation,[f] median (IQR)[g]	4 (1–13)
Time from awakening to successful extubation,[h] median (IQR)[g]	6 (1–17)
Reintubation after awakening, n (%)[i]	29 (27.4%)
Tracheostomy after awakening, n (%)	24 (20.7)
Length of stay in ICU (days), median (IQR)	24 (15–35)
Death in ICU, n (%)	18 (15.5)
Length of stay in hospital (days), median (IQR)	45 (29–73)
Death in hospital, n (%)	27 (24.1)

IQR, interquartile range; SAPS, Simplified Acute Physiology Score (18); ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome.

[a]Diagnosis of COPD and cardiac failure was based on clinical history; [b]septic shock was defined as the administration of catecholamines and a concomitant documented infection after exclusion of other causes of shock; [c]renal, hepatic, and hematologic failures were defined according to the ODIN score (19); [d]indication for corticosteroids was septic shock in 41 patients (56.2%), COPD exacerbation in 16 (21.9%) patients, non-resolving ARDS in five patients (6.8%), nonseptic shock in four patients (5.5%), miscellaneous reasons in five patients (6.8%, including laryngeal edema in two patients, severe acute asthma in two patients, thrombotic thrombocytopenic purpura in one patient, and systemic vasculitis in one patient), and unclear reason in two patients (2.7%); [e]at least one injection of a nondepolarizing neuromuscular blocking agent; [f]with no need for reintubation within 48 hrs after extubation; [g]Kaplan-Meier estimates of the median value and IQR; [h]successful extubation was defined as absence of reintubation within 15 days after extubation; [i]the reintubation rate was determined in the 106 patients who underwent a first episode of extubation.

costeroids between the onset of MV and awakening. Awakening occurred after a median duration of MV of 10 days (8–14). There were 15 patients who died before extubation, and two additional patients died within the 15 days after extubation.

Limb and Respiratory Muscle Strength Measurements. The median (interquartile range) MRC score obtained at awakening in 115 patients (99.1%) was 41 (21–52). Due to a technical problem with the spirometer in one participating center that precluded complete assessment of respiratory variables for 3 months, only 105 patients were tested for their MIP, MEP, and VC at awakening. Among these 105 patients, measurements of MIP, MEP, and VC were obtained in 79 (75.2%), 78 (74.3%), and 73 (69.5%) patients, respectively. The median (interquartile range) value of MIP was 30 (20–40) cm H_2O, MEP was 30 (20–50) cm H_2O, and VC was 11.1 (6.3–19.8) mL/kg. Reasons for not obtaining MIP, MEP, and VC measurements were major anxiety or poor respiratory tolerance immediately after disconnection from the ventilator. There was no significant difference between patients with or without measured MIP, MEP, or VC in terms of Simplified Acute Physiology Score II (30 [25–36] vs. 27 [19–37], $p = .46$) or MRC (39 [21–51] vs. 36 [17–56], $p = .59$) at awakening or in number of days with two or more failed organs (6 [3–10] vs. 5 [3–7], $p = .17$) before awakening.

Correlation Between Respiratory and Limb Muscle Strength. There were significant correlations between MRC score and MIP (rho = 0.35, $p = .001$), MEP (rho = 0.49, $p < .0001$), and VC (rho = 0.31, $p = .007$) at awakening. The distributions of MIP, MEP, and VC according to MRC tertiles are shown in Figure 1.

