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Impact of sleep disturbances on outcomes in intensive care units

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Abstract

Background Sleep deprivation is common in intensive care units (ICUs) and may alter respiratory performance. Few studies have assessed the role of sleep disturbances on outcomes in critically ill patients.

Objectives We hypothesized that sleep disturbances may be associated with poor outcomes in ICUs.

Methods Post-hoc analysis pooling three observational studies assessing sleep by complete polysomnography in 131 conscious and non-sedated patients included at different times of their ICU stay. Sleep was assessed early in a group of patients admitted for acute respiratory failure while breathing spontaneously (n = 34), or under mechanical ventilation in patients with weaning difficulties (n = 45), or immediately after extubation (n = 52). Patients admitted for acute respiratory failure who required intubation, those under mechanical ventilation who had prolonged weaning, and those who required reintubation after extubation were considered as having poor clinical outcomes. Durations of deep sleep, rapid eye movement (REM) sleep, and atypical sleep were compared according to the timing of polysomnography and the clinical outcomes.

Results Whereas deep sleep remained preserved in patients admitted for acute respiratory failure, it was markedly reduced under mechanical ventilation and after extubation ($p < 0.01$). Atypical sleep was significantly more frequent in patients under mechanical ventilation than in those breathing spontaneously ($p < 0.01$). REM sleep was uncommon at any time of their ICU stay. Patients with complete disappearance of REM sleep (50% of patients) were more likely to have poor clinical outcomes than those with persistent REM sleep (24% vs. 9%, $p = 0.03$).

Conclusion Complete disappearance of REM sleep was significantly associated with poor clinical outcomes in critically ill patients.

Keywords Sleep, Rapid eye movement sleep, Polysomnography, Intensive care unit, Ventilator weaning, Endotracheal intubation, Airway extubation

Introduction

Sleep is an essential physiological periodic activity permitting physical and neurobehavioral restoration, which can be severely impaired during an ICU stay, especially in mechanically ventilated patients (1–5). In critically ill patients, sleep is characterized by a high proportion of light sleep (mainly stages N1 and N2), fragmented by numerous awakenings, and with loss of the circadian rhythm, with sleep occurring during the daytime as

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well as the night (1–5). Deep sleep (sleep stage N3) and rapid eye movement (REM) sleep, which are two essential stages of sleep, may completely disappear in the ICU, even in patients conscious and not under sedation. In some patients, normal sleep architecture may completely disappear and be replaced by electroencephalogram (EEG) aspects suggesting atypical sleep recordings, characterized by the absence of stage-2 markers (absence of K complexes and sleep spindles) (1, 6–9). Many factors may promote sleep disturbances, including not only underlying disease severity, mechanical ventilation, use of sedation, anxiety, but also aggressive environments including light exposure, noise, pain or factors related to nursing (1–5). Two studies have shown that sleep disturbances may impair ability to breathe without the ventilator in patients under mechanical ventilation, suggesting that brain dysfunction influences the ability to breathe spontaneously (6, 7). In line with these findings, it has been shown in healthy subjects that sleep deprivation may alter respiratory endurance by altering cortical respiratory command (10, 11), and may reduce response to hypoxia and hypercapnia (12, 13). Consequently, sleep disturbances observed in ICU-patients such as atypical sleep or absence of restorative sleep such as deep sleep and REM sleep may impair respiratory function and precipitate respiratory failure.

Few studies have assessed the influence of sleep disturbances on outcomes in critically ill patients. Therefore, we aimed at assessing sleep quantity and quality, and the role of sleep disturbances on outcomes of critically ill patients at different times during their ICU stay, *i.e.* at the beginning of the ICU stay in patients who are breathing spontaneously, during the weaning period in patients still under mechanical ventilation, or in patients who had just been extubated.

Methods

Study design and patients

This is a post-hoc analysis pooling three prospective observational studies assessing sleep by complete polysomnography in critically ill patients admitted to the University Hospital of Poitiers (6, 14, 15). All studies were approved by the independent ethics committee of Poitiers (CPP Ouest III). Patients and/or their next of kin were informed and gave their written consent before being included in studies.

