Impact of sleep alterations on weaning duration of mechanically ventilated patients: how much is bad?

To the Editor:

Sleep alterations and deprivation are common in mechanically ventilated patients in the intensive care unit (ICU). However, there is scarce information on how this is associated with mechanical ventilation and outcomes [1]. We therefore read with great interest the report on the effects of sleep alteration on weaning by Thille *et al.* [2]. Those authors have shown that atypical sleep is associated with longer weaning duration but there are some key aspects to take into account in this regard.

Firstly, paroxysmal activity is frequent in unsedated patients who are unresponsive to voice, but the clinical implications of this remain to be determined [3]. Secondly, noise and light are integral parts of any ICU, and environmental noise has been shown to affect arousals and awakenings from sleep [4]. Noise and light levels could be monitored and standardised in future studies. Thirdly, information about bicarbonate levels would have been informative, as this has a negative correlation with sleep efficacy, sleep quality and weaning success [5]. Similarly, further information about patient–ventilator asynchrony or pre-existing sleep-disordered breathing is missing, which could have further confounded these findings [6, 7]. Lastly, weaning duration was defined as the time that elapsed between polysomnography (PSG) and extubation in this study. In this context, the length of stay in the ICU and mechanical ventilation prior to the recording of the PSG is important, and table 1 indicates that the patient groups were not similar in this aspect (*i.e.* atypical sleep groups had a significantly longer duration of ICU stay, mechanical ventilation, cumulative dose and duration of sedation). Although the authors evaluated consciousness and delirium prior to the PSG, and found no difference, we feel that comparing patients with similar ICU stay, mechanical ventilation duration and sedation would have given us better insight, as it would help to avoid selection bias of patients in weaning failure. Neither group of patients received continuous sedatives but the potential implications of sedative drugs (benzodiazepines *etc.*) used before weaning could be important to understand the observed sleep disturbance [8].

Sleep alterations are a frequent observation in critically ill patients; an important question that needs to be addressed is, what are the real consequences and treatment of disturbed sleep in the ICU [9]? This includes our understanding of whether they can resolve over time. The current study restarts the discussion of a controversial hot topic in critical care medicine; yet, it is important to more precisely classify atypical sleep and clinical implications to direct future research.

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From the authors:

Sleep is markedly altered in intensive care unit (ICU) patients under mechanical ventilation [1–4]. Sleep in these patients is fragmented by numerous arousals and awakenings and mainly comprises light sleep. The deep sleep allowing physical restoration and the rapid eye movement (REM) sleep allowing neurobehavioral restoration may completely disappear. In some ICU patients, normal sleep architecture may disappear and be replaced by electroencephalogram aspects suggesting atypical sleep [5–7]. Whereas it has been shown that sleep deprivation could alter physical and cognitive functions in animals [8], the potential deleterious effects of such sleep disturbances in critically ill patients are unknown.

In a recent issue of the *European Respiratory Journal*, we reported that sleep alterations, especially atypical sleep or the absence of REM sleep stage, may be associated with poor outcomes in patients under mechanical ventilation with weaning difficulties [9]. Patients with atypical sleep or no REM sleep on polysomnography had prolonged duration of mechanical ventilation as compared to patients with normal sleep. In their correspondence, A.M. Esquinas and colleagues justifiably raise a number of concerns, and it is a great pleasure to reply and to provide supplementary findings to support our results.

It is true that multiple factors may disrupt sleep in the ICU, particularly noise, light, patient care activities, patient–ventilator asynchronies or central apnoeas, which can provoke numerous arousals and awakenings [1–4]. In ICU patients it has been shown that the sleep fragmentation index, *i.e.* the number of arousals and awakenings per hour of sleep, is very close to that in patients with severe obstructive sleep apnoea syndrome (>30 events·h^{-1}) [1–4]. In our study, sleep fragmentation was high but did not differ between patients with atypical sleep and those with normal sleep (median 33 events·h^{-1} (interquartile range (IQR) 25–40 events·h^{-1}) *versus* 31 events·h^{-1} (IQR 8–46 events·h^{-1}); p=0.57). Although this result was not indicated in our article, it makes it clear that the environment was similar in the two groups.

