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Effects of Sedatives on Sleep Architecture Measured With Odds Ratio Product in Critically Ill Patients

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OBJECTIVES: Evaluation of sleep quality in critically ill patients is difficult using conventional scoring criteria. The aim of this study was to examine sleep in critically ill patients with and without light sedation using the odds ratio product, a validated continuous metric of sleep depth (0 = deep sleep; 2.5 = full wakefulness) that does not rely on the features needed for conventional staging.

DESIGN: Retrospective study.

SETTINGS: A 16-bed medical-surgical ICU.

PATIENTS: Twenty-three mechanically ventilated patients who had previously undergone two nocturnal sleep studies, one without and one with sedation (propofol, $n = 12$; dexmedetomidine, $n = 11$).

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Sleep architecture was evaluated with odds ratio product analysis by the distribution of 30-second epochs with different odds ratio product values. Electroencephalogram spectral patterns and frequency of wake intrusions (3-s odds ratio product > 1.75) were measured at different odds ratio product levels. Thirty-seven normal sleepers were used as controls. Compared with normal sleepers, unsedated critically ill patients spent little time in stable sleep (percent odds ratio product < 1.0: 31% vs 63%; $p < 0.001$), whereas most of the time were either in stage wake (odds ratio product > 1.75) or in a transitional state (odds ratio product 1.0–1.75), characterized by frequent wake intrusions. Propofol and dexmedetomidine had comparable effects on sleep. Sedation resulted in significant shift in odds ratio product distribution toward normal; percent odds ratio product less than 1.0 increased by 54% ($p = 0.006$), and percent odds ratio product greater than 1.75 decreased by 48% ($p = 0.013$). In six patients (26%), sedation failed to improve sleep.

CONCLUSIONS: In stable critically ill unsedated patients, sleep quality is poor with frequent wake intrusions and little stable sleep. Light sedation with propofol or dexmedetomidine resulted in a shift in sleep architecture toward normal in most, but not all, patients.

KEY WORDS: dexmedetomidine; mechanical ventilation; propofol; sleep quality

Assessment of sleep quality in critically ill patients is of major importance (1) in view of accumulated evidence that sleep in such patients is of poor quality and quantity (2–5) and of extensive research showing that poor sleep adversely affects the function of several organ systems (6–15). Direct support for the importance of normal sleep in these patients was recently provided in two studies in which patients who displayed abnormal sleep were less likely to pass a weaning trial (15) and stayed longer on the ventilator (16).

Assessment of sleep quality in critically ill patients is, however, not easy. Recent studies have shown that conventional scoring criteria for evaluation of

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sleep and wakefulness are difficult to apply in critically ill patients (17, 18).

Although a widely held belief is that sedation in critically ill patients promotes sleep and thus reduces the detrimental consequences of poor sleep quality (19), the effects of sedatives on sleep are controversial (20–23). A Cochrane systematic review found insufficient evidence to determine whether administration of propofol would improve the quality and quantity of sleep in critically ill patients (24). The discrepancy between studies might be partly due to difficulties in evaluating sleep in these patients using conventional criteria.

The odds ratio product (ORP) is a continuous index of sleep depth measured in 3-second intervals (25). It is derived from powers in different electroencephalogram (EEG) frequencies relative to each other and ranges between 0 (very deep sleep) and 2.5 (full wakefulness). Considerable evidence supports ORP as a measure of sleep depth and arousability (25–29). Recently, ORP was measured in critically ill patients in the weaning phase (15). Patients who failed the weaning trial had markedly reduced time (< 2% of recording time) in full wakefulness (ORP > 2.0).

By measuring sleep depth over short intervals, ORP may reveal subtle effects of sedatives on sleep in critically ill patients. Furthermore, ORP does not rely on spindles or duration of delta waves to determine sleep depth (25) making it insensitive to the technical issues that complicate conventional scoring in these patients (17, 18). In this study, ORP was used to reevaluate sleep and effects of dexmedetomidine and propofol on sleep quality in critically ill patients using data from two previous studies (20, 21).