Sleep was assessed in three groups of patients at different times during the ICU stay: 1) at the beginning of the ICU stay in patients breathing spontaneously just after ICU admission for acute hypoxemic respiratory failure (defined as a respiratory rate above 25 breaths per minute or clinical signs suggesting respiratory distress and PaO_2/FiO_2 below 300 mmHg while receiving high-flow nasal oxygen therapy) (15); 2) in patients still under mechanical ventilation with difficult weaning (*i.e.* those who experienced at least one SBT failure) (6); 3) in patients breathing spontaneously just after being extubated, and who were considered at high risk of extubation failure according to the following criteria (14): older than 65 years of age, with any underlying cardiac or chronic lung disease, or intubated for more than 7 days prior to extubation.

All patients were awake, conscious and free from sedation on the day of polysomnography. Patients with altered consciousness, central nervous system or psychiatric disorders, or those receiving sedative agents or neuroleptic medication were excluded. Patients with urgent need for intubation or reintubation and those with do not intubate or do not reintubate order were also excluded.

Sleep assessment and EEG reactivity

Sleep was evaluated by complete polysomnography (PSG) that started in the afternoon 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 (16). 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 (XD). Duration of REM sleep and non-REM sleep stages including light sleep (sleep stages N1 and N2) and deep sleep (sleep stage N3) was assessed using the standard 2007 criteria of the American Academy of Sleep Medicine (17). The presence of atypical sleep was detected according to a modified classification (9), and the duration of atypical sleep was counted in addition to other usual sleep stages. 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. To be able to differentiate atypical sleep from pathological wakefulness characterized by excessive slow wave activity, an eyes-open test was systematically performed by the neurophysiologist before PSG in order to assess EEG frequency in the wakefulness state. EMG and EOG were more active during wakefulness than during sleep, while decreased EMG was required as evidence of REM sleep. EEG reactivity at eyes-open test was assessed during wakefulness by the neurologist at the beginning of PSG according to the EEG rhythm on an O2-A1 electrode as previously described (9). Immediate disappearance or frank attenuation (> 90%) of the background EEG rhythm at eyes-open test, 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.

Sleep quantity and quality

Sleep quantity included measurement of total sleep time, duration of light, deep and REM sleep stages in minutes or hours, and sleep efficiency as the ratio of total sleep time divided by the total recording time in percentage. Sleep quality was assessed by measurement of atypical sleep, and deep sleep or REM sleep (the two most restorative sleep stages). Sleep fragmentation was defined as the number of arousals and awakenings per hour of sleep.

Outcomes

The primary endpoint was the clinical outcome in the ICU. Patients were considered to have poor clinical outcomes according to the group of patients studied. Poor patient clinical outcomes included: 1) need for intubation in patients admitted for acute respiratory failure while breathing spontaneously, 2) prolonged weaning defined according to the weaning classification as a duration of more than seven days between the initial spontaneous breathing trial and extubation (18), and 3) need for reintubation in patients who were included after extubation while breathing spontaneously.

Intubation and reintubation were decided according to well-established criteria used in several large-scale randomized clinical trials coordinated by our team (19–22), and including the following: cardiac or respiratory arrest, hemodynamic failure requiring vasopressors, altered consciousness defined as a Glasgow coma scale below 12, or severe respiratory failure defined by at least two criteria among the following; respiratory rate above 35 breaths per minute, clinical signs suggesting respiratory distress, hypoxemia defined as PaO_2/FiO_2 below 100 mm Hg or FIO_2 at least 80% to maintain SpO_2 at least 92%, or respiratory acidosis defined as pH below 7.25 and $PaCO_2 > 45$ mmHg.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range [IQR, 25th-75th percentiles] according to their distribution, and qualitative variables were expressed as number and percentage. Patient and sleep characteristics were compared between the three cohorts of patients using ANOVA or Kruskal–Wallis as appropriate for continuous variables, and using the $\chi 2$ test for categorical variables.

Comparison between patients with poor clinical outcomes and the others were compared using a Wilcoxon rank-sum test for continuous variables, and the Fisher exact test for categorical variables. A two-tailed p-value < 0,05 was considered as statistically significant. All analyses were performed using the R software version 4.2.1 (www.R-project.org).