Another major concern is that patients with atypical sleep could be more likely to have pre-existing sleep disorders, alkalosis or higher levels of bicarbonates, which may induce sleep alterations. In our overall population (45 patients), only two patients had known sleep apnoea syndrome and 12 (27%) had underlying chronic obstructive pulmonary disease (COPD). Although the proportion of COPD patients was similar in the two groups (25% among those with atypical sleep *versus* 28% among those with normal sleep; p>0.99), we cannot exclude the possibility that patients with atypical sleep may have had sleep difficulties before ICU admission. By contrast, the level of bicarbonates on the day of polysomnography did not differ between

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TABLE 1 Comparison of patients with normal sleep *versus* atypical sleep after matching by intensive care unit (ICU) length of stay and cumulative dose of midazolam

	Normal sleep[#]	Atypical sleep[#]	p-value
Patients n	18	18	
Patient characteristics			
Age years	61 (56–65)	68 (54–76)	0.37
Male sex	12 (67%)	14 (78%)	0.71
Body mass index kg·m^{-2}	31 (27–36)	27 (24–36)	0.83
SAPS II at admission	48 (34–56)	49 (38–65)	0.14
Length of ICU stay days[¶,+]	10 (5–14)	13 (8–19)	0.29
Duration of MV days[+]	9 (4–14)	13 (7–18)	0.33
Number of days with sedation[+]	5 (3–11)	8 (5–14)	0.44
Cumulative dose of midazolam mg[¶,+]	528 (264–1848)	1308 (498–2796)	0.21
Respiratory parameters at time of PSG			
Maximal inspiratory pressure cmH_2O	41 (33–53)	41 (34–57)	0.97
$P_{0.1}$ cmH_2O	3.6 (3.4–3.8)	3.6 (3.4–3.8)	0.51
pH	7.43 (7.40–7.47)	7.43 (7.41–7.48)	0.68
Bicarbonates level mmol·L^{-1}	32 (28–35)	27 (25–34)	0.27
P_{CO_2} mmHg	48 (43–56)	42 (40–47)	0.19
P_{aO_2}/F_{IO_2} mmHg	203 (186–238)	217 (179–252)	0.70
Clinical parameters at time of PSG			
SOFA score	3 (2–4)	3 (3–4)	0.60
RASS score	0 (0–0)	0 (−0.8–0)	0.34
ICDSC score	1 (0–3)	3 (1–4)	0.13
Delirium	4 (22%)	8 (44%)	0.29
MRC score	55 (43–60)	34 (25–57)	0.11
ICU-acquired weakness[§]	6 (33%)	11 (61%)	0.18
Outcomes			
Duration of MV after PSG days	2 (1–2)	4 (2–8)	0.01
Prolonged weaning of >48 h	2 (11%)	12 (67%)	0.002

Data are presented as median (interquartile range) or n (%), unless otherwise stated. SAPS: Simplified Acute Physiological Score; MV: mechanical ventilation; PSG: polysomnography; $P_{0.1}$: 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. [#]: evaluated by PSG; [¶]: variable used for propensity score-matched analysis; [+]: prior to PSG; [§]: MRC score <48.

patients with atypical sleep and those with normal sleep (29±6 *versus* 30±6 mmol·L^{-1}; p=0.41). Likewise, the proportion of patients with alkalosis (pH >7.42), which is a major factor for central apnoeas and subsequent arousals [10], was similar in the two groups (45% in patients with atypical sleep (nine out of 20 patients) *versus* 42% in those with normal sleep (10 out of 24 patients); p>0.99). It must also be emphasised that all patients were conscious, responsive to voice and non-sedated, so that paroxysmal activity was unlikely.

Lastly, and this is probably the most important limitation of our study, patients who exhibited atypical sleep on polysomnography had spent more time in the ICU and had received more sedation prior to polysomnography than patients with normal sleep. Consequently, atypical sleep may be rendered more likely by sleep deprivation due to a more prolonged ICU stay, or may simply be the result of acute brain dysfunction due to more marked impregnation with sedative drugs rather than the result of sleep disturbances. We fully agree that we clearly cannot claim that sleep alterations are necessarily the cause of prolonged weaning and delayed extubation.

Given the baseline differences between patients with atypical sleep and those with normal sleep, we performed a propensity score-matched analysis according to their ICU length of stay and cumulative dose of sedation (midazolam) received prior to polysomnography (R software, MatchIt package; www.r-project.org). Baseline characteristics and outcomes of the 36 patients included in the propensity score-matched cohort (80% of the initial population) are displayed in table 1. After matching by ICU length of stay and cumulative dose of sedation prior to polysomnography, the duration of weaning remained significantly longer in patients with atypical sleep than in patients with normal sleep. Using multivariate analysis in this matched cohort, ICU-acquired weakness and atypical sleep were the two independent factors associated with prolonged weaning from mechanical ventilation, with an adjusted odds ratio for atypical sleep of 16.5 (95% CI 2.7–174; p=0.006).

In view of these findings, we therefore believe that a strong relationship might exist between sleep and weaning from mechanical ventilation in the ICU and that sleep alterations may be an underexplored aspect of weaning difficulties.

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