To sleep: perchance to ditch the ventilator

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An adequate quality and quantity of sleep are essential for good health [1, 2]. Sleep loss impairs the function of virtually all systems required to cope with the challenges of critical illness and the intensive care unit (ICU) environment, including respiratory muscle strength [3], neuroendocrine and metabolic function [4–6], immune function [7, 8], and cardiovascular responses [9], and is an important risk factor for psychiatric disorders [10], delirium [11] and death [12].

Patients in ICUs are subjected to numerous sleep-disrupting influences. In addition to pain, discomfort and anxiety related to the primary disorder, they are exposed to excessive noise and light, and nursing/medical interventions [13]. In addition, those on mechanical ventilation have the added discomfort of being intubated and of dealing with a ventilator that, except when an automatically synchronous mode (proportional assist ventilation (PAV) [14] or neurally adjusted ventilatory assist (NAVA) [15]) is used, often forces air in when they are trying to exhale and refuses to give them air when they are trying to breathe in (asynchrony) [16].

It has long been known that ICU patients sleep poorly. Abnormalities include loss of the normal circadian rhythm (sleeping during the day), reduced rapid eye movement (REM) sleep and excessive sleep fragmentation (sleep occurring in multiple short bouts rather than a consolidated block) [17–20]. Most importantly, total sleep time varies widely, from <1 h·day^{-1} to nearly the entire 24 h [17, 18]. This latter observation indicates that a substantial fraction of patients experience severe sleep deprivation [20].

Apart from the above changes in sleep macrostructure, electroencephalography (EEG) patterns during wakefulness and sleep are abnormal in an important fraction of ICU patients such that the sleep records cannot be scored according to the conventional criteria used in non-ICU patients [21]. These abnormalities include absence of spindles and K complexes that characterise non-REM (NREM) stage 2 sleep (atypical sleep) and presence of slow (theta and delta) waves during wakefulness [17, 18, 22]. This last pattern was initially observed in patients in coma [17] or sepsis [18]. More recently, it has become clear that this pattern occurs in many unsedated ICU patients, without sepsis, who are confirmed to be awake by behavioural criteria [22, 23]. DROUOT *et al.* [23] further characterised this pattern (pathologic wakefulness) by absence/attenuation of the usual EEG response to eye opening.

In patients with pathologic wakefulness, EEG can be similar to NREM sleep such that, without confirming wakefulness by behavioural criteria, it is not possible to distinguish wakefulness from sleep by simply observing the EEG [18, 22]. This likely explains cases where excessive sleep time (*e.g.* >10 h per 24 h) was

scored in earlier studies [17, 18]. Since in patients with normal or decreased sleep time, sleep is seriously fragmented [17–19], the majority of ICU patients either suffer from sleep deprivation/fragmentation or an abnormal EEG pattern that resembles that in encephalopathy [24].

The impact of sleep abnormalities on patient outcomes in the ICU has been little explored. There are several reasons to suspect that sleep loss may adversely affect clinical outcome in ICU patients. These include the following reported effects of sleep loss. 1) Reduction in ventilatory responses to hypoxaemia and hypercapnia and in respiratory muscle endurance [3, 25]. Such effects may reduce the patient's ability to be weaned. 2) Impairment of immune responses to infections [7]. 3) Impairment in neurocognitive function [1], resulting in reduced ability of the patient to cooperate with care providers. 4) Increased risk of hallucinations and delirium [26].

Given the high frequency of sleep abnormalities in ICU patients and the multiple potential negative effects of these abnormalities on clinical outcome, information about sleep disturbances and outcome is highly desirable. The only relevant report so far is a study of a few elderly patients (age ~80 years) with severe chronic obstructive pulmonary disease and respiratory failure on noninvasive ventilation (NIV) [27]. Patients who failed NIV had more severe sleep abnormalities. However, delirium was present in a majority of the failures which, along with severe hypercapnia [28], makes it difficult to conclude that sleep abnormalities were due to the ICU environment or that NIV failure was related to abnormal sleep pattern.