Results

One hundred and thirty-one patients had complete polysomnography in the ICU, including 34 patients breathing spontaneously with acute respiratory failure (26%), 45 mechanically ventilated patients with weaning difficulties (34%), and 52 patients breathing spontaneously after extubation (40%) **(**Fig. 1**).** PSG was performed the

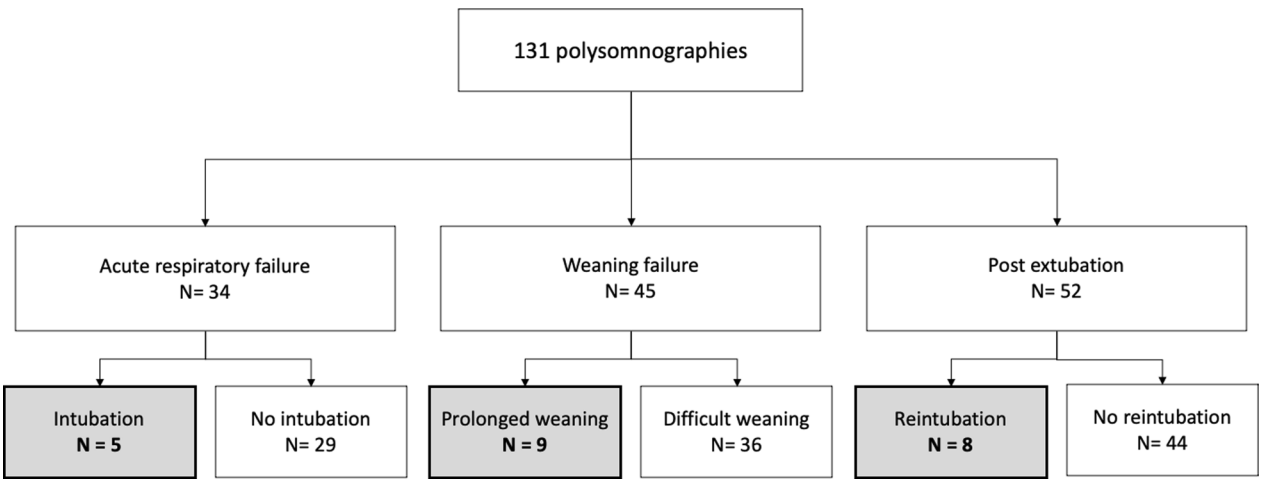

Fig. 1 Flowchart of the patients. Poor outcomes occurred in 22 out of the 131 patients (17%), including patients admitted for acute respiratory failure who needed intubation, patients under mechanical ventilation with prolonged weaning (> 7 days), and extubated patients who needed reintubation

first night after meeting patient eligibility criteria in 87% of cases (114 out of the 131 patients), *i.e.* the first night following ICU admission in patients admitted for acute respiratory failure, following SBT failure in patients with weaning difficulties, or following extubation in the others. No patient received any continuous sedative agents or opioids during polysomnography recordings. The proportion of patients considered as having poor outcomes in ICUs was similar between the three groups: five patients (15%) among the 34 patients included with acute respiratory failure required intubation, nine patients among the 45 patients included under mechanical ventilation had prolonged weaning (20%), and eight patients (15%) among the 52 patients included after extubation required reintubation ($p=0.77$). Mortality in ICU was significantly higher in patients considered as having with poor outcomes than the others: 32% (7 out of 22 patients) vs. 3% (3 out of 109 patients), $p<0.01$.

Comparison of sleep characteristics between the different timings of sleep assessment in the ICU.

Sleep characteristics significantly differed according to the timing of polysomnography in the ICU (Table 1 **and** Fig. 2).

Patients admitted for acute respiratory failure had relatively well-preserved total sleep time (4.2 h [IQR 2.9–6.8] in median) and deep sleep (31% of total sleep time). REM sleep was markedly short and represented only 4.9% of total sleep time. Complete disappearance of REM sleep was observed in 38% of patients (13/34).

Patients included under mechanical ventilation with weaning difficulties had relatively well-preserved total sleep time (4.6 h [IQR 2.1–7.3] in median). Deep sleep and REM sleep were markedly short and represented only 14% and 6% of total sleep time, respectively. Complete disappearance of REM sleep was observed in 44% of patients (20/45).