MV Duration and Relationship with Respiratory Muscle Strength. The median (interquartile range) time from awakening to successful extubation was 6 (1–17) days. Time from awakening to successful extubation was significantly longer in patients with low MIP and in those with low VC, and there was a trend toward longer time from awakening to successful extubation in those with low MEP (Table 2). Kaplan-Meier curves are shown in Figure 2. Other variables significantly associated with delayed successful extubation in univariate analysis were presence of septic shock and number of days with two or more failed organs before awakening and Simplified Acute Physiology Score II at awakening (Table 2). In the three multivariate models, each including either MIP, MEP, or VC at awakening as a marker of the respiratory involvement, low MIP (hazard ratio, 1.86; 95% CI, 1.07–3.23; $p = .03$) and low MEP (hazard ratio, 2.18; 95% CI, 1.44–3.84; $p = .007$) were independent predictors of delayed successful extubation (Table 3). Similarly, in the model with the MRC score, the MRC score was an independent predictor of delayed successful extubation (hazard ratio, 1.96; 95% CI, 1.27–3.02; $p = .002$). Univariate and multivariate analyses of the risk of successful extubation delayed for ≥7 days after awakening are displayed in Tables 4 and 5, respectively. Low MIP, low MEP, and low MRC were independent predictors of delayed successful extubation, with odds ratios of 8.02 (95% CI, 2.12–30.36; $p = .002$), 4.15 (95% CI, 1.16–14.82; $p = .03$), and 3.03 (95% CI, 1.23–7.43; $p = .02$), respectively. Among the 106 patients who underwent extubation, reintubation was necessary in 29 patients (27.4%) and occurred >48 hrs after extubation in 11 patients (37.9% of patients requiring reintubation). There was no significant difference in the frequency of reintubations

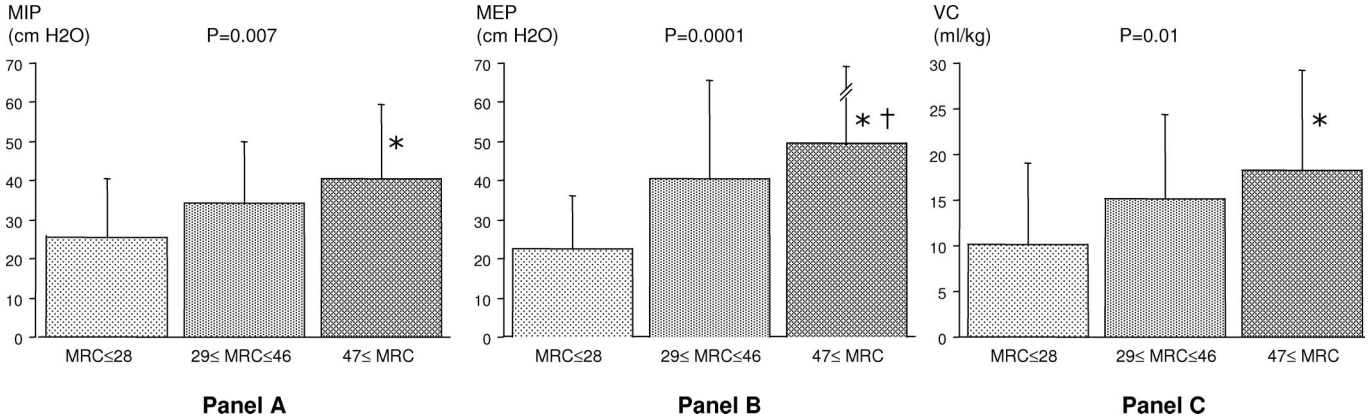

Figure 1. Distribution of maximal inspiratory pressure (*MIP*), maximal expiratory pressure (*MEP*), and vital capacity (*VC*) according to Medical Research Council score of limb muscle strength (*MRC*) tertiles. Mean (*bars*) and SD (*lines*) values of MIP (*Panel A*), MEP (*Panel B*), and VC (*Panel C*) according to the MRC score split on tertiles. MRC tertiles were compared using analysis of variance. Global *p* values are displayed at the top of each graph; *p* values for Bonferroni/Dunn *a posteriori* analyses are as follows: *Panel A*, **p* = .002 for comparison with MRC ≤28; *Panel B*, **p* < .001 for comparison with MRC ≤28, †*p* = .003 for comparison with 29 ≤ MRC ≤ 46; *Panel C*, **p* = .004 for comparison with MRC ≤28.

