Impact of sleep alterations on weaning duration in mechanically ventilated patients: a prospective study

Arnaud W. Thille[1,2], Faustine Reynaud[1,2], Damien Marie[1,2], Stéphanie Barrau[1,2], Ludivine Rousseau[1,2], Christophe Rault[1,3], Véronique Diaz[1,3], Jean-Claude Meurice[1,4], Rémi Coudroy[1,2], Jean-Pierre Frat[1,2], René Robert[1,2] and Xavier Drouot[1,3]

Affiliations: [1]INSERM CIC 1402, Groupe ALIVE, Université de Poitiers, Poitiers, France. [2]Réanimation Médicale, CHU de Poitiers, Poitiers, France. [3]Neurophysiologie Clinique et Explorations Fonctionnelles, CHU de Poitiers, Poitiers, France. [4]Pneumologie, CHU de Poitiers, Poitiers, France.

Correspondence: Arnaud W. Thille, Réanimation Médicale, CHU de Poitiers, 2 rue la Milétrie, 86021 Poitiers Cedex, France. E-mail: aw.thille@gmail.com

ABSTRACT   Sleep is markedly altered in intensive care unit (ICU) patients and may alter respiratory performance. Our objective was to assess the impact of sleep alterations on weaning duration.

We conducted a prospective physiological study at a French teaching hospital. ICU patients intubated for at least 24 h and difficult to wean were included. Complete polysomnography (PSG) was performed after the first spontaneous breathing trial failure. Presence of atypical sleep, duration of sleep stages, particularly rapid eye movement (REM) sleep, and electroencephalogram (EEG) reactivity at eyes opening were assessed by a neurologist.

20 out of 45 patients studied (44%) had atypical sleep that could not be classified according to the standard criteria. Duration of weaning between PSG and extubation was significantly longer in patients with atypical sleep (median (interquartile range) 5 (2–8) versus 2 (1–2) days; p=0.001) and in those with no REM sleep compared with the others. Using multivariate logistic regression analysis, atypical sleep remained independently associated with prolonged weaning (>48 h after PSG). Altered EEG reactivity at eyes opening was a good predictor of atypical sleep.

Our results suggest for the first time that brain dysfunction may have an influence on the ability to breathe spontaneously.

Introduction

In the intensive care unit (ICU), performing a spontaneous breathing trial (SBT) before extubation of intubated patients enables assessment of their ability to breathe on their own without a ventilator. Weaning is considered as difficult when the first trial has failed and weaning is delayed at least 24 h [1–3]. Difficult weaning occurs in ~25–50% of ICU patients [3–7] and the longer the weaning duration, the higher the mortality [3–7]. Accordingly, identification of the reasons for weaning failure is crucial.

Switching from mechanical to spontaneous ventilation may unmask latent left ventricular heart failure [8] and subsequent weaning-induced pulmonary oedema is one of the most common causes of respiratory distress leading to SBT failure [9–11]. Diaphragmatic dysfunction at the time of weaning may also correlate clinically with hypoventilation and inefficient cough, and several studies have shown this to be associated with longer weaning times and higher weaning failure rates [12, 13]. It has also been suggested that delirium may promote weaning failure and delayed extubation [14, 15]. However, patients with delirium were also more severe and the actual impact of delirium on weaning duration consequently remains unclear.

Sleep is an essential physiological activity that is severely altered in ICU patients under mechanical ventilation [16–20]. In these patients, sleep is characterised by a high proportion of light sleep (mainly stages 1 and 2), fragmented by numerous awakenings, and with a loss of the circadian rhythm, *i.e.* sleep occurring during the daytime as well as during the night [16–20]. Deep sleep (sleep stage 3) and rapid eye movement (REM) sleep, which are two essential stages of sleep, may completely disappear under mechanical ventilation, even in patients conscious and not under sedation [19]. In some ICU patients, normal sleep architecture may disappear and be replaced by electroencephalogram (EEG) aspects suggesting atypical sleep recordings that cannot be classified according to the standard criteria [20–23]. Atypical sleep, characterised by the absence of stage 2 markers (absence of K complexes and sleep spindles), is a form of sleep frequently observed in ICU patients [20–23]. Loss of normal sleep may alter inspiratory muscle endurance in healthy subjects [24] and possibly lead to neurobehavioral disorders such as ICU delirium [25]. However, the influence of sleep on respiratory performance and weaning duration in patients under mechanical ventilation has never previously been studied. Consequently, we aimed to assess the potential impact of altered sleep quality on weaning duration in ICU patients.

Methods

Design and setting

We conducted a prospective single-centre physiological study between December 2014 and June 2017 at the medical ICU of the University Hospital of Poitiers (Poitiers, France). The study was approved by the independent ethics committee of Poitiers and was registered at ClinicalTrials.gov (identifier NCT02920281).

Patients and/or their next of kin were informed and gave their consent before being included in the study. All patients intubated for at least 24 h and difficult to wean, *i.e.* those who experienced at least one SBT failure, could be included. Patients with continuous sedation or neuroleptic medication and those with central nervous system disorders were not included.