Patients included after extubation had particularly short total sleep time (2.4 h [IQR 1.1–4.1] in median). Deep sleep was relatively well-preserved (24% of total sleep time) whereas REM sleep was markedly short (3% of total sleep time). Complete disappearance of REM sleep was observed in 63% of patients (33/52).

By comparing the three groups, patients included after extubation were those with the shortest total sleep time and the shortest REM sleep duration ($p<0.01$), whereas patients included under mechanical ventilation were those with the most impaired deep sleep ($p<0.01$) (Fig. 2). In patients under mechanical ventilation, deep sleep was mainly replaced by atypical sleep. Atypical sleep occurred in 44% of patients under mechanical ventilation and in only 19% of patients after extubation and in only one patient admitted for acute respiratory failure ($p<0.01$ between the three groups).

REM sleep was uncommon at any time of the ICU stay, and was completely abolished in 50% of patients (66 out of 131 patients). Complete disappearance of REM sleep occurred in 63% of patients after extubation, whereas it occurred in 44% of patients under mechanical ventilation, and 38% of patients admitted for acute respiratory failure ($p<0.01$ between the 3 three groups).

Comparison of sleep characteristics between patients with poor outcomes and the others.

Characteristics of the patients and severity scores (SAPS II at inclusion and SOFA at inclusion) did not significantly differ between patients with subsequent poor outcomes and those with good outcomes.

Whereas sleep quantity indicated by total sleep time did not differ regardless of the outcomes, sleep quality was significantly more altered in patients with poor outcomes than in the others (Table 2**).** Patients with poor outcomes had shorter duration of light sleep stage and shorter duration of REM sleep stage than those with good outcomes. Whereas duration of deep sleep did not differ between groups, patients with poor outcomes had longer duration of atypical sleep than the others. Patients with complete disappearance of REM sleep were more likely to have poor outcomes than those with persistent REM sleep (24% vs. 9%, $p=0.03$) (Fig. 3). In-ICU mortality did not significantly differ between patients with complete disappearance of REM sleep and those with persistent REM sleep (12% vs. 3%, respectively, $p=0.11$).

Discussion

In this observational study assessing sleep by complete polysomnography in conscious and non-sedated critically ill patients, total sleep time and deep sleep remained well-preserved in patients admitted for acute respiratory failure, whereas it was frequently replaced by atypical sleep in patients under mechanical ventilation. By contrast, total sleep time was markedly reduced after extubation. REM sleep was uncommon at any time of the ICU stay and complete disappearance of REM sleep was significantly associated with poor outcomes.

Sleep characteristics according to the timing of the ICU stay.

To our knowledge, this is the first study comparing sleep characteristics in critically ill patients at different times during their ICU stay. Sleep is deeply altered in ICUs and it is common to observe complete disappearance of the restorative sleep stages of deep sleep and REM sleep, which are sometimes replaced by abnormal sleep called

Table 1 Comparison of patients and sleep characteristics between the different times of inclusion