Table 2. Univariate Cox analysis of factors associated with delayed successful extubation

	Time from Awakening to Successful Extubation, Median (IQR)	Hazard Ratio	95% CI	*p* Value
At ICU admission				
Age ≤64	6 (0–17)	1 (ref)		
Age >64	7 (1–20)	1.11	0.74–1.65	.6
Male sex	5 (0–15)	1 (ref)		
Female sex	12 (2–20)	1.43	0.93–2.18	.1
SAPS II ≤46	4 (0–14)	1 (ref)		
SAPS II >46	8 (1–21)	1.46	0.98–2.19	.06
COPD, no	3 (0–17)	1 (ref)		
COPD, yes	8 (2–21)	1.36	0.90–2.06	.15
Cardiac insufficiency, no	5 (0–15)	1 (ref)		
Cardiac insufficiency, yes	13 (2–22)	1.44	0.91–2.28	.12
Before awakening				
Duration of MV ≤10 days	5 (0–17)	1 (ref)		
Duration of MV >10 days	8 (2–19)	1.22	0.81–1.83	.3
Days with two or more failed organs ≤6	3 (0–15)	1 (ref)		
Days with two or more failed organs >6	11 (3–21)	1.59	1.05–2.41	.03
Septic shock, no	4 (0–12)	1 (ref)		
Septic shock, yes	11 (1–26)	1.71	1.14–2.57	.01
ARDS, no	7 (1–18)	1 (ref)		
ARDS, yes	5 (1–15)	0.83	0.54–1.29	.4
At awakening				
SAPS II ≤30	3 (0–11)	1 (ref)		
SAPS II >30	15 (1–42)	2.58	1.66–4.02	<.001
Respiratory neuromuscular variables				
MIP >30 cm H_2O	3 (1–17)	1 (ref)		
MIP ≤30 cm H_2O	13 (5–30)	1.82	1.10–3.02	.02
MEP >30 cm H_2O	6 (1–12)	1 (ref)		
MEP ≤30 cm H_2O	13 (3–19)	1.61	0.98–2.65	.06
VC >11.1 mL/kg	3 (0–14)	1 (ref)		
VC ≤11.1 mL/kg	11 (2–22)	1.73	1.03–2.90	.04
Limb neuromuscular variable				
MRC score >41	2 (0–9)	1 (ref)		
MRC score ≤41	14 (2–22)	2.00	1.34–3.00	.001

IQR, interquartile range; CI, confidence interval; ICU, intensive care unit; ref, reference category for the elimination of the hazard ratio; SAPS, Simplified Acute Physiology Score (18); COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation; ARDS, acute respiratory distress syndrome; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; VC, vital capacity; MRC score, Medical Research Council score of limb muscle strength.

Quantitative variables were dichotomized on their median value. Patients who did not reach the end point of successful extubation (i.e., those who died before or within the 15 days after extubation) were censored (n = 17).

in patients with low MIP (32.5% vs. 25.0% in those with a high MIP, $p = .6$), low MEP (32.4% vs. 25.7%, $p = .6$), or low VC (33.3% vs. 15.2%, $p = .2$).

Factors Influencing Respiratory Muscle Weakness. Septic shock before awakening was significantly associated with a low MIP or MEP (≤30 cm H_2O) at awakening (Table 6). In multivariate logistic regression analysis, septic shock before awakening was the only factor associated with a low MIP or MEP