METHODS

Subjects and Conventional Measurements

Twenty-five critically ill patients from two previous studies (20, 21) who were assigned to receive either propofol (n = 12) or dexmedetomidine (n = 13) during the night were reanalyzed (**Supplemental Digital Content**, http://links.lww.com/CCX/A747). The Ethics Committee of the University Hospital of Heraklion had approved the conduct of these studies (11868-16/10/09, 7244-20/06/2011). The results were compared with those obtained from 38 normal sleepers (30).

Patients' selection criteria were similar in the two studies (20, 21). All patients were on mechanical ventilation for greater than 48 hours, hemodynamically stable, and ventilated on assisted modes. Patients characteristics are shown in **Table S1** (http://links.lww.com/CCX/A744). In both studies, patients were monitored during two consecutive nights, with or without sedation. Noise, nursing, and other interventions were minimized during the nights of the study. In addition, during the nights, light was decreased to a minimum level that did not interfere with patients' assessment. Care was taken to ensure similar environmental conditions among the two study nights. The doses of sedatives were adjusted to maintain either level 3 on the Ramsay Scale (with propofol) or –1 to –2 on Richmond Agitation-Sedation Scale (RASS, with dexmedetomidine) (Table S1, http://links.lww.com/CCX/A744).

Sleep data, obtained with a commercial system (Alice; Respironics, Pittsburgh, PA), were scored manually using standard criteria (31). Digital analysis was performed using Michele Sleep Scoring System (Cerebra, Winnipeg, MB, Canada). ORP was calculated from the EEG recorded between 10 PM and 7 AM in the propofol study and 9 PM to 6 AM in dexmedetomidine study. ORP analysis was performed by an author (M.Y.), who was blinded to patient and sedation status.

ORP Analysis

ORP Calculation. The method of calculating ORP was described in detail previously (25) (Supplemental Digital Content, http://links.lww.com/CCX/A747). Briefly, fast Fourier transform was applied to consecutive nonoverlapping 3-second epochs of EEG (C3/A2 and C4/A1) throughout each recording. For each 3-second epoch, sum of powers was calculated in four different EEG frequency ranges: 0.33–2.33 Hz (slow delta), 2.67–6.33 Hz (range-2), 7.0–14.0 Hz (alpha-sigma), and 14.3–35.0 Hz (beta). ORP in each 3-second epoch is derived from the relationship of powers of these frequency ranges to each other and varies from 0 (very deep sleep) to 2.5 (full wakefulness). ORP less than 1.0 predicts sleep, and ORP greater than 1.75 predicts wakefulness, with greater than 90% accuracy. The range between 1.0 and 1.75 represents unstable sleep with considerable interrater variability in scoring (**Fig. S1**, http://links.lww.com/CCX/A743) (25).

Sleep Architecture, Assessed by ORP, and Effects of Sedatives Thereon. Each 30-second epoch was characterized by an average ORP (average ORP of 10 3-s epochs). The number of 30-second epochs with average ORP within each of 10 ORP deciles covering the entire ORP range (0.0–2.5) was calculated and expressed as percent of total recording time. The effects of sedation on sleep architecture were further characterized by the change in percent of epochs with ORP less than 1.0 (corresponding to stable sleep characterized by minimal wake intrusions and high agreement between scorers) (Fig. S1, http://links.lww.com/CCX/A743), between 1.0 and 1.75 (unstable sleep characterized by frequent wake intrusions), and greater than 1.75 (wakefulness). A sedation-induced increase greater than 5% in the percentage of epochs with ORP less than 1.0 was considered as sleep quality improvement.

EEG Spectral Patterns at Different ORP Levels. Changes in sleep depth are normally associated with paradoxical changes in high- and low-frequency powers (25, 32–35). To determine if the same pattern applies in critically ill patients and whether sedatives alter this pattern, average ORP and average log power in different frequency ranges were calculated for all 3-second epochs within each ORP decile. Significant correlations and their slope (falling, rising, or no significant trend) between log power and ORP were calculated, and the number of patients with negative, positive, and no significant slope was determined for each frequency.

Number of Wake Intrusions in Epochs With Different 30-Second ORP Values. Three-second ORP values vary within the same 30-second epochs staged as sleep and may reach values seen during stage wake (wake intrusions, defined as ORP > 1.75) (25). We measured the number of such intrusions in each 30-second epochs in each subject/condition. Frequency of wake intrusions was averaged for all 30-second epochs within each of the 10 ORP deciles.