Sleep assessment

Sleep was evaluated by complete polysomnography (PSG) that started in the afternoon following SBT failure and was continuously performed until the next morning. A trained investigator positioned the electrodes, which consisted of six EEG channels (F3-A2, F4-A1, C4-A1, C3-A2, O2-A1 and O1-A2) referenced to the contralateral mastoid according to the international 10-20 system for electrode placement [26]. Two electromyograms (EMGs) (chin) and two electro-oculograms (EOGs) were recorded to score REM and non-REM sleep. Sleep recordings were manually scored by a neurologist blinded to the patient's status. Duration of REM sleep and non-REM sleep stages including deep sleep (*i.e.* sleep stage 3) was assessed using the standard 2007 criteria of the American Academy of Sleep Medicine [27]. The presence of atypical sleep, a form of sleep frequently observed in ICU patients [20–23], was detected according to a recent classification [23]. Indeed, due to the absence of stage 2 markers (absence of K complexes and sleep spindles) atypical sleep cannot be classified according to the standard criteria. It is no longer possible to identify the three usual non-REM sleep stages and only REM sleep can still be detected. It nevertheless remains possible to differentiate the sleep state from the wakefulness state and to thereby quantify sleep duration. To be able to differentiate atypical sleep from pathological wakefulness characterised by excessive slow wave activity, an eyes opening test was systematically performed by the neurophysiologist before PSG in order to assess the EEG frequency in the wakefulness state. EMG and EOG were more active during wakefulness than during sleep, while a decreased EMG was required as evidence of REM sleep.

Assessment of EEG reactivity at eyes opening

EEG reactivity at eyes opening was assessed during wakefulness by the neurologist investigator (X. Drouot) at the beginning of PSG according to the EEG rhythm on an O2-A1 electrode as previously described [23]. Immediate disappearance or frank attenuation (>90%) of the background EEG rhythm at eyes opening, which was replaced by fast low-amplitude frequencies and maintained as long as the eyes were open, was considered as normal EEG reactivity. Moderate and brief attenuation (30–50% decrease in amplitude) was considered as altered EEG reactivity. Undetectable or a very small difference between EEG patterns with the eyes closed and the eyes open was considered as no EEG reactivity.

Clinical assessment

Strength of limb muscles was measured at the time of PSG using the Medical Research Council (MRC) score and ICU-acquired paresis was defined as a MRC score <48 points [28]. Strength of inspiratory muscles and neural drive were assessed with a portable monitor by measuring maximal inspiratory pressure (MIP) and negative airway pressure generated against occlusion during the first 0.1 s of spontaneous inspiration ($P_{0.1}$).

Neurological function was clinically assessed at the time of PSG by measuring the Richmond Agitation–Sedation Scale (RASS) for consciousness [29] and the Intensive Care Delirium Screening Checklist (ICDSC) for delirium [30]. Altered consciousness was defined as RASS <0 and delirium was defined as ICDSC ⩾4. As the dose of sedation may promote delirium [31], we collected the cumulative dose of hypnotics and analgesics used for sedation from intubation to PSG.

Weaning protocol

Weaning duration was defined as the time elapsed between PSG and extubation. All intubated patients were screened every morning and a SBT was systematically performed using a T-piece for 1 h in all patients who fulfilled the following weaning criteria: patient awake without continuous infusion of sedation, arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) ⩾92% with inspiratory oxygen fraction (F_{IO_2}) ⩽0.4 and positive end-expiratory pressure ⩽8 cmH$_2$O, and no need for vasopressors. In the case of SBT failure, a once-daily SBT was performed every day until extubation, whereas in the case of SBT success patients were extubated on the day of the trial. Failure of SBT was defined as the development of any of the following events: respiratory rate >35 breaths·min^{-1}, S_{pO_2} persistently <90% (on F_{IO_2} 0.4), heart rate persistently >140 beats·min^{-1}, systolic blood pressure <90 or >180 mmHg, increased accessory muscle activity, profuse sweating, appearance of mottling, agitation, or depressed mental status.

Statistical analysis

Continuous variables were expressed as median (interquartile range (IQR)) and qualitative variables were expressed as number (percentage).

Patients with altered sleep, *i.e.* with atypical sleep or no REM sleep, were compared with those with normal sleep using the nonparametric Fisher exact test for categorical variables and the Mann–Whitney test for continuous variables. Kaplan–Meier curves were plotted to assess time from PSG to extubation in patients with atypical sleep or no REM sleep and in those with normal sleep, and also in patients with altered EEG reactivity or delirium and in those with normal EEG reactivity or no delirium, and compared by the log-rank test. Based on our previous studies on weaning [32, 33], we estimated a mean weaning duration of ~3±2 days in the case of difficult weaning. Considering that a difference of at least 2 days could be clinically significant, we estimated that weaning duration could be 2 days in patients with normal sleep and 4 days in patients with altered sleep. To show such a difference with a risk of 0.05 and a power of 90%, around 40–45 patients were needed.

Patients with prolonged weaning *versus* those with short weaning were compared using the nonparametric Fisher exact test for categorical variables and the Mann–Whitney test for continuous variables. Weaning was considered as prolonged when weaning duration was longer than the median duration in our population. Variables associated with prolonged weaning were assessed by means of multivariate logistic regression analyses with the use of a backward selection procedure. A two-tailed p-value <0.05 was considered as statistically significant. All analyses were performed using the R statistical package (www. R-project.org).

