Intensive Care Med (2016) 42:853–861
DOI 10.1007/s00134-015-4125-2

ORIGINAL

Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure

Boris Jung
Pierre Henri Moury
Martin Mahul
Audrey de Jong
Fabrice Galia
Albert Prades
Pierre Albaladejo
Gerald Chanques
Nicolas Molinari
Samir Jaber

Received: 24 July 2015
Accepted: 26 October 2015
Published online: 16 November 2015
© Springer-Verlag Berlin Heidelberg and ESICM 2015

B. Jung and P. H. Moury contributed equally to this study.

Clinical Trials.gov Identifier: NCT01968889.

Take-home message: We report for the first time the evaluation of diaphragm function and related outcome in a prospective study performed in 40 consecutive patients with ICU-acquired weakness (MRC score < 48) among 185 consecutive patients ventilated for more than 48 h.

Electronic supplementary material The online version of this article (doi:10.1007/s00134-015-4125-2) contains supplementary material, which is available to authorized users.

B. Jung · P. H. Moury · M. Mahul · A. de Jong · F. Galia · A. Prades · G. Chanques · S. Jaber (✉)
Intensive Care Unit, Anesthesia and Critical Care Department, Saint Eloi Teaching Hospital, 80 Av Fliche, 34295 Montpellier Cedex 5, France
e-mail: s-jaber@chu-montpellier.fr
Tel.: (33) 4-67-33-72-71

B. Jung · G. Chanques · N. Molinari · S. Jaber
Centre National de la Recherche Scientifique (CNRS 9214), Institut National de la Santé et de la Recherche Médicale (INSERM U-1046), Montpellier University, Montpellier, France

P. Albaladejo
Pôle Anesthésie-Réanimation, UJF-Grenoble, Grenoble, France

P. Albaladejo
Université Grenoble Alpes/CNRS, ThEMAS TIMC UMR 5525, 38041 Grenoble, France

N. Molinari
Department of Statistics, University of Montpellier Lapeyronie Hospital, Montpellier, France

Abstract *Purpose:* Diaphragm function is rarely studied in intensive care patients with unit-acquired weakness (ICUAW) in whom weaning from mechanical ventilation is challenging. The aim of the present study was to evaluate the diaphragm function and the outcome using a multimodal approach in ICUAW patients. *Methods:* Patients were eligible if they were diagnosed for ICUAW [Medical Research Council (MRC) Score <48], mechanically ventilated for at least 48 h and were undergoing a spontaneous breathing trial. Diaphragm function was assessed using magnetic stimulation of the phrenic nerves (change in endotracheal tube pressure), maximal inspiratory pressure and ultrasonographically (thickening fraction). Diaphragmatic dysfunction was defined by a change in endotracheal tube pressure below 11 cmH_2O. The endpoints were to describe the correlation between diaphragm function and ICUAW and its impact on extubation. *Results:* Among 185 consecutive patients ventilated for more than 48 h, 40 (22 %) with a MRC score of 31 [20–36] were included. Diaphragm dysfunction was observed with ICUAW in 32 patients (80 %). Change in endotracheal tube pressure and MRC score were not correlated. Maximal inspiratory pressure was correlated with change in endotracheal tube pressure after magnetic stimulation of the phrenic nerves ($r = 0.43$; $p = 0.005$) and MRC score ($r = 0.34$; $p = 0.02$). Thickening fraction was less than 20 % in 70 % of the patients and was statistically correlated with change in endotracheal tube pressure ($r = 0.4$; $p = 0.02$) but not with MRC score. Half of the patients could be extubated without needing reintubation within 72 h. *Conclusion:* Diaphragm dysfunction is frequent in patients with ICU-acquired weakness (80 %) but poorly correlated with the ICU-acquired weakness MRC score. Half of the patients with ICU-acquired weakness were successfully extubated. Half of the patients who failed the weaning process died during the ICU stay.

Keywords Diaphragmatic dysfunction · Mechanical ventilation · Weaning · Intensive care unit-acquired weakness · Respiratory muscles

Introduction

Intensive care unit (ICU)-acquired weakness (ICUAW) is a complication observed in critically ill patients that combines myopathy and neuropathy [1–3]. Its incidence varies but may rise up to 100 % in patients with multi-organ failure [4, 5]. It is associated with delayed weaning from mechanical ventilation (MV) [6], longer ICU stay, frailty and poor outcome [7, 8]. The diaphragm, the main inspiratory muscle, is also a victim of critical illness. However, the extent of diaphragmatic dysfunction compared to limb muscle weakness during critical illness is a matter of debate [9, 10]. Some studies have indeed reported particular diaphragm sensitivity to aggression while others have reported the opposite [11–13]. MV by itself has been proven to impair diaphragm force (a term labelled ventilator-induced diaphragmatic dysfunction) and to promote diaphragm atrophy in the critically ill [14–17] without affecting limb muscles [14, 18].

Weaning from the MV in ICUAW patients may be difficult, and studying the potential diaphragmatic dysfunction in these patients is therefore of interest. To date, two studies have explored the relationship between ICUAW and diaphragm dysfunction using a pulmonary function test at the bedside [maximal inspiratory pressure (MIP)] [19] or electromyography [20] and reported conflicting results. Using a dedicated cutting edge multimodal tool combining magnetic stimulation of the phrenic nerves, diaphragm ultrasound and pulmonary function tests to study diaphragmatic function at the bedside, we designed this study with the aim of assessing the diaphragm function in ICUAW patients undergoing a spontaneous breathing trial (SBT). We hypothesized that such dysfunction would be associated with ICUAW.