Spindle Density. Spindles were identified digitally using a validated algorithm within Michele Sleep Scoring (36, 37). Their density is reported as number/min in non-rapid eye movement sleep.

Statistical Analysis

Continuous variables are reported as means and SD. Normality of distribution was assessed visually by means of normal probability plots. Categorical variables were compared using chi-square or Fisher exact test and continuous variables by one-way analysis of variance and paired and unpaired *t* tests, as appropriate. For each frequency range, Pearson correlation was used to determine the relation between ORP and log power as ORP increased. A two-tailed *p* value of less than 0.05 was considered significant.

RESULTS

ORP analysis was not feasible in two patients from dexmedetomidine study because the EEG signals during the night without sedation were corrupt throughout the files with artifacts. In one normal subject, the record was 11 hours long with the last 4 hours having very little sleep. Accordingly, we could not determine his values during the proper duration of the study. Therefore, 23 patients (Table S1, http://links.lww.com/CCX/A744) (12 with and without propofol and 11 with and without dexmedetomidine) and 37 normal sleepers were analyzed. **Table S2** (http://links.lww.com/CCX/A745) shows conventional sleep scoring.

There were no significant differences in ORP architecture between the two studies at baseline or in the effect of the two drugs (Supplemental Digital Content, http://links.lww.com/CCX/A747; **Figs. S2–S5**, http://links.lww.com/CCX/A743; and **Table S3**, http://links.lww.com/CCX/A746). Accordingly, in the main article, results of both studies were combined and compared with normal sleepers.

Sleep Architecture as Measured by 30-Second ORP Values

Total recording time did not differ between normal sleepers (451 ± 49 min) and patients (Table S2, http://links.lww.com/CCX/A745). Compared with normal sleepers, unsedated critically ill patient spent little time in stable or deep sleep (ORP < 1.0), whereas most of the time were either awake or in a transitional state characterized by frequent wake intrusions (**Figs. 1** and **2**) (individual data in **Fig. S6**, http://links.lww.com/CCX/A743). Sedation caused a significant leftward shift, toward normal, in frequency distribution (Figs. 1 and 2). However, even with sedation, frequency of epochs in deciles that characterize deep sleep (ORP 0.0–0.5) was significantly lower than in normal sleepers (12% vs 28%; $p < 0.001$). In 17 of 23 patients (74%), sedation improved sleep quality by increasing (at least > 5%) the