Results

Over a 30-month period, 45 patients were retained in the analysis (figure 1). The main reason for intubation was acute respiratory failure in 37 patients (82%), shock in five patients (11%), cardiac arrest in two patients (4%) and surgery in one patient (2%). All patients were extubated, but three were re-intubated and three died without re-intubation.
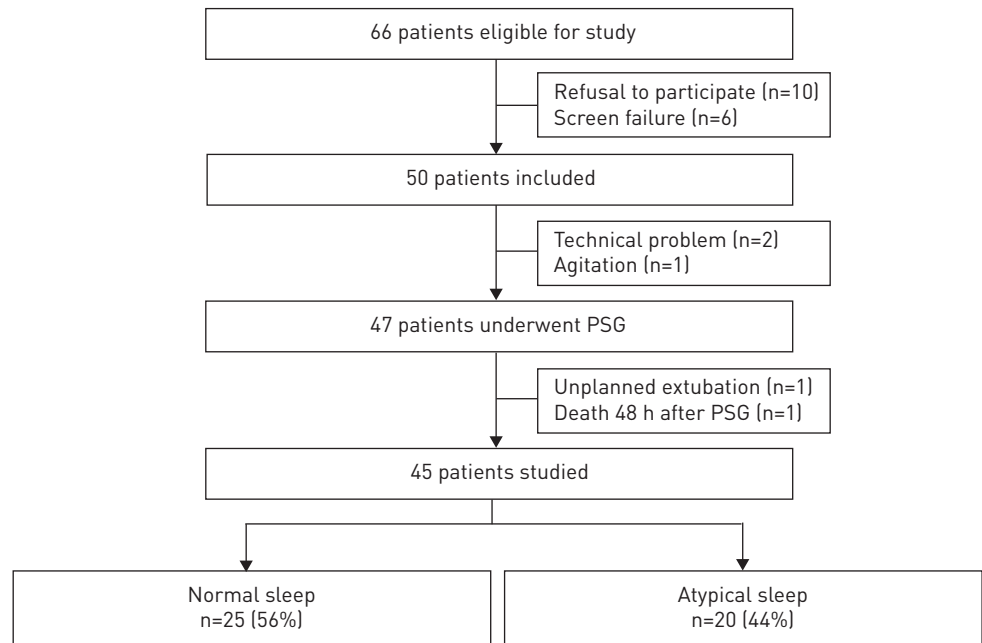
FIGURE 1 Flowchart of the study. PSG: polysomnography.

PSG was performed the night following the first SBT failure in 33 patients (73%), the second night in six patients (13%), the third night in three patients (7%) and the fourth night in the other three patients (7%). At the time of PSG, 32 patients (71%) were awake, alert and calm (RASS 0), four patients were restless (RASS +1), four patients were drowsy (RASS −1), and five patients were lightly sedated (RASS −2). The proportion of patients with delirium was 36% (16 out of 45 patients).

Altered sleep

Atypical sleep was found in 20 out of the 45 patients (44%). Duration of weaning was significantly longer in patients with atypical sleep than in those with normal sleep (median (IQR) 5 (2–8) versus 2 (1–2) days; p<0.001 by log-rank test) (figure 2). Weaning duration was also significantly longer in patients with no REM sleep compared with the others (median (IQR) 4 (2–7) versus 2 (1–2) days; p=0.03 by log-rank test). Prior to PSG, patients with atypical sleep had received more sedation and been under mechanical ventilation for a longer duration than patients with normal sleep (table 1). However, at the time of PSG, the level of consciousness and the delirium score did not differ between patients with atypical sleep and those with normal sleep. The proportion of patients with delirium was 40% (eight out of 20 patients) in those with atypical sleep and 32% (eight out of 25 patients) in those with normal sleep (p=0.58). At the
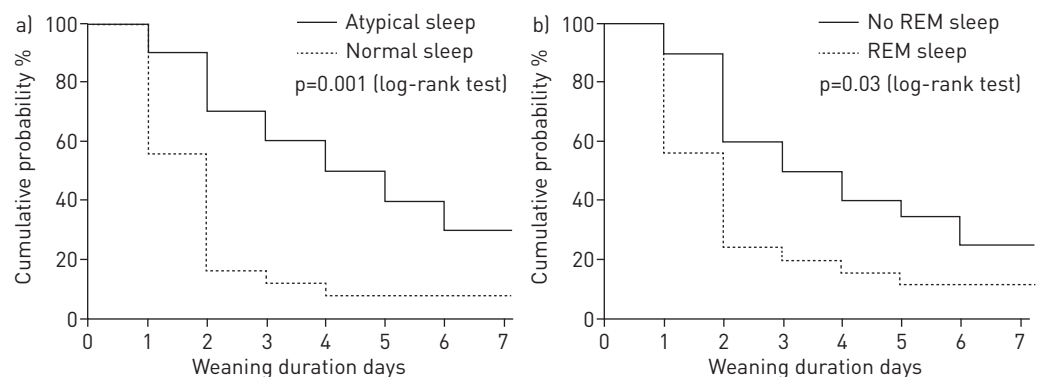

FIGURE 2 Kaplan–Meier curves showing weaning duration from polysomnography to extubation and the cumulative probability of remaining intubated under mechanical ventilation according to a) the presence of atypical sleep or normal sleep and b) the presence or not of rapid eye movement (REM) sleep. Patients with altered sleep, i.e. atypical sleep or absence of REM sleep, had significantly longer durations than the others.