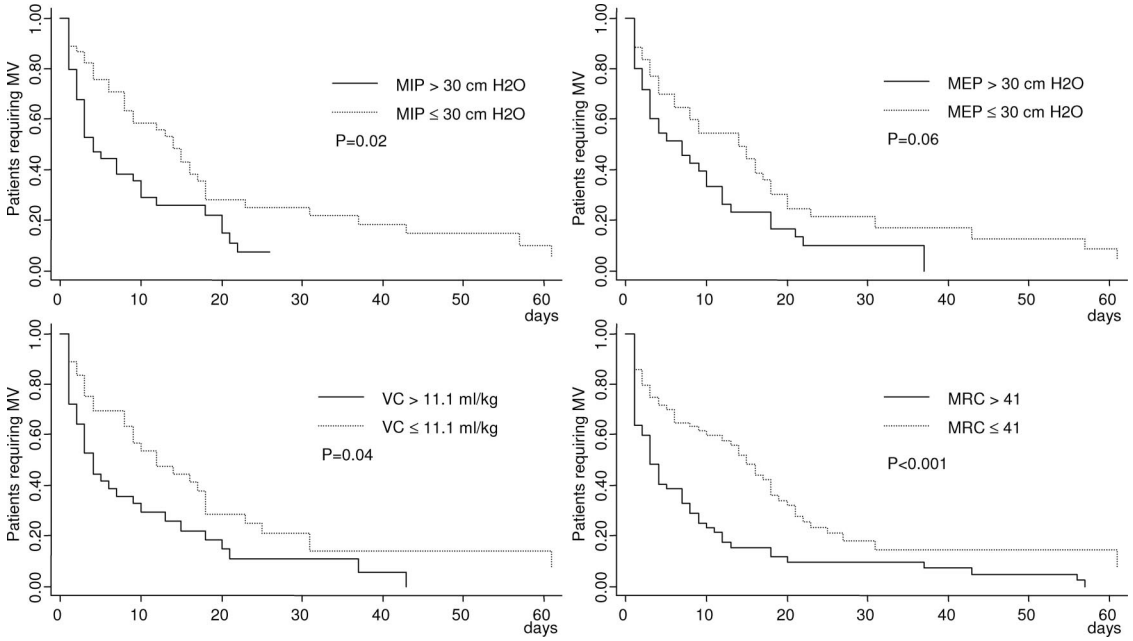

Figure 2. Time to successful extubation according to maximal inspiratory pressure (*MIP*), maximal expiratory pressure (*MEP*), and vital capacity (*VC*), and Medical Research Council score of limb muscle strength (*MRC*) scores. Kaplan-Meier curves of time from awakening to successful extubation according to MIP, MEP, VC, and MRC scores measured at awakening and dichotomized on their median values. Successful extubation was significantly delayed in patients with low MIP, low VC, or low MRC scores. *MV*, mechanical ventilation.

Table 3. Independent determinants of delayed successful extubation

Model with MIP				Model with MEP				Model with VC				Model with MRC			
	HR	95% CI	*p* Value		HR	95% CI	*p* Value		HR	95% CI	*p* Value		HR	95% CI	*p* Value
MIP ≤30 cm H_2O	1.86	1.07–3.23	.03	MEP ≤30 cm H_2O	2.18	1.44–3.84	.007	VC ≤11.1 mL/kg	1.33	0.77–2.29	.3	MRC score ≤41	1.96	1.27–3.02	.002
COPD	2.32	1.33–4.05	.003	COPD	3.23	1.75–5.98	<.001	COPD	2.33	1.29–4.21	.005	COPD	1.89	1.22–2.92	.004
SAPS II at awakening	2.85	1.57–5.16	.001	SAPS II at awakening	2.96	1.68–5.20	<.001	SAPS II at awakening	3.38	1.85–6.17	<.001	SAPS II at awakening	2.45	1.50–3.91	<.001
Female sex	1.92	1.09–3.39	.02	Female sex	2.14	1.21–3.76	.008	Female sex	1.82	1.01–3.30	.04	Female sex	1.63	1.05–2.54	.03
Cardiac insufficiency	1.87	1.04–3.34	.04												
Days with ≥2 failed organs	1.77	1.01–3.09	.05												

MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; VC, vital capacity; MRC, Medical Research Council score of limb muscle strength; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score (18).