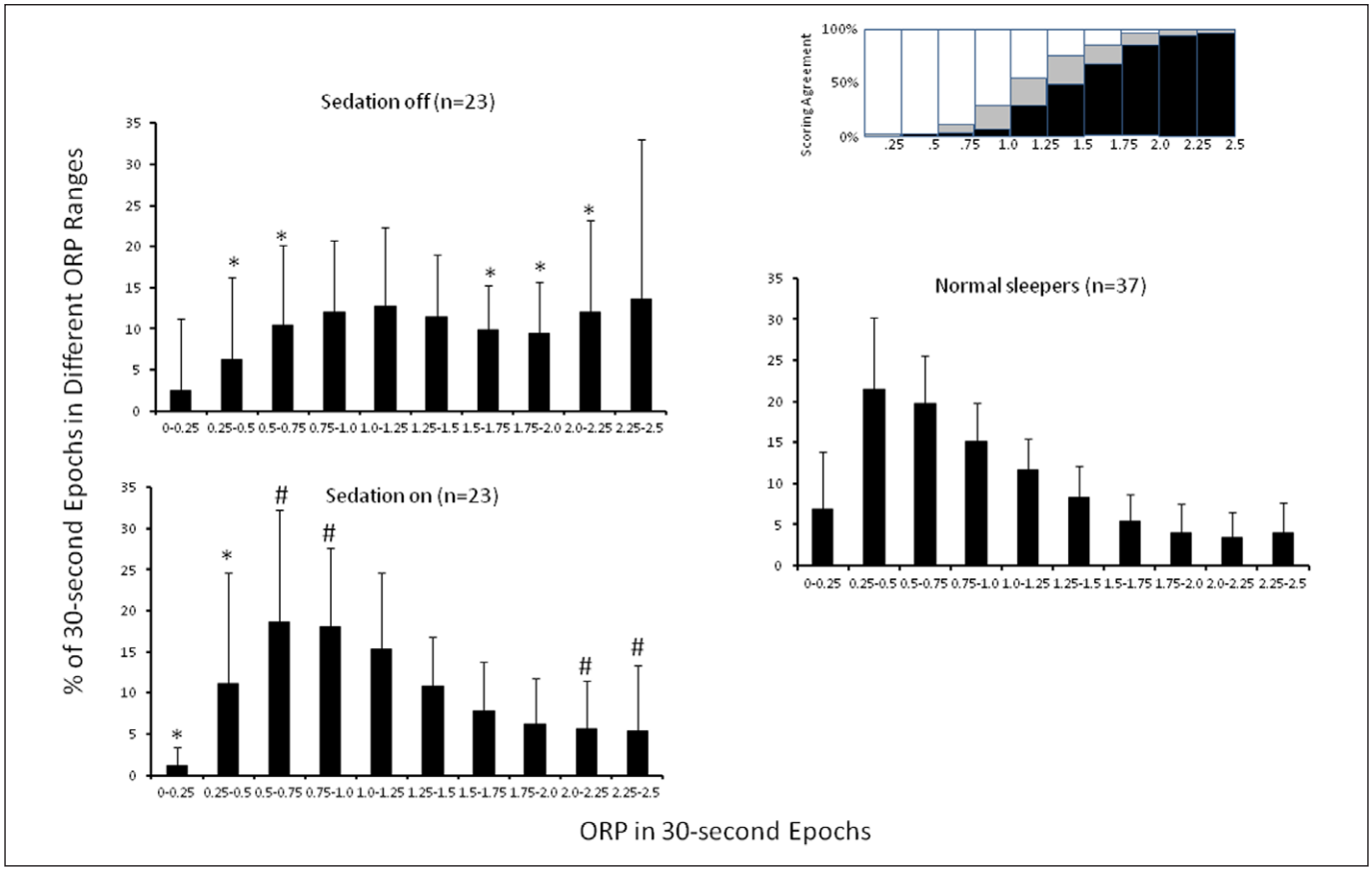

Figure 1. Mean ± SD distribution of 30-s epochs with different odds ratio product (ORP) in normal sleepers and patients with and without sedation. The probability of such epochs being scored wake or sleep by conventional criteria is shown in the upper inset with *black* (wake) and *white* (sleep) zones indicating agreement between two scorers, whereas *gray* zones indicate a split decision. Note that agreement between scorers is very high when ORP is less than 1.0 or greater than 1.75, whereas in the range 1.0–1.75, disagreement between scorers is common. Note the leftward shift in ORP distribution with sedation. *Significantly different from normal sleepers (unpaired *t* test with Bonferroni correction). #Significantly different from patients without sedation (paired *t* test).

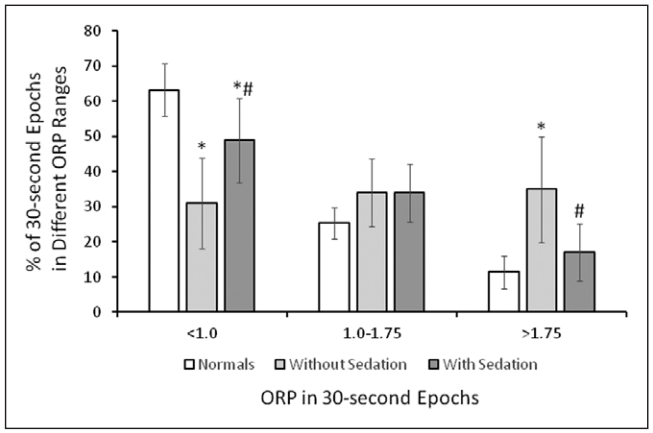

Figure 2. Mean ± SD distribution of 30-s epochs in stable sleep (odds ratio product [ORP] < 1.0), intermediate state (ORP 1.0–1.75), and wake (ORP > 1.75) in normal sleepers and patients with and without sedation. *Significantly different from normal sleepers (unpaired *t* test with Bonferroni correction). #Significantly different from patients without sedation (paired *t* test).

percentage of epochs with ORP less than 1.0 (**Table 1**). In four unsedated patients, sleep efficiency was reported as zero, but ORP showed varying number of epochs with ORP consistent with sleep (**Fig. S7**, http://links.lww.com/CCX/A743).