TABLE 1 Comparison of patients with normal sleep *versus* atypical sleep on polysomnography (PSG)

	Normal sleep	Atypical sleep	p-value
Subjects	25	20	
Patient characteristics			
Age years	62 (52–68)	66 (55–75)	0.58
Male	16 (64)	16 (80)	0.33
BMI kg·m^{-2}	30 (26–35)	27 (24–38)	0.66
SAPS II at admission	44 (38–54)	49 (37–64)	0.44
Underlying cardiac disease	9 (36)	6 (30)	0.76
Underlying chronic lung disease	11 (44)	7 (35)	0.76
SBT failure prior to PSG	1 (1–2)	1 (1–1)	0.22
Duration of mechanical ventilation prior to PSG days	5 (4–13)	13 (7–19)	0.02[#]
Length of ICU stay prior to PSG days	6 (4–14)	13 (10–20)	0.02[#]
Days with sedation n	3 (2–9)	10 (6–14)	0.02[#]
Cumulative dose of midazolam mg	360 (144–1200)	1308 (534–2670)	0.02[#]
Sedation-free days at time of PSG n	2 (1–3)	3 (1–5)	0.14
Respiratory parameters at time of PSG			
MIP cmH$_2$O	39 (34–54)	42 (34–61)	0.85
$P_{0.1}$ cmH$_2$O	3.6 (3.4–3.7)	3.6 (3.5–3.8)	0.59
pH	7.43 (7.40–7.46)	7.43 (7.41–7.48)	0.64
P_{CO_2} mmHg	46 (39–54)	42 (40–47)	0.20
P_{aO_2}/F_{IO_2} mmHg	235 (190–270)	233 (184–255)	0.79
Clinical parameters at time of PSG			
SOFA score	3 (2–4)	3 (3–4)	0.26
RASS score	0 (0–0)	0 (−0.3–0)	0.82
ICDSC score	1 (0–4)	3 (2–4)	0.18
Delirium	8 (32)	8 (40)	0.76
MRC score	55 (36–60)	36 (26–57)	0.06
ICU-acquired weakness (MRC score <48)	9 (36)	12/19 (63)	0.13
Severe weakness (MRC score <30)	3 (12)	8/19 (42)	0.03[#]
Sleep duration			
Duration of PSG recording h	17 (16–19)	17 (16–19)	0.93
Sleep duration h	5 (2–7)	3 (2–8)	0.62
Sleep efficiency %	30 (13–39)	19 (11–47)	0.54
Duration of sleep stage 1 min	31 (11–50)	0 (0–0)	<0.001[#]
Duration of sleep stage 2 min	150 (69–206)	0 (0–0)	<0.001[#]
Duration of deep sleep stage 3 min	57 (30–120)	0 (0–0)	<0.001[#]
Duration of REM sleep stage min	31 (0–53)	0 (0–4)	0.001[#]
Sleep quality			
Absence of deep sleep stage 3	2 (8)	20 (100)	<0.001[#]
Absence of REM stage	7 (28)	13 (65)	0.02[#]
Absence of EEG reactivity at eyes opening	0 (0)	12 (60)	<0.001[#]
Altered EEG reactivity at eyes opening	4/23 (17)	18 (90)	<0.001[#]
Outcomes			
Duration of mechanical ventilation after PSG days	2 (1–2)	5 (2–8)	<0.001[#]
Prolonged weaning (>48 h)	4 (16)	14 (70)	<0.001[#]
Total duration of mechanical ventilation days	10 (6–15)	21 (15–29)	<0.01[#]
Length of ICU stay days	13 (9–22)	24 (21–36)	<0.01[#]
Mortality in ICU	1 (4)	4 (20)	0.15

Data are presented as n, median (interquartile range), n (%) or n/N (%), unless otherwise stated. BMI: body mass index; SAPS: Simplified Acute Physiological Score; SBT: spontaneous breathing trial; ICU: intensive care unit; MIP: maximal inspiratory pressure; $P_{0.1}$: negative airway pressure generated against occlusion during the first 0.1 s of spontaneous inspiration; P_{CO_2}: carbon dioxide tension; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; SOFA: Sequential Organ Failure Assessment; RASS: Richmond Agitation–Sedation Scale; ICDSC: Intensive Care Delirium Screening Checklist; MRC: Medical Research Council; REM: rapid eye movement; EEG: electroencephalogram. [#]: p<0.05.

time of PSG, respiratory parameters (including MIP and $P_{0.1}$) did not differ between patients with atypical sleep and those with normal sleep. Although sleep duration was similar in patients with atypical sleep and in those with normal sleep, complete absence of REM sleep was more frequent in patients with atypical sleep (13 out of 20 patients (65%) *versus* seven out of 25 patients (28%); p=0.02) (table 1).