MIP, MEP, VC, and MRC were each entered into three separate multivariate Cox proportional hazards analyses of delayed successful extubation, along with other variables with a *p* value of ≤.20 in univariate analysis. Quantitative variables were dichotomized on their median value. Patients who did not reach the end point of successful extubation (i.e., those who died before or within the 15 days after extubation) were censored (n = 17). MIP, MEP, and MRC score (but not VC) were independent predictors of delayed successful extubation.

(odds ratio, 3.17; 95% CI, 1.17–8.58; $p = .02$).

DISCUSSION

In our study, we showed that alterations in bedside variables of respiratory neuromuscular function are extremely frequent after ≥1 wk of MV and are correlated with the severity of limb weakness quantified with the MRC score. Altered MIP and MEP are independent predictors of delayed successful extubation. Septic shock is a strong risk factor for low MIP or MEP.

This is the first study of systematic combined bedside assessment of respiratory and limb muscle strength in a broad range of ICU patients with prolonged MV. Although electrical or magnetic nerve stimulation have been proposed to measure isotonic or isometric limb muscle strength, regardless of the patient's level of cooperation (20, 21), only distal muscles can be assessed, and the sophistication of these methods limit their use in clinical practice. We used the MRC score, a readily available and simple instrument validated in patients with acute stroke (22) and Guillain-Barré syndrome undergoing MV (6). Return to satisfactory awakening and comprehension, a necessary condition to test patients using the MRC score, was systematically and comprehensively checked, and muscle weakness could be evaluated and analyzed in >99% of the patients. However, measur-

ing respiratory muscle strength at the bedside was challenging, even after ensuring that consciousness and comprehension were satisfactory. Although technical problems with a spirometer precluded some measurements, anxiety, fear, and immediate poor respiratory tolerance after disconnection from the ventilator and tracheal tube occlusion accounted for additional failed measurements. One factor that might explain this high rate of unsuccessful measurements in our population is the sudden disconnection from the ventilator after a prolonged (≥1 wk) duration of assisted ventilation. Furthermore, in this context of awakening from an acute critical illness, the relative sophistication of the respiratory muscle strength measurements compared with the measurement of limb muscle strength might also have contributed to the relatively high failure rate. Nevertheless, severity score and MRC score at awakening were not significantly different between patients who did and did not have successful measurements of respiratory variables. This suggests that among our study patients, failure to measure respiratory variables was not the marker of a subgroup of patients with different disease severity.

After awakening, we found that MIP, MEP, and VC values were lower than those observed in healthy subjects (23), with most values being highly abnormal: 75% of the patients had a MIP of ≤40 cm H_2O, a MEP of ≤50 cm H_2O, or a VC of ≤20 mL/kg. We also found a significant correlation between limb and respiratory muscle strength, suggesting that limb and respiratory muscle weakness are possibly linked and may represent two aspects of the same disease. Our findings are in accordance with results from previous studies in which respiratory involvement was assessed using electrophysiological investigation. In a prospective study of 43 patients with sepsis and multiple organ failure, 29 patients underwent a combined electrophysiological investigation of both diaphragm and four limbs, showing a significant correlation between diaphragmatic muscle compound action potential and the level of limb electrophysiological involvement (1). In patients with electrophysiological features of CINM and difficult weaning, respiratory electrophysiological abnormalities are present in >80% of the patients (24) and are more frequently observed in patients with severe limb electrophysiological involvement (25).