Methods

Design

The physiological prospective study, approved by the Comité de Protection des Personnes Sud-Méditerranée, Nîmes, France (2013-AA00487-38) and registered on clinical trial.gov (NCT01968889), was conducted over a 6-month period from May to November 2013 in a 16-bed medical and surgical ICU. Given that this study did not modify current diagnostic or therapeutic strategies, the need for written consent was waived according to the French Law (Law 88–1138 relative to Biomedical Research of December 20, 1988 modified on August 9, 2004).

Patients

Patients were eligible for inclusion in the study if they were diagnosed for ICUAW [defined by a Medical Research Council (MRC) Score <48] [1, 4, 21] and mechanically ventilated for at least 48 h and were undergoing a spontaneous breathing trial (SBT) as a step towards separation from the ventilator [22]. Routine MRC score evaluation by physiotherapists has been implemented in daily practice for years in our unit. Patient screening was performed jointly by the ICU physiotherapist and the main investigator (PHM) [1, 4].

Non-inclusion criteria were: contraindication to magnetic stimulation of the phrenic nerves (cardiac pacemaker or implanted defibrillator, cervical implants) [15, 16]; pre-existing neuromuscular disorders; cervical spine injury; bihemispheric or brain stem lesions; impossibility to assess muscular strength in a limb because of amputation or immobilization [1, 4].

Demographic data, severity scores, comorbidities, risk factors for ICUAW, reasons for admissions to the ICU and for initiating MV were prospectively recorded. The duration of mechanical ventilation, duration of ICU stay and ICU mortality were also collected.

Diaphragm assessment

Inspiratory muscle strength was assessed during a SBT both in T-tube and with a pressure support ventilation of 7 cmH_2O and a PEEP level of 0 cmH_2O in 20–30° upright position by three methods: magnetic stimulation of the phrenic nerve [12, 15, 16], maximal inspiratory pressure (MIP) [19] and ultrasonographically (diaphragm excursion and thickening fraction) (Fig. 1).

Bilateral supramaximal magnetic twitch stimulation of the phrenic nerves and its subsequent change in endotracheal tube pressure (Ptr,Stim) was used as previously described to approximate diaphragm function independently of the patients participation [12, 15, 16]. It is considered the gold standard to evaluate diaphragm function and serves as the reference method in this study. Briefly, patients were studied in a semi-recumbent position [23] and, after disconnection from the ventilator, they were allowed to exhale until the expiratory airflow reached zero. The tracheal tube was then occluded and tracheal pressure measured during the stimulation. The tracheal tube occlusion lasted approximately 5–10 s. Diaphragmatic dysfunction was defined by a Ptr,Stim <11 cmH_2O [16, 19, 24].

MIP was recorded following a maximum inspiratory effort against a closed airway without using a unidirectional valve permitting exhalation [19]. Ultrasound evaluation allowed the evaluation of thickness of the diaphragm after careful observation of the end of inspiration and expiration on real-time graphs of airflow and airway pressure. Measurements were averaged over at least three respiratory cycles. Diaphragmatic thickness was assessed in the zone of apposition of the diaphragm to the rib cage between the 8th and 10th intercostal spaces