Factors associated with prolonged weaning

The overall median (IQR) duration of weaning was 2 (1–5) days. Patients with prolonged weaning (*i.e.* >48 h after PSG) were more likely to exhibit atypical sleep, no deep sleep or no REM sleep than those with short weaning (table 2). Using multivariate logistic regression, atypical sleep was independently associated with prolonged weaning (OR 13.9, 95% CI 3.2–85.7; p=0.001), even after adjustment on severity score (table 3).

EEG reactivity

EEG reactivity was assessed in 43 patients after excluding two patients who were unable to keep their eyes open/closed for at least 30 s several times in a row. Although duration of weaning was significantly longer in patients with altered EEG reactivity compared with the others (median (IQR) 4 (2–8) *versus* 2 (1–2) days; p=0.0009 by log-rank test), it did not significantly differ between the patients with delirium and

TABLE 2 Comparison of patients with short weaning (<3 days from polysomnography (PSG) to planned extubation) *versus* prolonged weaning (⩾3 days after PSG)

	Short weaning	Prolonged weaning	p-value
Subjects	27	18	
Patient characteristics			
Age years	61 (55–69)	66 (62–76)	0.09
Male	18 (67)	14 (78)	0.51
BMI kg·m^{-2}	31 (26–37)	28 (25–34)	0.42
SAPS II at admission	45 (38–56)	46 (36–61)	0.95
Underlying cardiac disease	9 (33)	6 (33)	0.99
Underlying chronic lung disease	10 (37)	8 (44)	0.76
Duration of mechanical ventilation prior to PSG days	8 (4–13)	13 (5–20)	0.19
Days with sedation n	5 (3–13)	8 (4–14)	0.33
Days with midazolam n	4 (2–9)	8 (2–12)	0.44
Cumulative dose of midazolam mg	552 (213–1644)	1152 (276–2880)	0.34
Respiratory and clinical parameters at time of PSG			
MIP cmH$_2$O	39 (33–56)	43 (34–64)	0.58
$P_{0.1}$ cmH$_2$O	3.6 (3.3–3.8)	3.6 (3.5–3.7)	0.32
pH	7.43 (7.41–7.48)	7.42 (7.36–7.47)	0.39
P_{CO_2} mmHg	45 (38–51)	44 (40–47)	0.83
P_{aO_2}/F_{IO_2} mmHg	233 (193–279)	235 (175–252)	0.33
SOFA score	3 (2–3)	4 (3–6)	0.02[#]
Creatinine µmol·L^{-1}	59 (46–86)	106 (61–284)	0.02[#]
RASS score	0 (−0.5–0)	0 (0–0)	0.17
ICDSC score	2 (0–4)	3 (0.3–4)	0.72
Delirium	10 (37)	6 (33)	>0.99
MRC score	55 (39–60)	31 (24–55)	0.02[#]
ICU-acquired weakness (MRC score <48)	9 (33)	12/17 (71)	0.03[#]
Severe weakness (MRC score <30)	3 (11)	8/17 (47)	0.01[#]
Sleep characteristics			
Sleep duration h	5 (2–7)	4 (2–7)	0.59
Duration of sleep stage 1 min	16 (1–50)	0 (0–0)	<0.01[#]
Duration of sleep stage 2 min	130 (1–45)	0 (0–0)	<0.01[#]
Duration of sleep stage 3 min	36 (0–118)	0 (0–0)	<0.01[#]
Duration of REM sleep stage min	16 (0–52)	0 (0–5)	<0.01[#]
Atypical sleep	6 (22)	14 (78)	<0.01[#]
No deep sleep	8 (30)	14 (78)	<0.01[#]
No REM sleep	8 (30)	12 (67)	0.03[#]
No EEG reactivity at eyes opening	3/26 (12)	9/17 (53)	<0.01[#]
Altered EEG reactivity at eyes opening	8/26 (31)	14/17 (82)	<0.01[#]

Data are presented as n, median (interquartile range), n (%) or n/N (%), unless otherwise stated. BMI: body mass index; SAPS: Simplified Acute Physiological Score; MIP: maximal inspiratory pressure; $P_{0.1}$: negative airway pressure generated against occlusion during the first 0.1 s of spontaneous inspiration; P_{CO_2}: carbon dioxide tension; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; SOFA: Sequential Organ Failure Assessment; RASS: Richmond Agitation–Sedation Scale; ICDSC: Intensive Care Delirium Screening Checklist; MRC: Medical Research Council; ICU: intensive care unit; REM: rapid eye movement; EEG: electroencephalogram. [#]: p<0.05.