Without sedation, ORP-determined sleep architecture differed substantially among patients, particularly in the highest decile (ORP > 2.25), where percent of epochs ranged from 0% to 67% (Fig. S6, http://links.lww.com/CCX/A743). Since the effects of sedation might depend on EEG pattern off sedation, patients were divided into two groups, based on median value of percent ORP (%ORP) greater than 2.25 (median, 3.05%) (Supplemental Digital Content, http://links.lww.com/CCX/A747). The distribution of patients into high and low %ORP greater than 2.25 did not differ between propofol and dexmedetomidine studies

TABLE 1.
Individual Change in Percent of 30-Second Epochs Due to Sedation in Three Odds Ratio Product Ranges.

Change in Percent Odds Ratio Product[a]	< 1.0	1.0–1.75	> 1.75
Propofol			
1	40.1	−2.1	−37.9
2	7.8	−1.2	−6.6
3	35.0	−31.1	−66.1
4[b]	−26.7	47.8	−21.0
5	44.6	−13.9	−30.7
6	34.4	32	−66.3
7	52.8	−42.4	−10.5
8	13.4	2.1	−15.5
9[b]	−52.4	16.1	36.3
10[b]	−1.2	0.9	0.3
11	27.2	−21.4	−5.9
12	27.2	−40.7	13.5
Dexmedetomidine			
13	27.3	4.0	−31.3
14	24.6	1.2	−25.8
15[b]	−7.0	16.8	−9.8
16	25.6	39.1	−64.7
17	74.0	−1.1	−72.9
18	37.1	13.5	−50.5
19[b]	−2.8	2.8	0.0
20	39.7	−39.9	0.1
21[b]	−28.9	−12.2	41.1
22	12.2	−22.2	10.0
23	9.6	−13.6	4.0
Mean ± SD	18.0 ± 28.7	−0.14 ± 24.4	−17.8 ± 31.5

[a]Negative value in change in percent odds ratio product (%ΔORP) indicates that sedation decreases the percentage of odds ratio product in this range, whereas positive value an increase.
[b]Sedation did not improve sleep quality in these patients (< 5% increase in %ΔORP < 1.0).

($p > 0.05$, Fisher exact test). The effect of sedation varied significantly between these two groups (**Figs. S8** and **S9**, http://links.lww.com/CCX/A743), being more prominent in the patients with little time in full wakefulness (low %ORP > 2.25 group).

Power Spectral Patterns at Different ORP Levels

As expected (25, 32–35), in normal sleepers, range-2 power (2.67–6.3 Hz) decreased, whereas beta powers increased as ORP increased (**Fig. 3** and **Table 2**). Trends in the other frequencies were variable. Independent on sedation status, distribution of trajectories of beta and gamma powers in patients did not differ from those in normal sleepers. There was a minor but significant difference in distribution of trajectories of alpha-sigma between sedated and normal sleepers. By contrast to normal sleepers, slow delta power in most patients did not change or increased as ORP increased. Although range-2 behaved normally in most patients, with power decreasing as ORP increased, in a substantial minority (9/23), the trend was insignificant or positive due to a paradoxical increase in range-2 power when ORP was greater than 1.75 (Fig. 3) (**Fig. S10**, http://links.lww.com/CCX/A743). There was no difference in the relation between ORP and power spectral patterns with and without sedation.

Number of Wake Intrusions in Epochs With Different 30-Second ORP

In normal sleepers, frequency of wake intrusions was very low when ORP was less than 0.75 and increased progressively as ORP increased further (Table 2). The same pattern was observed in patients independent of sedation status. Although at the same ORP frequency of wake intrusions in patients was lower than in normal sleepers (Table 2), these differences were quantitatively small.

Spindle Density

In patients, spindle density was extremely low relative to normal sleepers (Table 2). Sedation did not affect spindle density.