Time from awakening to successful extubation was ≥1 wk in 50% of our patients, reflecting an important dependence on the ventilator after awakening from the acute phase of a critical illness in the ICU. Contrary to numerous studies in which MIP, MEP, or VC were used as

Table 4. Univariate analysis of risk of successful extubation delayed for ≥7 days after awakening

	Time to Successful Extubation ≥7 Days (n = 42)	Time to Successful Extubation <7 Days (n = 57)	*p* Value
At admission			
Age, median (IQR)	66 (53–77)	62 (47–78)	.9
Female sex, n (%)	16 (38.1)	15 (26.3)	.2
Admission SAPS II, median (IQR)	46 (37–56)	46 (37–50)	.3
COPD, n (%)	20 (47.6)	17 (29.8)	.07
Cardiac insufficiency, n (%)	15 (35.7)	11 (19.3)	.07
Before awakening			
Days of mechanical ventilation, median (IQR)	11 (8–16)	9 (7–13)	.1
Number of days with ≥2 organs failed, median (IQR)	6 (4–10)	5 (0–7)	.03
Septic shock, n (%)	21 (50.0)	24 (42.1)	.4
ARDS, n (%)	12 (28.6)	17 (29.8)	.9
At awakening			
SAPS II, median (IQR)	20 (25–37)	30 (21–35)	.6
Respiratory neuromuscular variables			
MIP, median (IQR)	30 (20–38)	40 (25–50)	.03
MEP, median (IQR)	23 (20–50)	40 (20–60)	.07
VC, median (IQR)	7.6 (5.2–12.6)	15.9 (9.6–24.6)	.002
Limb neuromuscular variable			
MRC, median (IQR)	38 (21–49)	48 (36–54)	.01

IQR, interquartile range; SAPS, Simplified Acute Physiology Score (18); COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; VC, vital capacity; MRC, Medical Research Council score of limb muscle strength.

Univariate analysis of factors associated with a time from awakening to successful extubation of ≥7 days in the 99 patients who reached the end point of successful extubation. Quantitative variables were compared between patients with time to definitive extubation of ≥7 and <7 days using the Mann-Whitney test. Categorical variables were compared using the chi-square or Fischer exact test, as appropriate.

Table 5. Independent determinants of the risk of successful extubation delayed for ≥7 days after awakening

Model with MIP				Model with MEP				Model with VC				Model with MRC			
	OR	95% CI	*p* Value		OR	95% CI	*p* Value		OR	95% CI	*p* Value		OR	95% CI	*p* Value
MIP ≤30 cm H_2O	8.02	2.12–30.36	.002	MEP ≤30 cm H_2O	4.15	1.16–14.82	.03	VC ≤11.1 mL/kg	2.75	0.82–9.18	.1	MRC ≤41	3.03	1.23–7.43	.02
COPD	4.43	1.20–16.41	.03	COPD	4.56	1.24–16.75	.02	COPD	4.43	1.3–14.79	.02	COPD	2.74	1.10–6.85	.03
Cardiac insufficiency	4.96	1.25–19.71	.02	Cardiac insufficiency	3.79	1.07–13.39	.04	Cardiac insufficiency	3.24	0.92–11.38	.07	Cardiac insufficiency	2.14	0.82–5.61	.1

MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; VC, vital capacity; MRC, Medical Research Council score of limb muscle strength; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

MIP, MEP, VC, and MRC were each entered into three separate multivariate stepwise backward logistic regression analyses of time from awakening to successful extubation of ≥7 days, along with other variables with a *p* value of ≤.20 in the univariate analysis. Quantitative variables were dichotomized on their median value. MIP, MEP, and MRC score (but not VC) were independent predictors of successful extubation delayed for ≥7 days after awakening.

Table 6. Analysis of risk factors for low maximal inspiratory pressure (MIP) or maximal expiratory pressure (MEP)