TABLE 3 Variables independently associated with prolonged weaning (>48 h after polysomnography (PSG) to extubation)

	Adjusted OR (95% CI)	p-value
SOFA score at time of PSG (by point)	1.66 (1.07–2.88)	0.04
Atypical sleep on PSG	13.9 (3.2–85.7)	0.001

SOFA: Sequential Organ Failure Assessment. All the following variables significantly associated with prolonged weaning with a p-value <0.10 were included in the model: age, SOFA score, intensive care unit-acquired weakness and atypical sleep. The model had an area under the receiver operating characteristic curve of 0.87 (95% CI 0.75–0.97) with a variance inflation factor of 1.03 between the two variables.

those without delirium (figure 3). Patients with atypical sleep were more likely to exhibit altered or no EEG reactivity than patients with normal sleep (table 1). Among the 20 patients with atypical sleep, only two patients (10%) had normal EEG reactivity, whereas 18 (90%) had altered EEG reactivity (including 12 patients with no EEG reactivity). Sleep was atypical among all 12 patients with no EEG reactivity. Altered EEG reactivity permitted prediction of atypical sleep with a sensitivity of 90% (95% CI 67–98%) and a specificity of 83% (95% CI 60–94%), whereas no EEG reactivity predicted atypical sleep with higher specificity (100%, 95% CI 82–100%) but lower sensitivity (60%, 95% CI 36–80%) (table 4).

Discussion

We found that patients with altered sleep, *i.e.* with atypical sleep or absence of REM sleep, had a markedly longer weaning duration than in patients with normal sleep. Patients with atypical sleep had no deep sleep and shorter REM sleep duration, which are the two essential stages of sleep. Atypical sleep was independently associated with prolonged weaning of >48 h after PSG. Although the delirium score did not permit prediction of patients with atypical sleep, detection of altered EEG reactivity at eyes opening seemed to be a good predictor of atypical sleep.

Sleep is an essential physiological activity permitting physical and neurobehavioral restoration. In animals, it has been shown that sleep deprivation could alter physical and cognitive functions [34]. In healthy subjects, sleep deprivation may alter inspiratory muscle endurance [24], and ventilatory response to hypoxia and hypercapnia [35, 36]. Sleep alterations are particularly frequent in mechanically ventilated patients enduring marked reduction or complete absence of deep and REM sleep stages [16, 18–20]. Therefore, altered sleep in ICU patients may have a deleterious impact on respiratory performance and reduce their ability to breathe without a ventilator. To date, the influence of sleep on respiratory performance and on weaning from mechanical ventilation has never been studied. To the best of our knowledge, we found for the first time that altered sleep characterised by atypical sleep or no REM sleep may have a deleterious effect on a patient's ability to breathe on his/her own.
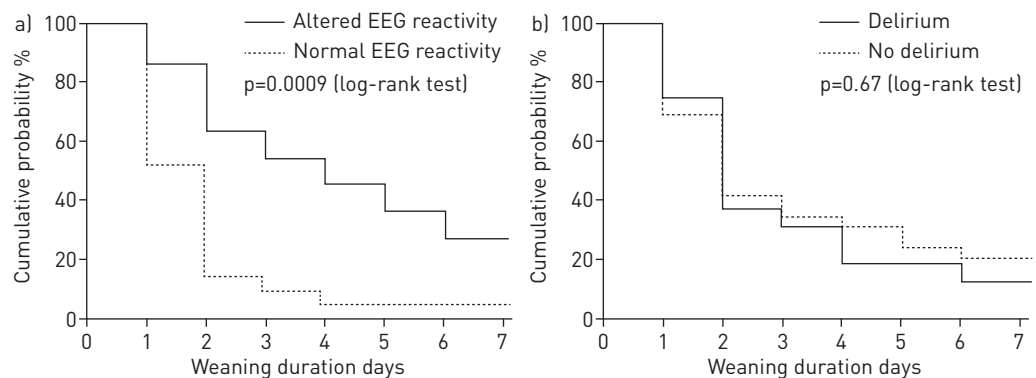

FIGURE 3 Kaplan–Meier curves showing weaning duration from polysomnography to extubation and the cumulative probability of remaining intubated under mechanical ventilation according to a) the presence of altered electroencephalogram (EEG) reactivity or normal reactivity at eyes opening and b) the presence or not of delirium. Although the duration of weaning was significantly longer in patients with altered EEG reactivity compared with the others, it did not significantly differ between the patients with delirium and those without delirium.

TABLE 4 Sensitivity and specificity of electroencephalogram (EEG) reactivity at eyes opening to detect atypical sleep on polysomnography

	Normal sleep n	Atypical sleep n	Sensitivity[#] % (95% CI)	Specificity[¶] % (95% CI)	PPV[+] % (95% CI)	NPV[§] % (95% CI)
Normal EEG reactivity	19	2				
Altered EEG reactivity	4	18	90 (67–98)	83 (60–94)	82 (59–94)	90 (68–98)
No EEG reactivity	0	12	60 (36–80)	100 (82–100)	100 (70–100)	74 (55–87)

Of the 45 patients retained in the study, two patients were excluded because EEG reactivity was not performed or impossible to evaluate. Data are from 43 patients, including 23 patients with normal sleep and 20 patients with atypical sleep. PPV: positive predictive value; NPV: negative predictive value. [#]: true positives/(true positives+false negatives) (true positives were patients with atypical sleep who had altered or no EEG reactivity; false negatives were patients with atypical sleep who had normal EEG reactivity); [¶]: true negatives/(true negatives+false positives) (true negatives were patients with normal sleep who had normal EEG reactivity; false positives were patients with normal sleep who had altered or no EEG reactivity); [+]: proportion of patients with atypical sleep among those with altered or no EEG reactivity; [§]: proportion of patients with normal sleep among those with normal or present EEG reactivity.