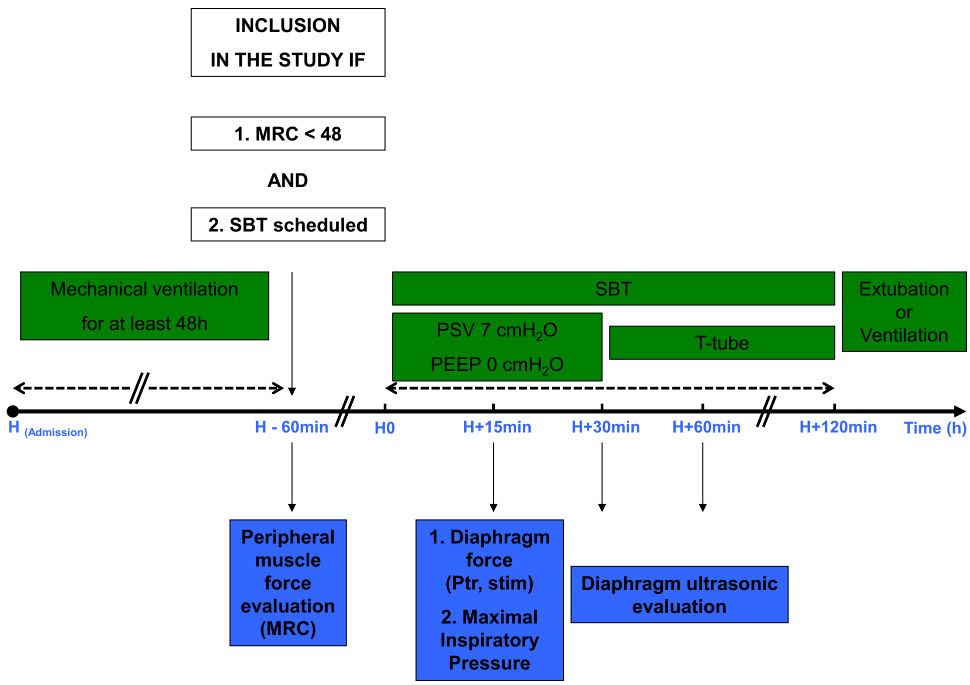

Fig. 1 Study protocol. Patients requiring mechanical ventilation for at least 48 h and presenting an intensive care unit-acquired weakness defined by a MRC score <48 were consecutively included. The MRC score was evaluated just before the beginning of the spontaneous breathing trial. After 15 min of spontaneous breathing trial using pressure support ventilation mode with 7 cmH_2O with 0 end expiratory pressure, the inspiratory muscles were explored. We used a multimodal evaluation combining diaphragm force measurement by bilateral phrenic nerve stimulation and maximal inspiratory pressure measurement. At the end of the 30 min of pressure support ventilation, ultrasound evaluation of the diaphragm was performed and repeated in T-tube. At the end of a 2-h spontaneous breathing trial, the attending physician in charge of the patient decided to extubate or to reventilate the patient without being aware of the results of the inspiratory muscle exploration. *MRC* Medical Research Council Score, *PEEP* positive end expiratory pressure, *PSV* pressure support ventilation, *Ptr,Stim* tracheal pressure after magnetic stimulation, *SBT* spontaneous breathing trial

using a 7.5- to 10-MHz probe [25, 26]. Briefly, thickness at end-expiration (TEE, mm) and at the end-inspiration (TEI, mm) were measured for at least three breaths to calculate the diaphragm thickening fraction as (thickness at the end-inspiration − thickness at the end-expiration)/thickness at the end-expiration) and expressed as a percentage. A thickening fraction below 20 % was considered a surrogate of diaphragmatic dysfunction [25] and 30 % was considered a surrogate to predict weaning success [27].

Weaning and postextubation care

According to existing guidelines and expert opinions, ICUAW patients were extubated by the physician on service if they succeeded the SBT [9, 22, 28]. Extubation was systematically followed by prophylactic non-invasive ventilation according to our protocol [29, 30]. Reintubation was performed in cases of respiratory, neurological or cardiovascular failure according to the guidelines [9, 28] and following local protocol [31].

Endpoints

The primary endpoint was, on the day of the SBT, to assess whether evaluated ICUAW was associated with diaphragmatic dysfunction defined by a Ptr,Stim below 11 cmH_2O. Secondary endpoints were to assess whether ICUAW and diaphragmatic dysfunction were associated with extubation failure, defined as a need for reintubation within 72 h after extubation.

Statistical analysis

Statistical analysis was performed with MedCalc® software (v.11.1; Ostend, Belgium;). The number of subjects needed was calculated to detect at least a 0.4 Spearmann correlation coefficient between MRC score and Ptr,Stim. Forty subjects were needed to test this hypothesis with a power of 0.8. Quantitative variables were expressed as mean (and standard deviation) or median (and interquartile 25–75 %) and compared using Student's *t* test or the Wilcoxon test as appropriate. Categorical variables were expressed as numbers (%) and compared using the Chi-square test or the Fisher test as appropriate. A p value below 0.05 was considered significant.

Results

During the 6-month study period, 185 patients were ventilated for more than 48 h of whom 40 were consecutively enrolled in the study (Fig. 1; Table 1). Evaluation and SBT took place 9 days [6–15] after the initiation of MV and 38 patients were subsequently extubated. At the time of evaluation, MRC was 31 [20–36] (Figs. 2, 3). Two patients underwent a tracheotomy without any extubation attempt; they were categorized as weaning failure patients.

Assessment of diaphragm function in ICUAW patients

Magnetic stimulation of the phrenic nerves and its subsequent variation in tracheal pressure (Ptr,Stim) was used as the reference measure to diagnose diaphragmatic dysfunction in the study. Among the 40 patients with ICUAW included in the present study, 32 (80 %) showed

Table 1 Characteristics of the 40 patients upon ICU admission and their characteristics the day of the spontaneous breathing trial

	All ($n = 40$)	No diaphragmatic dysfunction ($n = 8$)	Diaphragmatic dysfunction ($n = 32$)
Upon ICU admission			
Age (years)	58 (51–67)	50 (40–66)	60 (52–68)
Male (sex)	25 (63)	5 (63)	20 (63)
Body mass index (kg/m^2)	25 (22–28)	26 (24–27)	25 (22–29)
SAPS II	51 (42–60)	48 (41–71)	52 (43–58)
SOFA	10 (7–14)	8 (7–10)	11 (7–15)
Comorbidities			
Arterial hypertension	10 (25)	1 (13)	9 (28)
Coronaropathy	3 (5)	1 (13)	2 (2)
Myocardial insufficiency	4 (10)	1 (13)	3 (9)
COPD	5 (13)	0	5 (16)
Cancer	12 (30)	2 (25)	10 (31)
Liver cirrhosis	16 (40)	4 (50)	12 (38)
Upon ICU admission			
Recent surgery	29 (73)	4 (50)	25 (78)
Septic shock	39 (98)	7 (88)	32 (100)
Reason for mechanical ventilation			
Acute respiratory failure	26 (65)	6 (74)	20 (63)
Coma	4 (10)	1 (13)	3 (9)
Other	10 (25)	1 (13)	9 (28)
Risk factors for ICUAW			
Use of vasoactive agents	38 (95)	7 (88)	31 (97)
Use of aminoglycosides	28 (70)	6 (75)	22 (69)
Use of neuromuscular blocking agents	27 (68)	4 (50)	23 (72)
Use of steroids	29 (73)	5 (63)	24 (75)
Use of dialysis	12 (30)	2 (25)	10 (31)
Day of SBT			
Ptr,Stim (cmH_2O) ($n = 40$)	6.5 (3.5–10.0)	14.2 (13.2–17.5)	4.7 (3.2–7.2)*
MRC score ($n = 40$)	31 (20–36)	31 (18–36)	31 (23–36)
Pulmonary functional tests ($n = 40$)			
TV (ml)	440 (360–604)	515 (395–665)	440 (358–581)
RR (c/min)	23 (17–27)	24 (17–30)	23 (17–26)
RR/TV (c/min/ml)	50 (33–69)	49 (26–69)	50 (34–69)
MIP (cmH_2O)	18 (13–25)	27 (24–29)	16 (12–23)*
Ultrasound diaphragm assessment ($n = 33$)			
End-expiration thickness ($n = 33$) (mm)	2.2 (1.9–2.9)	2.1 (1.9–2.4)	2.2 (2.0–2.9)
Thickening fraction in PSV (%)	15 (10–22)	20 (14–32)	11 (5–17)*
Thickening fraction in T-tube (%)	16 (12–23)	21 (15–36)	13 (9–17)*