DISCUSSION

In this study, we used ORP to evaluate sleep and effects of commonly used sedatives thereon in stable critically ill patients. The main findings are as follows: 1) Compared with normal sleepers, almost all unsedated critically ill patients spent most of the time awake (ORP > 1.75) or in a transitional state (ORP 1.0–1.75) characterized by frequent wake intrusions. 2) Propofol and dexmedetomidine had comparable

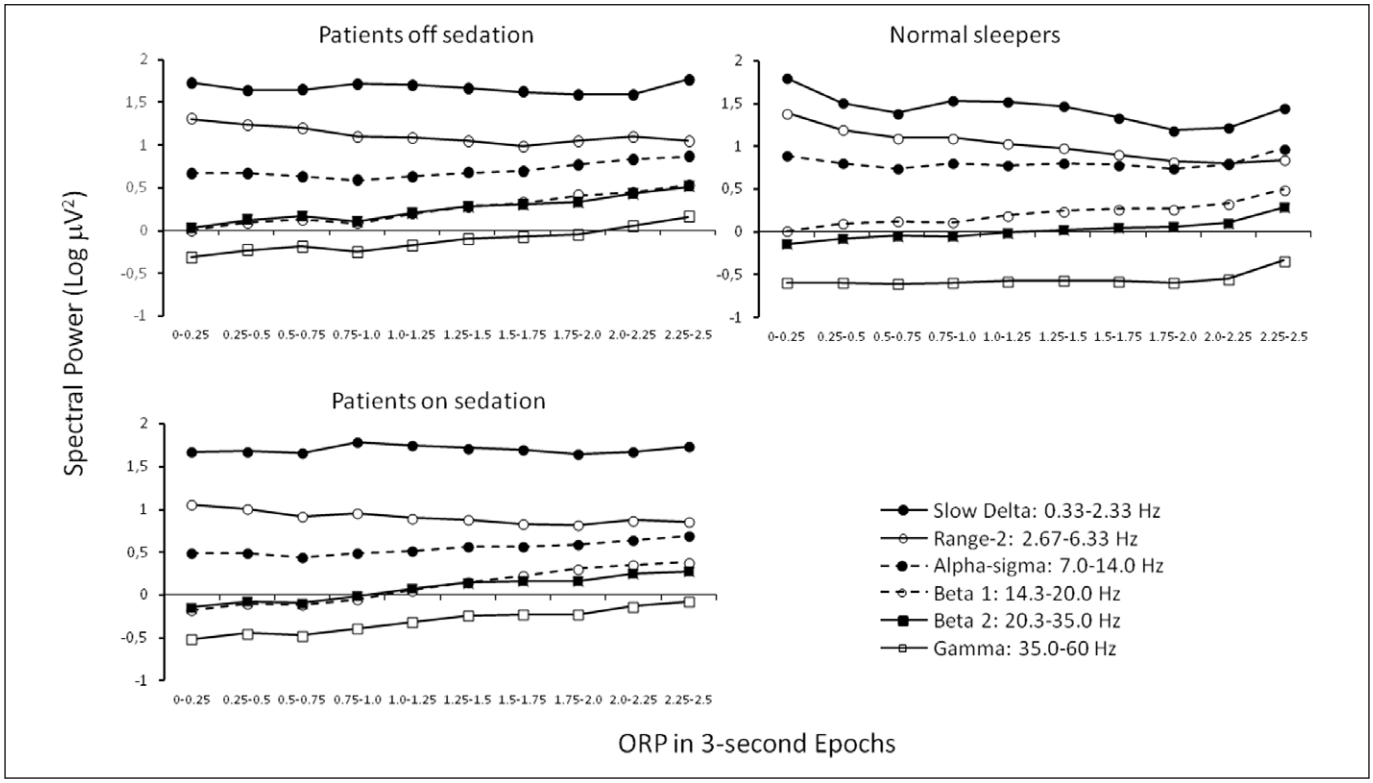

Figure 3. Mean changes in log power in different electroencephalogram frequency ranges (inset) as odds ratio product (ORP) increased from deep sleep (ORP near zero) to full wakefulness (ORP near 2.5). SD was omitted for clarity of presentation.

effects on sleep architecture. Both sedatives at doses titrated to achieve light sedation, resulted in a shift in sleep architecture toward normal. 3) Independent of sedation, there was a tendency for range-2 power (theta and fast delta) to increase concurrently with the increase in beta power at ORP greater than 1.75 in some patients, a pattern that was not observed in normal sleepers. 4) Spindle density was very low on or off sedation. 5) In ≈25% of patients, sedation failed to improve sleep.