In our study, 20 patients exhibited atypical sleep (44%), which is slightly higher than the 28% we previously reported in ICU patients [23], but markedly lower than the 85% reported by another group [21]. In the case of atypical sleep, all sleep stages disappear (absence of deep sleep) except for REM sleep, which can still be detected. No REM sleep was found in 20 patients (44%) in the overall population, which is in keeping with other studies that reported that around half of patients had no REM sleep during the weaning period [37, 38]. However, in addition to the absence of deep sleep, patients with atypical sleep were more likely to exhibit complete lack of REM sleep than the others.

It could be argued that the existence of atypical sleep and the disappearance of REM sleep is not really a sleep alteration, but rather a sign of acute brain dysfunction and a result of greater disease severity. Although we agree with that, atypical sleep seems to be a strong predictor of prolonged weaning even after adjustment on severity score. Prior to PSG, patients with atypical sleep had received more sedation and had spent more time in the ICU than other patients. Consequently, sleep alterations might be favoured by higher doses of sedation or by more pronounced sleep deprivation within the previous days subsequent to longer ICU stay.

Although sedation may alter sleep and favoured delirium, patients with atypical sleep had similar levels of consciousness and delirium scores as the others. In a previous study it was found that patients with delirium had a longer duration of weaning compared with patients without delirium [14]. Unlike our study, delirium was assessed earlier at weaning initiation, *i.e.* long before initial SBT, with an overall prevalence of 67% [14]. Our patients were awake at the time of PSG and had been free from any sedation for several days. All in all, only 36% of them had delirium at the time of PSG, and weaning duration did not significantly differ between patients with delirium and those without delirium. In contrast, patients with altered EEG reactivity had a significantly longer duration of weaning than patients with normal EEG reactivity. The results we obtained on EEG reactivity suggest that this parameter could be a useful means of detecting atypical sleep. No EEG reactivity was particularly specific and all patients with an absence of EEG reactivity at eyes opening exhibited atypical sleep on PSG. Complete PSG is not a routine exam in clinical practice for ICU patients. Although we had few technical problems, assessment of EEG reactivity could be easier to perform and may in many cases detect acute brain dysfunction without full-night PSG. A major limitation of our study is that, while we found frequent sleep alterations at the time of weaning trial failure, we did not repeat PSG or EEG recordings over time to demonstrate whether or not sleep quality was improved at the time of weaning trial success. Although patients were not systematically studied after the first weaning trial failure, we do not believe that delaying PSG would have impacted our results. Indeed, three-quarters of the patients were studied at the first weaning trial and our main objective was to assess the time from PSG (and not the first weaning trial) until extubation. Another limitation is that we did not assess diaphragmatic strength. Diaphragmatic dysfunction could be associated with higher rates of weaning failure [12]. In our study, patients with prolonged weaning also more frequently had limb muscle weakness and we cannot exclude the possibility that they also had more severe diaphragmatic dysfunction. However, it has been shown that altered MIP was correlated with diaphragmatic dysfunction, suggesting that the lower the MIP, the more severe the diaphragmatic dysfunction [39]. Although only surrogates of diaphragmatic function, we found no difference in terms of MIP or $P_{0.1}$ in patients with prolonged weaning compared with those with short weaning.

Although this was a single-centre study including only a small sample of patients, we believe this to be a first strong signal suggesting that sleep alterations may delay extubation of ICU patients who are difficult

to wean. We considered prolonged weaning when weaning duration was >48 h between PSG and extubation, *i.e.* more than the median duration of weaning of our overall population, and we believe that sleep alterations are likely to have an immediate impact on the first days of weaning.

In conclusion, we found that ICU patients under mechanical ventilation with altered sleep, *i.e.* patients with atypical sleep or no REM sleep, had markedly longer weaning duration than did others. Atypical sleep was a strong predictor of prolonged weaning and could be detected using EEG reactivity. Our results show for the first time that brain dysfunction may have an influence on ability to breathe spontaneously in patients under mechanical ventilation.