Univariate Analysis	MIP or MEP ≤30 cm H_2O (n = 53)	MIP and MEP >30 cm H_2O (n = 26)	*p* Value
At ICU admission			
Age in years, median (IQR)	67 (53–78)	70 (54–76)	.9
Female sex, n (%)	22 (41.5)	7 (26.9)	.3
Admission SAPS II, median (IQR)	46 (36–58)	44 (38–50)	.4
COPD, n (%)	20 (37.7)	13 (50)	.3
Before awakening			
Days of MV, median (IQR)	10 (8–14)	10 (8–13)	.9
Days with ≥2 failed organs, median (IQR)	6 (4–10)	5 (0–9)	.2
Use of corticosteroids, n (%)	33 (62.3)	16 (61.5)	.9
Use of neuromuscular blockers, n (%)[a]	13 (24.5)	11 (42.3)	.1
Average daily morning BGL (mmol/L), median (IQR)	8.1 (7.0–9.3)	7.5 (6.8–8.6)	.1
Septic shock, n (%)	31 (58.5)	8 (30.8)	.02
Multivariate Logistic Regression Analysis of Low MIP or MEP ≤30 cm H_2O	OR	95% CI	*p* Value
Septic shock	3.17	1.17–8.58	.02

ICU, intensive care unit; IQR, interquartile range; SAPS, Simplified Acute Physiology Score (18); COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation; BGL, blood glucose level; OR, odds ratio; CI, confidence interval.

[a]At least one injection of a nondepolarizing neuromuscular blocking agent.

Potential risk factors for low MIP or MEP at awakening were compared in univariate analysis using the Mann-Whitney test for quantitative variable and the chi-square or Fisher exact test for categorical variables. Variables with a *p* value of ≤.2 were entered into a multivariate stepwise backward logistic regression analysis.

predictors of immediate success or failure of extubation (26), in our study, MIP, MEP, and VC were used as potential predictors of prolonged MV after awakening. We found that both MIP and MEP measured at awakening were independent determinants of delayed successful extubation. The adjusted risk of successful extubation delayed for ≥1 wk after awakening was more than four times higher in those patients with low MEP compared with those with high MEP, and it was almost eight times higher in those patients with low MIP compared with those with high MIP. As MIP and MEP were also significantly correlated with the MRC score, our finding provides further evidence that the previously identified association between limb weakness and duration of MV (12, 13) is mediated by respiratory muscle weakness. The reason why altered VC was not an independent determinant of prolonged MV in our study is unclear. One explanation might be that the current not-ideal body weight was used as the denominator. Another explanation is that VC is influenced not only by expiratory muscle strength but also by lung parenchymal or chest wall compliance abnormalities frequently encountered in ICU patients, including those with atelectasis, pneumonia, or pulmonary edema.

Although risk factors for limb involvement, including prolonged immobilization, duration and severity of organ dysfunction, hyperglycemia, and use of corticosteroids or neuromuscular blockers, have been extensively studied (27), to our knowledge, this study represents a first attempt to identify risk factors for respiratory muscle weakness. Septic shock was the only independent risk factor identified. This is in accordance with numerous animal studies of sepsis-induced diaphragmatic dysfunction and structural changes (28, 29). Other animal studies have emphasized the deleterious effect on diaphragmatic strength of complete diaphragmatic immobilization under MV (30–32). In our patients, duration of MV before awakening was not a risk factor for low MIP. However, periods during which diaphragmatic contraction under MV was abolished or partially preserved were not recorded. The opportunity for animals to trigger the ventilator dramatically reduces diaphragmatic weakness induced by controlled MV (33). Therefore, the level of preserved diaphragmatic contraction under MV might be a more relevant explanatory variable for diaphragmatic weakness than duration of MV *per se*.