In critically ill patients, conventional scoring criteria for evaluation of sleep and wakefulness are difficult to apply due to presence of atypical sleep and/or pathologic wakefulness (15, 17, 18). Given the difficulty of distinguishing conventional stages in critically ill patients, we evaluated the effects of sedation on sleep architecture by the distribution of time among 10 ORP ranges, thus, largely overcoming the shortcomings of conventional sleep scoring (virtual absence of spindles and presence of delta/theta waves during wakefulness). Indeed, the inability of conventional scoring to capture sleep depth is highlighted in four unsedated patients in whom sleep was absent by conventional criteria, but ORP demonstrated considerable sleep depth variability. In three of these four patients, changes in ORP distribution and sleep efficiency with sedation pointed to different conclusions (Fig. S7, http://links.lww.com/CCX/A743).

Except for higher delta/theta power during wake periods in some patients (Fig. S10, http://links.lww.com/CCX/A743), we observed that changes in EEG power spectrum and frequency of wake intrusion as ORP increased were comparable with the changes observed in these EEG variables in ambulatory normal sleepers (Fig. 3). This suggests that the relation between ORP and arousability established in ambulatory subjects (25, 29) applies equally in critically ill patients. Furthermore, the similar effects of the two sedatives on ORP distribution, power spectrum, and wake intrusion (Figs. S2–S5, http://links.lww.com/CCX/A743 and Table S3, http://links.lww.com/CCX/A746) are consistent with recent findings suggesting a common pathway for the action of various sedatives/anesthetics (38).

Sleep pattern varied among unsedated patients. Based on the amount of time in full wakefulness (ORP > 2.25), two distinct groups were identified, low and high %ORP greater than 2.25 groups. Patients with low %ORP greater than 2.25 spent most of the time in an intermediate state between sleep and wakefulness (ORP 1.0–1.75). Although

TABLE 2.
Sleep Variables as Measured With Odds Ratio Product Analysis in Normal Sleepers and Patients Off and on Sedation

	Normal Sleepers	Patients Off Sedation	Patients on Sedation
Number of studies	37	23	23
Number/direction of significant slopes of log spectral power vs ORP[a]			
Slow delta: *n*–, *n*0, *n*+	31, 6, 0	5, 13, 5[c]	4, 16, 3[c]
Range 2: *n*–, *n*0, *n*+	37, 0, 0	14, 8, 1[c]	14, 9, 0[c]
Alpha: *n*–, *n*0, *n*+	4, 25, 8	2, 9, 12	0, 9, 14[c]
Beta 1: *n*–, *n*0, *n*+	0, 0, 37	0, 1, 22	0, 0, 23
Beta 2: *n*–, *n*0, *n*+	0, 0, 37	0, 4, 19	0, 1, 22
Gamma: *n*–, *n*0, *n*+	0, 8, 29	0, 5, 18	0, 2, 21
3-s epochs with ORP > 1.75 per 30-s epoch at different average ORP values[b]			
Average of 30-s ORP, mean ± SD			
0.00–0.25	0.0 0± 0.01	0.00 ± 0.00	0.00 ± 0.00
0.25–0.50	0.16 ± 0.05	0.07 ± 0.10[c]	0.08 ± 0.07[c]
0.50–0.75	0.55 ± 0.10	0.38 ± 0.34	0.43 ± 0.19
0.75–1.00	1.28 ± 0.20	1.01 ± 0.55	0.94 ± 0.25[c]
1.00–1.25	2.27 ± 0.21	1.74 ± 0.56[c]	1.73 ± 0.39[c]
1.25–1.50	3.55 ± 0.24	3.01 ± 0.62[c]	2.88 ± 0.49[c]
1.50–1.75	5.03 ± 0.26	4.62 ± 0.60[c]	4.48 ± 0.60[c]
1.75–2.00	6.69 ± 0.31	6.47 ± 0.48	6.23 ± 0.38[c]
2.00–2.25	8.33 ± 0.30	8.32 ± 0.29	8.10 ± 0.30[c]
2.25–2.50	9.77 ± 0.10	9.65 ± 0.20	9.64 ± 0.20
Spindle density[b], mean ± SD			
Per minute	2.30 ± 1.2	0.16 ± 0.21[c]	0.27± 0.36[c]