	Acute respiratory failure (N = 34)	Weaning failure (N = 45)	After extubation (N = 52)	P value
Patient characteristics				
- Age, years	62 ± 11	65 ± 11	67 ± 11	0.14
- Male sex, n (%)	25 (74%)	32 (71%)	35 (67%)	0.82
- Body mass index, kg/m2	27 ± 4	32 ± 11	30 ± 7	**0.04**
- Underlying cardiac disease, n (%)	12 (35%)	15 (33%)	19 (37%)	0.95
- Underlying respiratory disease, n (%)	12 (35%)	18 (40%)	18 (35%)	0.84
- SAPS II at admission, points	31 ± 11	48 ± 16	50 ± 19	**< 0.01**
- Respiratory failure as reason for admission, n (%)	34 (100%)	34 (76%)	43 (83%)	**0.01**
Characteristics at time of polysomnography				
- SOFA severity score, points	4.5 ± 1.9	3.5 ± 1.9	3.4 ± 2.4	0.07
- Previous duration of mechanical ventilation, days	–	11 [4–16]	9 [4–16]	0.56
- pH, units	7.45 ± 0,06	7.43 ± 0,06	7.34 ± 0,11	**< 0.01**
- PaO_2/FiO_2, mm Hg	143 ± 46	233 ± 63	194 ± 137	**< 0.01**
- PCO_2, mm Hg	34 ± 6	47 ± 11	44 ± 14	**< 0.01**
- Delirium, n (%)	0 (0%)	16 (36%)	8 (15%)	**< 0.01**
Sleep quantity				
- Duration of polysomnography recording, hours	16.0 [14.6 -17.6]	17.3 [15.9 -18.8]	16.7 [14.8 -17.4]	0.05
- Total sleep time, hours	4.2 [2.9–6.8]	4.6 [2.1–7.3]	2.4 [1.1–4.1]	**< 0.01**
- Sleep efficiency, %	30 ± 17	31 ± 26	18 ± 15	**< 0.01**
- Duration of light sleep (stage N1), min	12 [6–28]	2 [0–32]	8 [0–28]	0.19
- Duration of light sleep (stage N2), min	146 [60–227]	13 [0–151]	46 [5–79]	**< 0.01**
- Duration of deep sleep (stage N3), min	70 [34–127]	4 [0–67]	17 [0–66]	**< 0.01**
- Duration of REM sleep stage, min	9 [0–28]	3 [0–33]	0 [0–8]	**0.01**
- Duration of atypical sleep, min	0 [0–0]	0 [0–145]	0 [0–0]	**< 0.01**
Sleep quality				
- Fragmentation index, events/hour	28 ± 15	35 ± 21	37 ± 20	0.09
- Absence of deep sleep stage, n (%)	2 (6%)	22 (49%)	15 (29%)	**< 0.01**
- Absence of REM sleep stage, n (%)	13 (38%)	20 (44%)	33 (63%)	**0.04**
- Atypical sleep, n (%)	1 (3%)	20 (44%)	10 (19%)	**< 0.01**
EEG reactivity at eyes-open test				
- Normal reactivity, n (%)	30 (88%)	21 (49%)	33 (69%)	**< 0.01**
- Pathological wakefulness, n (%)	4 (12%)	22 (51%)	15 (31%)	**< 0.01**
Outcomes				
- Poor outcomes, n (%)	5 (15%)	9 (20%)	8 (15%)	0.77
- Mortality, n (%)	4 (12%)	5 (11%)	1 (2%)	0.14

Values are given in mean ± standard deviation and median [25–75 percentiles]

***Abbreviations**: SAPS II = Simplified Acute Physiology Score; PSG = polysomnography; SOFA = Sequential Organ Failure Assessment; REM = Rapid Eye Movement;*

Poor clinical outcome was defined as (1) the need for intubation in patients admitted for acute respiratory failure, 2) prolonged weaning (more than 7 days between the initial spontaneous *breathing trial and extubation) in patients under mechanical ventilation, and 3) the need for reintubation in patients who were included after extubation.*\

atypical sleep (1–3, 5–8). However, sleep studies in ICUs have mainly explored patients under mechanical ventilation having previously received sedation. Sedation favors sleep disturbances and it has been shown that patients having received high doses of sedation had reduced total sleep time and that they were more likely to exhibit atypical sleep (6, 14). Sleep may also directly be altered by mechanical ventilation itself via patient-ventilator asynchronies or sleep apneas, especially those induced by excessive ventilation (4, 5, 23–25). By contrast, few studies have assessed sleep in patients breathing spontaneously either early upon ICU admission or after extubation (14, 26–28). Among those studies, several have included patients treated with noninvasive ventilation and who had hypercapnic encephalopathy, which may also have markedly altered sleep (26, 27). Although all patients