Data are median and first and third quartile or number and percentages. Neuromuscular blocking agents use was taken into account when such treatment was administered for at least 48 h. Diaphragm thickness measurement was feasible in 33 patients. The reason for not measuring was poor acoustic window ($n = 7$)

COPD chronic obstructive pulmonary disease, *ICUAW* intensive care unit-acquired weakness, *MIP* maximal inspiratory pressure (cmH_2O), *MRC* Medical Research Council, *PSV* pressure support ventilation, *RR* respiratory rate *SAPS II* Simplified Acute Physiology Score [45], *SOFA* Sequential Organ Failure Assessment Score [46]

* $p < 0.05$

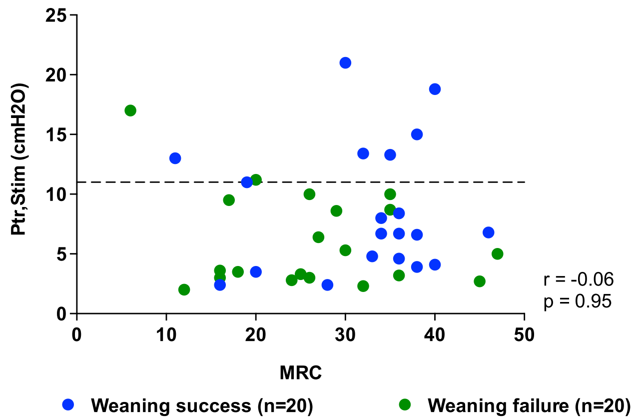

Fig. 2 Individual values of endotracheal tube pressure induced by bilateral phrenic nerve stimulation (Ptr,stim) according to the MRC score. No correlation was found between Ptr,stim and MRC score. patients who succeeded extubation are represented by *white dots* whereas those who needed reintubation within 72 h following extubation are represented as *black dots*. *Dashed line* represents the threshold of Ptr,stim to diagnose diaphragm dysfunction in the critically ill. [15, 16]. *MRC* Medical Research Council Score, *Ptr,Stim* tracheal pressure in response to bilateral phrenic nerve stimulation

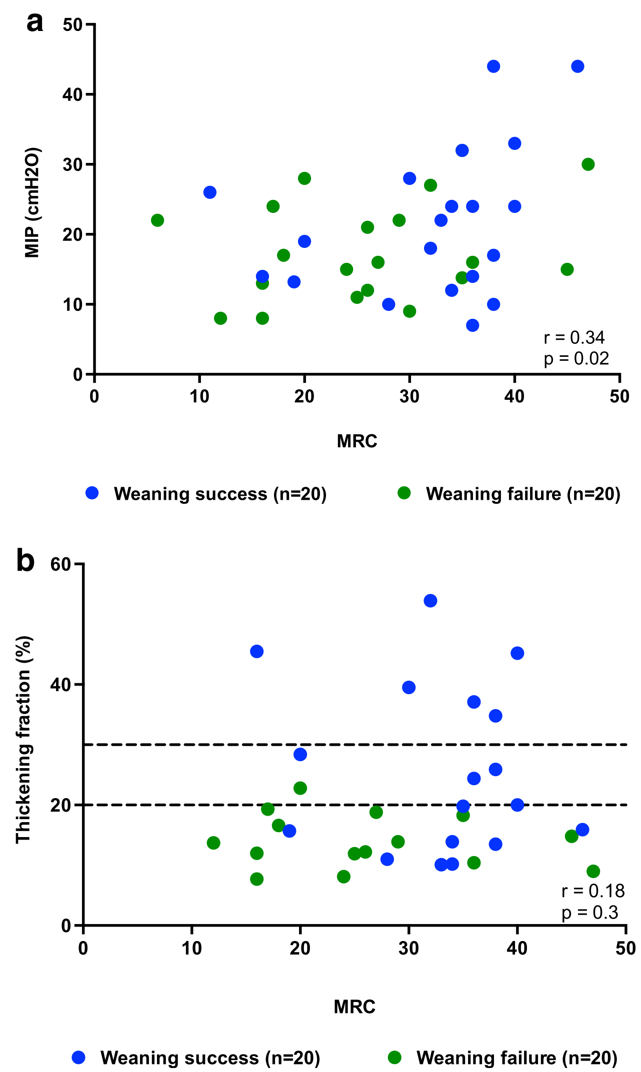

Fig. 3 **a** Individual values of maximal inspiratory pressure (MIP) according to the MRC score. MIP was statistically correlated with MRC score ($r = 0.34$; $p = 0.02$). patients who succeeded extubation are represented by *white dots* whereas those who needed reintubation within 72 h following extubation are represented as *black dots*. *MIP* maximal inspiratory pressure, *MRC* Medical Research Council Score. **b** Individual values of diaphragm thickening fraction according to the MRC score; no correlation between diaphragm thickening fraction and MRC score was found ($p < 0.05$). patients who succeeded extubation are represented by *white dots* whereas those who needed reintubation within 72 h following extubation are represented as *black dots*. *Dashed lines* represent the thresholds of diaphragm thickening fraction of 20 and 30 % that have been reported to be associated with weaning failure [27, 47]. *MRC* Medical Research Council Score

signs of diaphragmatic dysfunction (Table 1; Fig. 2). There was no correlation between Ptr,Stim and MRC score (Fig. 2).