Our study has several limitations. First, the abnormal values observed in our study may have overestimated respiratory muscle weakness. The patient's cooperation is an important prerequisite to measure respiratory muscle strength. MIP measurement in poorly responsive patients shows poor reproducibility (34), whereas in ready-to-wean patients, reproducibility of MIP is satisfactory (35). In our study, adequate awakeness and comprehension, assessed using a five-command instrument, were required to consider that patients were awake. Furthermore, the day MIP, MEP, and VC were measured, a MRC score requiring performance of upper and lower limb movements to assess limb muscle strength was obtained in all but one of our patients. Therefore, patients in our study could not be considered poorly cooperative. In addition, even when nonvolitional tests are used to measure respiratory muscle strength, severe alterations are observed. In a study of 18 patients whose respiratory muscle strength was measured, after a duration of MV ranging from 2 to 190 days, using transdiaphragmatic twitch pressure after magnetic phrenic nerve stimulation at the onset of weaning, all but one had a transdiaphragmatic twitch pressure of <20 cm H_2O, indicating a severe reduction in diaphragmatic strength (36). In our study, a convenience sample (data not shown) of 11 patients among the patients in whom measures MIP, MEP, and VC were obtained underwent cervical magnetic stimulation, with twitch pressure measured at the proximal end of the tracheal tube. Twitch pressures were extremely low (median of 4.0 [3.4] cm H_2O). In addition, interpolated twitch after a voluntary inspiratory effort of 50% and 100% resulted in only slight additional tracheal depression (median of 2.0 [2.0] and 0 [1.4] cm H_2O, respectively), reflecting that patients were able to make an inspiratory effort close to the maximum. Finally, there was a strong correlation in our study between limb muscle strength on one side, and MIP, MEP, and VC on the other side, with particularly high *r* values. For all these reasons, in our study conditions, low MIP and MEP values very likely reflect a true respiratory muscle involvement. It is nevertheless noteworthy that slightly different MIP and MEP values might have been obtained using a different method of measurement, such

as measurement at the functional residual capacity or after a prolonged occlusion on a unidirectional valve. A second limitation is that neither low MIP, MEP, nor VC was significantly associated with a higher risk of reintubation. This might be attributable to the threshold used to define low values (i.e., the median value of each variable) or to a lack of power to detect a difference in this specific end point. The absence of an association between respiratory muscle strength variables and reintubation rate might also reflect the fact that, in our study, patients with respiratory weakness were protected from extubation–reintubation by previous failure of the daily T-piece trials, which precluded extubation, according to the procedure published by the two French critical care societies (14) and very similar to that recommended by the American College of Critical Care Medicine (37). Whether a less strict weaning strategy would have resulted in a higher rate of reintubation is unknown. Third, using the MRC score to detect CINM, we were unable to distinguish between neuronal and muscular involvement. Of importance is the fact that standard electrophysiological investigation is also frequently unable to distinguish between these two involvements. The precise identification of each of the three components commonly encountered in patients with CINM, including sensory-motor axonopathy, muscle membrane inexcitability, and specific myopathy with various degrees of necrosis, which all contribute to the common abnormal pattern on standard electrophysiological examination, would have required additional sophisticated (direct muscle stimulation) and semi-invasive (muscle biopsy) investigations. In this context, clinical detection of muscle weakness, a uniform manifestation of CINM, whether the axon, muscle contractile proteins, or muscle membrane excitability are involved alone or in combination, represents an interesting alternative to electrophysiological detection. Finally, as the MRC score can be used in cooperative patients only, patients who did not regain satisfactory consciousness and comprehension before being transferred to another unit could not be evaluated. Clinical detection of CINM in these patients remains particularly challenging. However, as return to normal consciousness is a common prerequisite criteria for starting the weaning process, most mechanically ventilated patients in nonneurologic ICUs usually reach the stage at which CINM can be detected clinically.

CONCLUSION

In summary, after awakening from an acute illness requiring intensive care, including >1 wk of MV, definitive extubation is frequently delayed. Bedside measurement of muscle strength at awakening reveals severe respiratory muscle weakness associated with limb weakness. Respiratory CINM is a predictor of delayed weaning, independent of potential confounders such as chronic obstructive pulmonary disease, and likely contributes to the prolonged MV observed in patients with limb CINM. In our study, septic shock seems to be a strong predictor of respiratory muscle weakness. In patients with low MIP, MEP, or MRC at awakening, further investigation is warranted to determine whether interventions such as tracheostomy performed at awakening might reduce the time to definitive extubation.

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