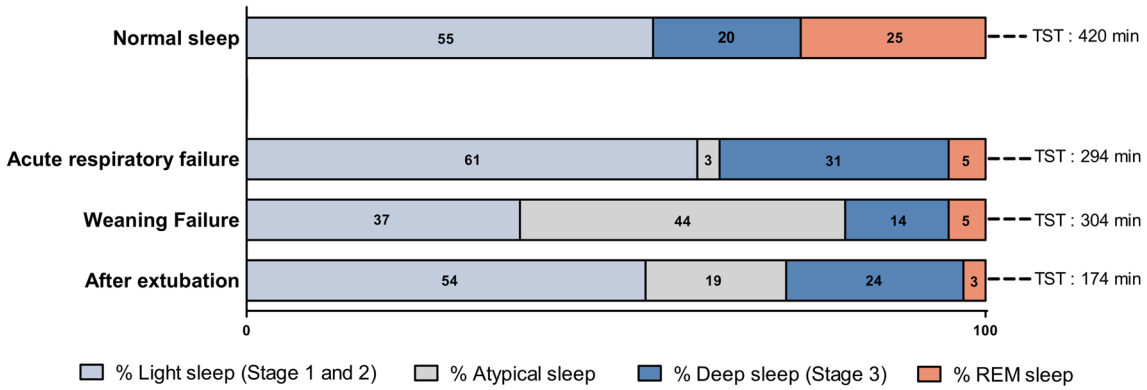

Fig. 2 Distribution of sleep stages according to the timings of polysomnography recordings. From the top to the bottom, theoretical distribution of sleep stages in healthy volunteers with normal sleep, patients with acute respiratory failure explored upon ICU admission while breathing spontaneously, patients under mechanical ventilation with weaning difficulties, and patients explored after extubation while breathing spontaneously. TST = Total Sleep Time

included in the present study were conscious and free of sedation, main sleep disturbances differed according to the timing of the ICU stay and to the course of acute respiratory failure. If atypical sleep was predominant under mechanical ventilation, it may have been because sedation had been stopped shortly before sleep recording. Atypical sleep was still observed after extubation but in a lesser proportion than under mechanical ventilation, probably because it was more distant from sedation cessation. By contrast, atypical sleep was almost non-existent in patients admitted for acute respiratory failure who had never received sedation. In these patients, total sleep time and deep sleep remained preserved, which was not the case in patients breathing spontaneously after extubation, reinforcing the hypothesis that sleep disturbances are mainly favored by sedation or by sleep deprivation after prolonged ICU length of stay. Nevertheless, the only constant sleep alteration observed, whatever the timing of sleep recordings, was frequent disappearance of REM sleep. REM sleep completely disappeared in half of patients, and could be the most reliable marker to assess sleep quality at any time of the ICU stay. During REM sleep, accessory inspiratory muscles are inhibited, and as a result, the diaphragm remains the only active inspiratory muscle (29, 30). Several studies have reported a decreased ventilatory response to hypercapnia and hypoxia during REM sleep leading to hypoxemic episodes (12, 13). Consequently, REM sleep is a sleep stage that may precipitate or worsen underlying respiratory failure, and it might be hypothesized that disappearance of REM sleep is a protective mechanism to cope with respiratory failure. However, disappearance of REM sleep was rather associated with poor clinical outcomes and might be more deleterious to brain function than protective of respiratory muscle function.

Role of sleep disturbances in ICU outcomes

Only a few studies have assessed the role of sleep on the prognosis of critically ill patients (6, 7, 26, 31). Two of these studies showed that mechanically ventilated patients with sleep disturbances were more likely to exhibit weaning difficulties (6, 7). In both studies, not only atypical sleep, but also pathological wakefulness, were particularly frequent and were associated with more prolonged weaning and delayed extubation (6, 7). One of these studies showed that respiratory muscle strength was not more altered in patients with atypical sleep, suggesting that sleep disturbances may evidence brain dysfunction possibly precipitating respiratory failure. In line with these findings, it has been shown that in healthy subjects sleep deprivation may reduce respiratory endurance by altering cortical respiratory command (10, 11). In another prospective study including 52 conscious mechanically ventilated patients, atypical sleep was for the first time shown to be associated with an increased risk of death (31). All of these studies showing potential deleterious effects of atypical sleep on patient outcomes were limited to mechanically ventilated patients (6, 7, 31). Atypical sleep seems mainly observed in mechanically ventilated patients and does not allow assessment of sleep disturbances in all critically ill patients admitted to ICUs. In our study, only one-third of patients were under mechanical ventilation at the time of polysomnography, while the others were breathing spontaneously. This could explain why we did not observe any significant impact of atypical sleep on poor clinical outcomes. By contrast, we showed that disappearance of REM sleep was significantly more frequent in patients with poor clinical outcomes. Even though atypical sleep and disappearance of REM sleep could both be predictors of poor clinical outcomes, complete absence of REM sleep is

Table 2 Characteristics, sleep and reactivity EEG comparison between patients who developed poor outcomes (intubation. prolonged weaning. or reintubation) and the others