The day of the SBT, MIP was obtained for 40 patients and was equal to 18 cmH_2O [13–25], significantly lower in patients with diaphragmatic dysfunction compared to patients without diaphragmatic dysfunction (Table 1) and values reported in healthy volunteers [19, 32]. MIP was correlated both with Ptr,Stim ($r = 0.46$; $p = 0.003$) and MRC score ($r = 0.31$; $p = 0.05$) (Fig. 3a).

Ultrasound evaluation of the diaphragm during SBT is summarized in Table 1. Diaphragm exploration was completed by thickening fraction, a surrogate of the work of breathing [26, 34] and a predictor of weaning success [27]. In the present study, 23 patients among 32 (70 %) with criteria of ICUAW presented a thickening fraction below 20 % and 28 (85 %) below the threshold of 30 % [27]. The thickening fraction was statistically correlated with Ptr,Stim ($r = 0.47$; $p = 0.006$) but not with MRC score (Fig. 3a, b).

Outcome

Among the 40 patients included, 20 were successfully extubated and 20 failed the weaning process (18 were extubated but needed reintubation within 72 h and 2 were tracheotomised after SBT failure) (Figs. 2, 3, 4). Among the 13 patients (33 %) who died during the ICU stay, 10 presented signs of diaphragmatic dysfunction the day of SBT. Weaning failure in patients who presented signs of ICUAW was associated with a 50 % mortality rate. Ptr,Stim was 4.3 cmH_2O [3–9] the day of the SBT in patients who were ultimately reintubated and 6.8 cmH_2O [4–13] ($p = 0.08$) in patients who were not reintubated (Table 2). MIP measurement the day of SBT was not associated with the need for subsequent reintubation and was 16 cmH_2O [12–23] versus 20.5 cmH_2O [14–27],

Table 2 Characteristics of the 40 studied patients the day of the spontaneous breathing trial according to their outcome

	All patients ($n = 40$)	Weaning success ($n = 20$)	Weaning failure ($n = 20$)	p
Age (years)	58 (51–67)	56 (50–65)	63 (55–76)	0.1
Male (sex)	25 (63)	11 (55)	14 (70)	0.5
Body mass index (kg/m^2)	25 (22–28)	27 (23–29)	25 (21–26)	0.1
IGSII	51 (42–60)	47 (41–55)	55 (49–63)	0.07
SOFA	10 (7–14)	8 (6–13)	11 (9–15)	0.1
Comorbidities				
Arterial hypertension	10 (25)	5 (25)	4 (10)	1
Coronaropathy	2 (5)	1 (5)	1 (5)	1
Myocardial insufficiency	4 (10)	1 (5)	3 (15)	1
COPD	5 (13)	1 (5)	4 (20)	0.3
Cancer	12 (30)	5 (25)	7 (35)	0.7
Liver cirrhosis	16 (40)	9 (45)	7 (35)	0.7
Upon ICU admission				
Recent surgery	29 (73)	14 (70)	15 (75)	1
Septic shock	35 (88)	16 (80)	19 (95)	0.3
ICU LOS, days	25 (15–35)	28 (14–33)	24 (15–37)	0.9
Reason for mechanical ventilation				
Acute respiratory failure	26 (65)	11 (55)	15 (75)	0.3
Coma	4 (10)	2 (10)	2 (10)	1
Other	10 (25)	7 (35)	3 (15)	0.3
Physiological measurements				
Ptr,Stim (cmH$_2$O)	6.5 (3.5–10.0)	6.8 (4–13)	4.3 (3–9)	0.08
MRC score	31 (20–36)	35 (30–38)	26 (18–33)	0.03
Pulmonary function tests				
TV (ml)	440 (360–604)	405 (348–508)	499 (398–619)	0.2
RR (c/min)	23 (17–27)	23 (17–30)	23 (18–25)	0.9
RR/TV (c/min/ml)	50 (33–69)	53 (33–80)	46 (33–61)	0.5
MIP (cmH$_2$O)	18 (13–25)	20.5 (14–27)	16 (13–23)	0.3
Ultrasound diaphragm assessment				
End-expiration thickness (mm)	2.2 (1.9–2.9)	2.2 (2–3)	2.2 (2–3)	1
Thickening fraction in PSV (%)	15 (10–22)	20 (7–33)	9 (2–13)	0.008
Thickening fraction in T-tube (%)	16 (12–23)	20 (13–35)	12 (6–15)	0.008

Data are median and first and third quartile or number and percentages. Ultrasound measurements were feasible in 33 patients *COPD* chronic obstructive pulmonary disease, *ICUAW* intensive care unit-acquired weakness, *SAPS II* Simplified Acute Physiology Score [45], *SOFA* Sequential Organ Failure Assessment Score [46], *MIP* maximal inspiratory pressure (cmH$_2$O), *MRC* Medical Research Council, *PSV* pressure support ventilation, *RR* respiratory rate, *TV* tidal volume

$p = 0.3$, in patients who needed to be reintubated versus patients who were successfully extubated. Among the ultrasound criteria, thickening fraction was associated with extubation success. Thickening fraction was 12 (6–15 %) versus 20 % (13–38 %), $p = 0.008$ in patients who needed to be reintubated versus patients who did not (Table 2).