In this issue of the *European Respiratory Journal*, THILLE *et al.* [29] report on the relation between atypical sleep and time to weaning in 45 normocapnic patients with difficult weaning. Polysomnography (PSG) was performed soon after the first failed weaning trial. 20 patients had atypical sleep and an absence of REM or deep sleep. Weaning attempts continued daily until extubation. Time to weaning was 3 days longer in patients with atypical sleep (5 *versus* 2 days). Patients with atypical sleep had been longer on mechanical ventilation and in the ICU than those with a "normal" sleep pattern and had received more sedation prior to the PSG. Importantly, however, there was no difference between those with short and long weaning times in these variables (duration of mechanical ventilation, ICU stay or sedation), or in level of consciousness or presence of delirium at the time of the PSG. Sequential Organ Failure Assessment (SOFA) score was higher and muscle weakness was more frequent and severe in patients with long weaning time, and these confound the interpretation. However, in multivariate analysis, which included muscle weakness as a variable, the only variables that significantly affected weaning time were presence of atypical sleep (OR 13.9) with SOFA score being a distant second (OR 1.7). These findings provide strong evidence that the atypical sleep pattern contributed to increased weaning time and was not simply a consequence of more severe physiological abnormalities.

The importance of this study is that it is the first to strongly suggest a causal link between sleep abnormalities and length of mechanical ventilation. This outcome variable importantly affects length of stay in the ICU, with considerable economic implications. In addition, it is strongly associated with long-term outcome and mortality [30, 31]. As such, it should stimulate further research to confirm these findings and to address several relevant unknowns, including the following.

1) Are the current findings [29] limited to difficult-to-wean patients or do they apply to all patients? The answer will determine whether sleep assessment is needed only in patients with difficult weaning. Addressing this issue requires assessment of EEG patterns before the first weaning trial.

2) What is the prevailing mechanism of atypical sleep/pathologic wakefulness? Given that sleep loss is very common in the ICU, and this can result in similar EEG patterns [1], sleep deprivation is obviously a strong candidate. Thus, it is possible that sleep loss, with normal EEG patterns in the early stages of ICU admission, ultimately leads to pathologic wakefulness/atypical sleep later on, resulting in excessive sleep time (or more likely, pathologic wakefulness mistakenly scored as sleep). This would account for the wide range in "sleep times" among ICU patients [17, 18]. On the other hand, similar EEG patterns occur in a variety of metabolic and toxic encephalopathies [24], which may also be present in ICU patients. Distinction between the two possibilities based on current metabolic status (*e.g.* SOFA) may be difficult since sleep deprivation itself may underlie the abnormal SOFA. Sequential PSGs, blood cultures and measurement of metabolic indices beginning early in the ICU admission would allow determination of which occurred first. Documentation of the type of medication used for sedation and for treatment of the primary disorder during such studies may reveal a connection between certain drugs and the abnormal EEG patterns.

3) What other outcomes are affected by the presence of atypical sleep? In this regard, given the impact of sleep on the immune system [7], increased likelihood of developing systemic sepsis and multisystem organ failure is potentially another very important outcome that should be evaluated. The aforementioned protocol, including sequential blood cultures, would address this possibility.

4) Assuming that sleep loss is the mechanism in a significant number of patients, what are the specific causes of sleep loss? The factors that promote sleep disruption in the ICU were reviewed recently [13]. Noise and patient care activities were found to contribute to arousals but only to a small degree [17, 19]. Many medications can affect sleep [32] but their role in the pathogenesis of sleep abnormalities in the ICU has not been established, but should be (see point 2).

Mechanical ventilation, and in particular the ventilator mode, are thought to play a small role in sleep disruption [33, 34]. Three studies compared sleep with an automatically synchronised mode (PAV [35, 36] or NAVA [37]). Although asynchrony during sleep was much reduced with the auto-synchronised modes in all three studies, changes in sleep quality were small and bidirectional, improving in two studies [36, 37] and worsening in the third [35]. This is quite surprising given the considerable discomfort conscious people experience when connected to a ventilator that provides fixed pressure, inspiratory time or volume. This issue should be revisited with different experimental paradigms. Because asynchrony occurs primarily during sleep and obtundation, there is a misconception that the sleep disruptive impact of asynchrony occurs only when the patient is asleep. Hence, such studies focused on evaluating sleep quality under the different modes. However, the presence of asynchrony during sleep simply means that the patient's respiratory mechanics are such that the ventilator mode used is not consistent with synchrony when the patient is unresponsive (high resistance and/or near normal compliance) [16]. In such cases, synchrony during wakefulness results from the patient trying to force the ventilator to become synchronous, by making stronger inspiratory efforts to force triggering early in the patient's inspiratory phase, or to cycle off the ventilator during the expiratory phase by activating expiratory muscles [38]. This kind of interaction during wakefulness may prevent him from falling asleep until he is no longer able to fight sleep, is sedated or is exhausted. Thus, the deleterious effect of an unsuitable ventilation mode may be present only when the patient is awake and the impact would be reduced sleep time and not poor quality during sleep.

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