	Poor outcomes (N = 22)	Good outcomes (N = 109)	P value
Patient characteristics			
- Age, years	63 ± 10	65 ± 11	0.30
- Male sex, n (%)	15 (68%)	77 (71%)	0.80
- Body mass index, kg/m2	29 ± 6	30 ± 9	0.43
- Underlying cardiac disease, n (%)	8 (36%)	38 (35%)	> 0.99
- Underlying respiratory disease, n (%)	9 (41%)	39 (36%)	0.64
- SAPS II at admission, points	40 ± 16	45 ± 18	0.20
- Respiratory failure as reason for admission, n (%)	19 (86%)	92 (94%)	> 0.99
Characteristics at time of polysomnography			
- SOFA severity score, points	4.0 ± 2.3	3.7 ± 2.1	0.49
- pH, units	7.38 ± 0.08	7.40 ± 0.10	0.15
- PaO_2/FiO_2, mm Hg	194 ± 81	197 ± 108	0.76
- PCO_2, mm Hg	45 ± 13	42 ± 12	0.33
- Delirium, n (%)	5 (23%)	19 (18%)	0.56
Sleep quantity			
- Duration of polysomnography recordings, hours	16.2 [15.4–18.1]	16.7 [15.0 -17.6]	0,91
- Total sleep time, hours	3.7 [1.6–5.3]	3.6 [1.6–6.0]	0.91
- Sleep efficiency, %	26 ± 24	26 ± 20	0.92
- Duration of light sleep (stage N1 + N2), min	33 [0–97]	100 [14–208]	**< 0.01**
- Duration of deep sleep (stage N3), min	14 [0–51]	34 [0–99]	0.23
- Duration of REM sleep stage, min	0 [0–2]	2 [0–24]	**0.02**
- Duration of atypical sleep, min	0 [0–158]	0 [0–0]	**0.02**
Sleep quality, n (%)			
- Fragmentation index, events/hour	29 ± 18	35 ± 20	0.09
- Absence of deep sleep stage, n (%)	9 (41%)	30 (28%)	0.21
- Absence of REM sleep stage, n (%)	16 (73%)	50 (46%)	**0.03**
- Atypical sleep, n (%)	9 (41%)	22 (20%)	0.05
EEG reactivity at eyes-open test			0.18
- Normal reactivity, n (%)	10 (53%)	74 (70%)	
- Pathological wakefulness, n (%)	9 (47%)	32 (30%)	

Values are given in mean ± standard deviation and median [25–75 percentiles]

***Abbreviations**: SAPS II = Simplified Acute Physiology Score; PSG = polysomnography; SOFA = Sequential Organ Failure Assessment; REM = Rapid Eye Movement;*

Poor clinical outcome was defined as (1) the need for intubation in patients admitted for acute respiratory failure, 2) prolonged weaning (more than 7 days between the initial spontaneous *breathing trial and extubation) in patients under mechanical ventilation, and 3) the need for reintubation in patients who were included after extubation*

probably easier to detect than atypical sleep, and may be assessed not only in mechanically ventilated patients, but also in all critically ill patients admitted to ICUs. A previous study showed that low REM sleep stage was associated with poor clinical outcomes in patients admitted to ICU for acute hypercapnic respiratory failure and who were breathing spontaneously (26).

Limitations

Poor outcomes included different events according to the timing of sleep exploration. However, each event was well-established as being associated with poor prognosis. Intubation occurs in around 30 to 50% in patients admitted to ICU for acute hypoxemic respiratory failure and is associated with high mortality rates (19). Reintubation occurs in around 15% of cases after planned extubation, and is associated with an increased risk of death (32–34). Similarly, prolonged weaning, defined as a duration of more than seven days between the initial spontaneous breathing trial and extubation attempt, is well defined in the literature, and also associated with increased risk of death as compared to more simple weaning (18, 35, 36). In our study, patients in whom these events occurred had significantly higher mortality than the others, confirming