Discussion

This study shows for the first time an association between diaphragmatic dysfunction and ICUAW in critically ill patients during weaning. In a prospective cohort of 40 patients presenting signs of ICUAW defined by an MRC score of 48 or less, symptoms of diaphragmatic dysfunction, evaluated using phrenic nerve magnetic stimulation, ultrasound and pulmonary function tests were present in 80 % of the patients (Figs. 2, 3). Half of the patients were weaned from the ventilator without being reintubated within 72 h, while the mortality rate in those patients who failed the weaning process was 50 % (Fig. 4). This highlights the need to better identify the patients who will not be weaned in this ICUAW population.

Our study presents some limitations. First, ICUAW was diagnosed in all patients and we were therefore unable to study diaphragmatic dysfunction in patients without ICUAW. Second, weaning was studied as a secondary endpoint and the study was not powered to predict factors independently associated with weaning success. Identifying these factors in the ICUAW population is challenged by the complexity and heterogeneity of critically ill patients. This highlights the necessity to tailor our weaning strategy based on a personalized physiologic assessment level. Third, ICUAW was diagnosed using MRC score and after ruling out other causes of limb weakness than critical illness. Although MRC accuracy has been questioned [35], it is reproducible [36, 37] and routinely performed by trained physiotherapists as a screening tool in our ICU. Furthermore, electromyography is currently not recommended

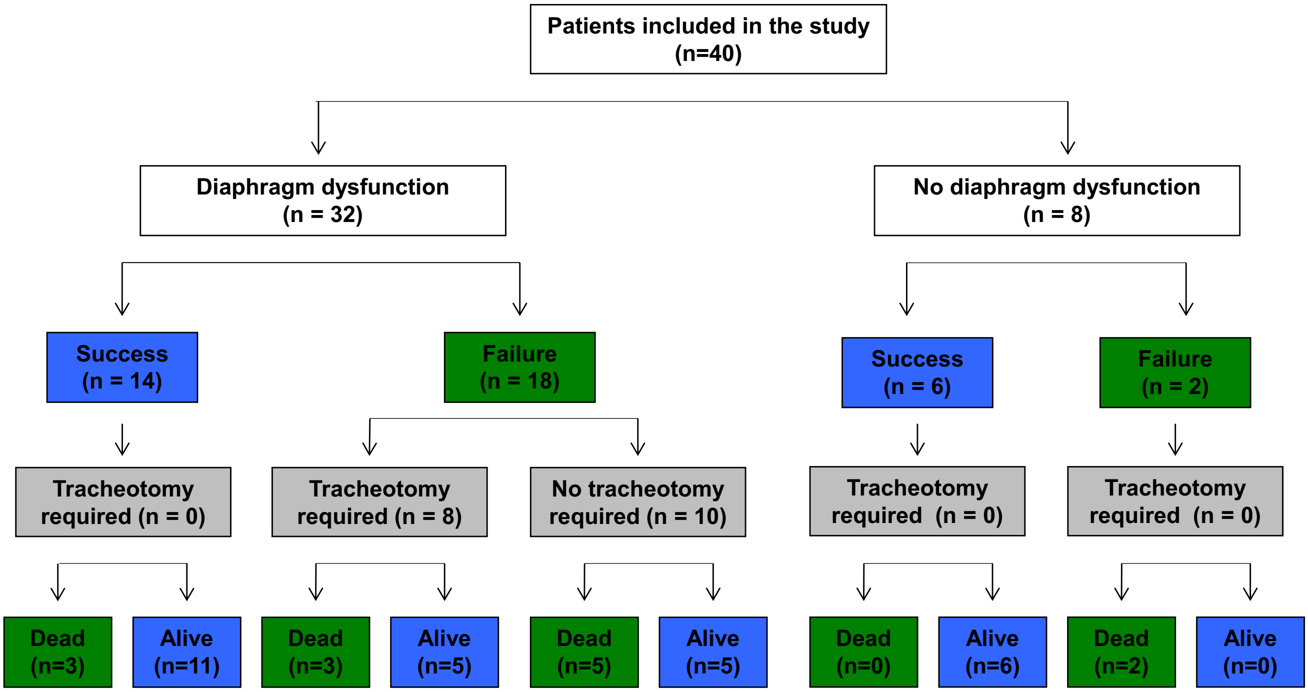

Fig. 4 Patient outcome. Outcome is presented as weaning success or failure, tracheotomy indication during the ICU stay and survival at ICU discharge. Although diaphragm dysfunction incidence was 80 % in the ICUAW patient population, almost half of the patients were successfully weaned from the ventilator. Eleven (34 %) of the patients with diaphragm dysfunction died during the ICU stay in comparison with 2 (25 %) of the patients without diaphragmatic dysfunction

when clinically detected weakness can be related to no other plausible cause than critical illness [1, 3]. Fourth, during the ICU stay or upon admission, most of the patients in the present study presented an infection (Table 1), a risk factor for both ICUAW and diaphragmatic dysfunction [3, 12, 15].