References

1   Boles JM, Bion J, Connors A, *et al.* Weaning from mechanical ventilation. *Eur Respir J* 2007; 29: 1033–1056.
2   Schmidt GA, Girard TD, Kress JP, *et al.* Official executive summary of an American Thoracic Society/American College of Chest Physicians clinical practice guideline: liberation from mechanical ventilation in critically ill adults. *Am J Respir Crit Care Med* 2017; 195: 115–119.
3   Beduneau G, Pham T, Schortgen F, *et al.* Epidemiology of weaning outcome according to a new definition. The WIND study. *Am J Respir Crit Care Med* 2017; 195: 772–783.
4   Funk GC, Anders S, Breyer MK, *et al.* Incidence and outcome of weaning from mechanical ventilation according to new categories. *Eur Respir J* 2010: 35: 88–94.
5   Sellares J, Ferrer M, Cano E, *et al.* Predictors of prolonged weaning and survival during ventilator weaning in a respiratory ICU. *Intensive Care Med* 2011; 37: 775–784.
6   Tonnelier A, Tonnelier JM, Nowak E, *et al.* Clinical relevance of classification according to weaning difficulty. *Respir Care* 2011; 56: 583–590.
7   Peñuelas O, Frutos-Vivar F, Fernández C, *et al.* Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. *Am J Respir Crit Care Med* 2011; 184: 430–437.
8   Lemaire F, Teboul JL, Cinotti L, *et al.* Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. *Anesthesiology* 1988; 69: 171–179.
9   Cabello B, Thille AW, Roche-Campo F, *et al.* Physiological comparison of three spontaneous breathing trials in difficult-to-wean patients. *Intensive Care Med* 2010; 36: 1171–1179.
10   Caille V, Amiel JB, Charron C, *et al.* Echocardiography: a help in the weaning process. *Crit Care* 2010; 14: R120.
11   Dres M, Teboul JL, Anguel N, *et al.* Passive leg raising performed before a spontaneous breathing trial predicts weaning-induced cardiac dysfunction. *Intensive Care Med* 2015; 41: 487–494.
12   Dres M, Dube BP, Mayaux J, *et al.* Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. *Am J Respir Crit Care Med* 2017; 195: 57–66.
13   Kim WY, Suh HJ, Hong SB, *et al.* Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Crit Care Med* 2011; 39: 2627–2630.
14   Dessap AM, Roche-Campo F, Launay JM, *et al.* Delirium and circadian rhythm of melatonin during weaning from mechanical ventilation: an ancillary study of a weaning trial. *Chest* 2015; 148: 1231–1241.
15   Mehta S, Cook D, Devlin JW, *et al.* Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015; 43: 557–566.
16   Freedman NS, Gazendam J, Levan L, *et al.* Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 2001; 163: 451–457.
17   Parthasarathy S, Tobin MJ. Effect of ventilator mode on sleep quality in critically ill patients. *Am J Respir Crit Care Med* 2002; 166: 1423–1429.
18   Gabor JY, Cooper AB, Crombach SA, *et al.* Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med* 2003; 167: 708–715.
19   Cabello B, Thille AW, Drouot X, *et al.* Sleep quality in mechanically ventilated patients: comparison of three ventilatory modes. *Crit Care Med* 2008; 36: 1749–1755.
20   Cooper AB, Thornley KS, Young GB, *et al.* Sleep in critically ill patients requiring mechanical ventilation. *Chest* 2000; 117: 809–818.
21   Watson PL, Pandharipande P, Gehlbach BK, *et al.* Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. *Crit Care Med* 2013; 41: 1958–1967.

22 Roche Campo F, Drouot X, Thille AW, *et al.* Poor sleep quality is associated with late noninvasive ventilation failure in patients with acute hypercapnic respiratory failure. *Crit Care Med* 2010; 38: 477–485.

23 Drouot X, Roche-Campo F, Thille AW, *et al.* A new classification for sleep analysis in critically ill patients. *Sleep Med* 2012; 13: 7–14.

24 Chen HI, Tang YR. Sleep loss impairs inspiratory muscle endurance. *Am Rev Respir Dis* 1989; 140: 907–909.

25 Flannery AH, Oyler DR, Weinhouse GL. The impact of interventions to improve sleep on delirium in the ICU: a systematic review and research framework. *Crit Care Med* 2016; 44: 2231–2240.

26 Rechtschaffen A, Kales A. A Manual for Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington, US Government Printing Office, 1968.

27 Iber C. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, American Academy of Sleep Medicine, 2007.

28 De Jonghe B, Sharshar T, Lefaucheur JP, *et al.* Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA* 2002; 288: 2859–2867.

29 Ely EW, Truman B, Shintani A, *et al.* Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003; 289: 2983–2991.

30 Bergeron N, Dubois MJ, Dumont M, *et al.* Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med* 2001; 27: 859–864.

31 Kamdar BB, Niessen T, Colantuoni E, *et al.* Delirium transitions in the medical ICU: exploring the role of sleep quality and other factors. *Crit Care Med* 2015; 43: 135–141.

32 Thille AW, Boissier F, Ben Ghezala H, *et al.* Risk factors for and prediction by caregivers of extubation failure in ICU patients: a prospective study. *Crit Care Med* 2015; 43: 613–620.

33 Thille AW, Harrois A, Schortgen F, *et al.* Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011; 39: 2612–2618.

34 Jouvet-Mounier D, Vimont P, Delorme F. Etude des effets de privations de sommeil chez le chat adulte. [Study of the effects of sleep deprivation in the adult cat.] *J Physiol* 1965; 57: 636–637.

35 Cooper KR, Phillips BA. Effect of short-term sleep loss on breathing. *J Appl Physiol* 1982; 53: 855–858.

36 White DP, Douglas NJ, Pickett CK, *et al.* Sleep deprivation and the control of ventilation. *Am Rev Respir Dis* 1983; 128: 984–986.

37 Alexopoulou C, Kondili E, Plataki M, *et al.* Patient–ventilator synchrony and sleep quality with proportional assist and pressure support ventilation. *Intensive Care Med* 2013; 39: 1040–1047.

38 Kondili E, Alexopoulou C, Xirouchaki N, *et al.* Effects of propofol on sleep quality in mechanically ventilated critically ill patients: a physiological study. *Intensive Care Med* 2012; 38: 1640–1646.

39 Jung B, Moury PH, Mahul M, *et al.* Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. *Intensive Care Med* 2016; 42: 853–861.