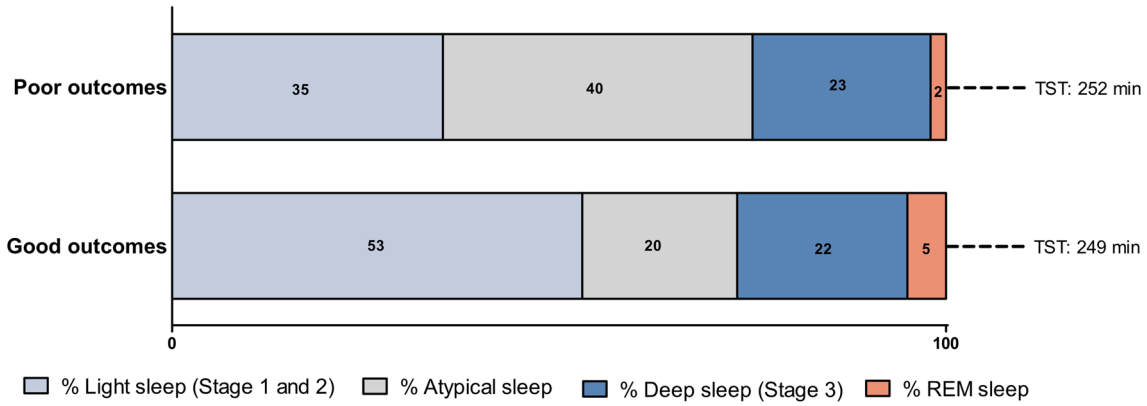

Fig. 3 Distribution of sleep stages according to the clinical outcomes of included patients. Poor outcomes included the need for intubation in patients admitted for acute respiratory failure while breathing spontaneously, prolonged weaning defined (> 7 days) in patients under mechanical ventilation, and the need for reintubation in patients who were included after extubation while breathing spontaneously. TST = Total Sleep Time

that they could be considered as being associated with a poor prognosis. However, we cannot rule out the possibility that patients with sleep disturbances and poor outcomes had increased underlying severity. Further studies are needed to determine whether sleep disturbances may actually contribute to poor clinical outcomes in ICUs.

This is obviously not a longitudinal analysis of sleep including several sleep explorations at different times of the ICU stay of the same patient. Even though we included three distinct populations, patients included under mechanical ventilation and those included after extubation had been admitted to ICU in more than 80% of cases for acute respiratory failure. Therefore, one may consider that sleep was explored in a similar population of patients with acute respiratory failure, and that the differences in sleep characteristics were due mainly to the timing of sleep assessment during the ICU stay.

Addition, polysomnographies were not recorded over an entire 24-h period or over several days, and sleep assessment may consequently have been incomplete. Polysomnographies were started in the afternoon until the next morning to assess sleep periods during the night as well as during the day. Indeed, the circadian rhythm is frequently altered in the ICU, and many patients may have sleep during the day. However, polysomnographies were not recorded during the morning when occur more medical and nursing care, potentially disruptive to sleep. Therefore, we believe that a period of a mean 16 h of recording, as in our study, including the afternoon and night seems reasonable to best assess sleep in the ICU. Another questionable point is that the recordings were not carried out over several days. Nevertheless, no study to date has evaluated sleep using polysomnography over very long periods in ICUs. Polysomnography is a difficult exam to perform in the ICU and even more difficult to record several nights. The clinical condition of patients can rapidly change in the ICU requiring medical interventions such as invasive procedures, or resumption of sedation agents, which may impact sleep. We believe that it will be very difficult to record sleep over several nights until simplified recording devices are available.

Last, the study was performed in a single center and the dramatically low duration of sleep recorded in the present study may have been due to an environment not conducive to sleep in that unit.

Conclusion

In conclusion, complete disappearance of REM sleep was frequently observed in ICUs (50% of patients) and may occur at all times during the ICU stay, as well as in patients breathing spontaneously, after admission or after extubation. Complete disappearance of REM sleep was significantly associated with poor outcomes.

Competing interests

The authors declare no competing interests.

Abbreviations

REM	Rapid Eye Movement
EEG	Electroencephalogram
PSG	Polysomnography
EMGs	Electromyograms
EOGs	Electro-oculograms

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Author contributions

LM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AWT designed the study. LM and AWT wrote the manuscript. SLP performed statistical analysis.

CR, QH and XD analyzed sleep recordings. All authors (LM, CR, SLP, FA, RC, JPF, VB, EMJ, QH, XD, AWT) contributed to drafting of the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Availability of data and materials
No datasets were generated or analysed during the current study.

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