We report that 32 out of 40 (80 %) experienced diaphragmatic dysfunction the day of SBT using the Ptr,Stim threshold of 11 cmH_2O after magnetic stimulation of the phrenic nerves (Fig. 2). This method is currently the gold standard to evaluate strength of the diaphragm at the bedside because it does not need the patients' participation [15, 16, 19]. We report values comparable to other studies performed in patients with duration of mechanical ventilation of more than 1 week [15, 38, 39] with no reported ICUAW [40]. Ultrasound evaluation of the diaphragm showed a similar incidence of diaphragmatic dysfunction, from 64 to 80 %, depending on its definition (Table 1; Fig. 3a, b). The intensity of ICUAW was not correlated with the degree of diaphragmatic dysfunction evaluated by magnetic stimulation or by ultrasound (Figs. 2, 3b). Despite sharing the same cellular pathways [41–43], both injury and repair of the diaphragm and limb muscles seem to be differently affected during critical illness with previous medical history, metabolic/nutritional disturbances, sepsis, shock, surgery, immobilization being the most reported factors associated with atrophy and contractility [11–13].

MIP showed a significant correlation ($r = 0.31$; $p = 0.05$) with MRC score (Fig. 3a), consistent with the findings of De Jonghe et al. [44]. MIP measurement should be interpreted not as a specific surrogate of the diaphragm but rather as a global inspiratory muscle assessment involving also the accessory muscles and the patients capacity to participate in the function test [19].

The aim of the present study was to evaluate diaphragm function in ICUAW patients and we only described succinctly the weaning outcome of these patients. Almost half of the patients included were successfully weaned from the ventilator despite showing signs of ICUAW and diaphragm dysfunction (Figs. 2, 3, 4).

In conclusion, in a prospective cohort of 40 critically ill patients with ICUAW and an MRC score below 48 the day of the spontaneous breathing trial, while 32 (80 %) also presented diaphragmatic dysfunction detected using multimodal evaluation of the diaphragm. There was no correlation between the MRC score and the degree of the diaphragmatic dysfunction evaluated by magnetic stimulation. Half of the patients were successfully weaned from the ventilator but mortality in the half that failed the weaning process was 50 %, highlighting the need for further studies aiming to predict weaning success or failure in this very high risk population.

Compliance with ethical standards

Conflicts of interest Boris Jung reports personal fees from Merck (Whitehouse Station, NJ, USA) and Astellas (Tokyo, Japan) without relations with the present study. Samir Jaber reports personal fees from Maquet, Draeger, Hamilton Medical, Fisher Paykel and Abbott without relations with the present study. Pierre Henri Moury, Martin Mahul, Audrey De Jong, Fabrice Gallia, Albert Prades, Pierre Albaladejo, Gerald Chanques and Nicolas Molinari have nothing to disclose related to the subject of the article.

Source of funding This study was supported by University Hospital of Montpellier.

References

1. Fan E, Cheek F, Chlan L et al (2014) An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med 190:1437–1446. doi:10.1164/rccm.201411-2011ST
2. Eikermann M, Latronico N (2013) What is new in prevention of muscle weakness in critically ill patients? Intensive Care Med 39:2200–2203. doi: 10.1007/s00134-013-3132-4
3. Kress JP, Hall JB (2014) ICU-acquired weakness and recovery from critical illness. N Engl J Med 370:1626–1635. doi:10.1056/NEJMra1209390
4. De Jonghe B, Sharshar T, Lefaucheur J-P et al (2002) Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 288:2859–2867
5. Tennilä A, Salmi T, Pettilä V et al (2000) Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med 26:1360–1363
6. De Jonghe B, Bastuji-Garin S, Sharshar T et al (2004) Does ICU-acquired paresis lengthen weaning from mechanical ventilation? Intensive Care Med 30:1117–1121. doi: 10.1007/s00134-004-2174-z
7. Herridge MS, Tansey CM, Matté A et al (2011) Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 364:1293–1304. doi: 10.1056/NEJMoa1011802
8. Hermans G, Van Mechelen H, Clerckx B et al (2014) Acute outcomes and 1 year mortality of ICU-acquired weakness: a cohort study and propensity matched analysis. Am J Respir Crit Care Med. doi: 10.1164/rccm.201312-2257OC
9. Perren A, Brochard L (2013) Managing the apparent and hidden difficulties of weaning from mechanical ventilation. Intensive Care Med 39:1885–1895. doi: 10.1007/s00134-013-3014-9
10. Goligher EC, Fan E, Herridge MS et al (2015) Evolution of diaphragm thickness during mechanical ventilation: impact of inspiratory effort. Am J Respir Crit Care Med. doi: 10.1164/rccm.201503-0620OC
11. Divangahi M, Matecki S, Dudley RWR et al (2004) Preferential diaphragmatic weakness during sustained *Pseudomonas aeruginosa* lung infection. Am J Respir Crit Care Med 169:679–686
12. Jung B, Nougaret S, Conseil M et al (2014) Sepsis is associated with a preferential diaphragmatic atrophy: a critically ill patient study using tridimensional computed tomography. Anesthesiology 120:1182–1191. doi: 10.1097/ALN.0000000000000201
13. Baldwin CE, Bersten AD (2014) Alterations in respiratory and limb muscle strength and size in patients with sepsis who are mechanically ventilated. Phys Ther 94:68–82
14. Levine S, Nguyen T, Taylor N et al (2008) Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358:1327–1335
15. Jaber S, Petrof BJ, Jung B et al (2011) Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med 183:364–371. doi: 10.1164/rccm.201004-0670OC
16. Demoule A, Jung B, Prodanovic H et al (2013) Diaphragm dysfunction on admission to ICU: prevalence, risk factors and prognostic impact—a prospective study. Am J Respir Crit Care Med. doi: 10.1164/rccm.201209-1668OC
17. Picard M, Jung B, Liang F et al (2012) Mitochondrial dysfunction and lipid accumulation in the human diaphragm during mechanical ventilation. Am J Respir Crit Care Med 186:1140–1149. doi:10.1164/rccm.201206-0982OC
18. Mrozek S, Jung B, Petrof BJ et al (2012) Rapid onset of specific diaphragm weakness in a healthy murine model of ventilator-induced diaphragmatic dysfunction. Anesthesiology 117:560–567. doi: 10.1097/ALN.0b013e318261e7f8
19. American Thoracic Society/European Respiratory Society (2002) ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med 166:518–624. doi: 10.1164/rccm.166.4.518
20. Santos PD, Teixeira C, Savi A et al (2012) The critical illness polyneuropathy in septic patients with prolonged weaning from mechanical ventilation: Is the diaphragm also affected? A pilot study. Respir Care 57:1594–1601. doi: 10.4187/respcare.01396
21. Kleyweg RP, van der Meché FG, Schmitz PI (1991) Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain–Barré syndrome. Muscle Nerve 14:1103–1109. doi: 10.1002/mus.880141111
22. Thille AW, Richard J-CM, Brochard L (2013) The decision to extubate in the intensive care unit. Am J Respir Crit Care Med 187:1294–1302. doi: 10.1164/rccm.201208-1523CI
23. Deye N, Lellouche F, Maggiore SM et al (2013) The semi-seated position slightly reduces the effort to breathe during difficult weaning. Intensive Care Med 39:85–92. doi: 10.1007/s00134-012-2727-5
24. Steier J, Kaul S, Seymour J et al (2007) The value of multiple tests of respiratory muscle strength. Thorax 62:975–980. doi: 10.1136/thx.2006.072884
25. Matamis D, Soilemezi E, Tsagourias M et al (2013) Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Med 39:801–810. doi: 10.1007/s00134-013-2823-1
26. Goligher EC, Laghi F, Detsky ME et al (2015) Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med 41:642–649. doi: 10.1007/s00134-015-3687-3

27. DiNino E, Gartman EJ, Sethi JM, McCool FD (2014) Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax 69:431–435. doi:10.1136/thoraxjnl-2013-204111
28. Boles JM, Bion J, Connors A et al (2007) Weaning from mechanical ventilation. Eur Respir J 29:1033–1056
29. Jaber S, Antonelli M (2014) Preventive or curative postoperative noninvasive ventilation after thoracic surgery: still a grey zone? Intensive Care Med 40:280–283. doi:10.1007/s00134-014-3213-z
30. Jaber S, Chanques G, Jung B (2010) Postoperative noninvasive ventilation. Anesthesiology 112:453–461. doi:10.1097/ALN.0b013e3181c5e5f2
31. De Jong A, Jung B, Jaber S (2014) Intubation in the ICU: we could improve our practice. Crit Care 18:209. doi:10.1186/cc13776
32. McCool FD, Tzelepis GE (2012) Dysfunction of the diaphragm. N Engl J Med 366:932–942
33. Kim WY, Suh HJ, Hong SB et al (2011) Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. Crit Care Med 39:2627–2630
34. Umbrello M, Formenti P, Longhi D et al (2015) Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. Crit Care 19:161. doi:10.1186/s13054-015-0894-9
35. Connolly BA, Jones GD, Curtis AA et al (2013) Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. Crit Care 17:R229. doi:10.1186/cc13052
36. Ali NA, O'Brien JM, Hoffmann SP et al (2008) Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med 178:261–268. doi:10.1164/rccm.200712-1829OC
37. Hermans G, Clerckx B, Vanhullebusch T et al (2012) Interobserver agreement of Medical Research Council Sum-Score and handgrip strength in the intensive care unit. Muscle Nerve 45:18–25. doi:10.1002/mus.22219
38. Watson AC, Hughes PD, Harris ML et al (2001) Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. Crit Care Med 29:1325–1331
39. Laghi F, Cattapan SE, Jubran A et al (2003) Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med 167:120–127. doi:10.1164/rccm.200210-1246OC
40. Vivier E, Mekontso Dessap A, Dimassi S et al (2012) Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Med 38:1–8
41. Batt J, dos Santos CC, Cameron JI, Herridge MS (2013) Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. Am J Respir Crit Care Med 187:238–246. doi:10.1164/rccm.201205-0954SO
42. Wollersheim T, Woehlecke J, Krebs M et al (2014) Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med 40:528–538. doi:10.1007/s00134-014-3224-9
43. Jaber S, Jung B, Matecki S, Petrof BJ (2011) Clinical review: ventilator-induced diaphragmatic dysfunction–human studies confirm animal model findings! Crit Care Lond Engl 15:206. doi:10.1186/cc10023
44. De Jonghe B, Bastuji-Garin S, Durand M-C et al (2007) Respiratory weakness is associated with limb weakness and delayed weaning in critical illness*. Crit Care Med 35:2007–2015. doi:10.1097/01.ccm.0000281450.01881.d8
45. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
46. Vincent JL, Moreno R, Takala J et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) Score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707–710
47. Gottesman E, McCool FD (1997) Ultrasound evaluation of the paralyzed diaphragm. Am J Respir Crit Care Med 155:1570–1574. doi:10.1164/ajrccm.155.5.9154859