n–, *n*0, *n*+ = number of significant negative, nonsignificant, and significant positive slopes of log spectral power vs odds ratio product, respectively, ORP = odds ratio product.

[a]Comparisons were made by Fisher exact test with Bonferroni correction for multiple comparisons.

[b]Comparisons between normal sleepers and unsedated and sedated patients were made by unpaired *t* test with Bonferroni correction and between patients off and on sedation by paired *t* test.

[c]Significantly different from normal sleepers.

sedatives caused a favorable leftward shift in both groups, the correction was less pronounced in the high %ORP greater than 2.25, who spent excessive time in full wakefulness. Whether the latter patients would achieve better sleep with higher doses remains to be determined.

The reason why some unsedated patients had virtually no time with full wakefulness while others had excessive wake time is unclear. There was no difference between the two groups in terms of age, Acute Physiology and Chronic Health Evaluation II, and length of ICU stay. Factors that might contribute include extent of stress encountered by the two groups and susceptibility to sleep deprivation. Different occurrence rate of pathologic wakefulness between groups may also be a factor (15). Further investigations are needed to address this issue.

Some patients displayed excessive fast delta and theta activity when ORP was in the full wakefulness range. In these patients, 30-second ORP values greater than 2.0 need not reflect full wakefulness. Such combination might represent an impaired state of consciousness or pathologic wakefulness (15). It is well known

that during sleep deprivation, theta power increases during wakefulness, and this correlates with the associated cognitive impairment (39–41). This phenomenon is therefore likely related to existing sleep deprivation in these patients. The inability of sedation to modify this pattern further supports this hypothesis, since it is highly unlikely that light sedation for one night can reverse the effect of long-standing sleep deprivation on theta power.

The current study confirmed previous findings (2, 15, 17) regarding the virtual absence of spindles in these patients. We have shown here that number of spindles was not affected by sedation. However, absence of spindles does not necessarily reflect on depth of sleep. Spindles are sporadic events that are important in learning and memory consolidation (42). Although they have historically been used to distinguish N2 from N1 sleep, thereby implying deeper sleep in their presence, there is no evidence that they are markers of deep sleep. In fact, there is considerable evidence to the contrary. For example, spindle density decreases after sleep deprivation, when sleep becomes deeper, and there is an inverse relation between spindle density and delta power (43). Thus, the low spindle density is consistent with sleep deprivation, and their failure to increase with sedation does not indicate that sleep did not improve.

Compared with normal sleepers, unsedated patients spent little time in stable sleep (31% vs 63% with ORP < 1.0). Light sedation improved ORP distribution. However, time in deep sleep (ORP < 0.5) was still considerably lower in patients. In addition, in six of 23 patients (26%), sedation did not improve sleep at the current doses (Table 1). Thus, titration of sedation with widely used sedation scales (Ramsay or RASS) does not guarantee normal sleep. Although it is likely that higher doses may result in better sleep in those who did not respond, individual adjustment of dosage necessitates real-time monitoring of sleep depth. No such methods are currently available. Measuring ORP is much simpler than full polysomnography (only one frontal electrode is adequate), and the results can be analyzed and displayed in real time (44). Whether this approach is practical to titrate sedation in these patients remains to be determined.

Our study has some limitations. First, titration of sedation in the two studies was performed using two different sedation scales. Both scales are used extensively in ICUs and have excellent interrater reliability, and there is a strong correlation between them (45, 46). Second, as recommended (47), both sedatives were administered to achieve light sedation. Thus, it is not known if different doses may change the observed sleep pattern response. Third, stable critically ill patients not requiring sedation were studied several days after ICU admission, and care was taken to ensure environmental conditions that facilitate sleep. Therefore, the results of this study should be applied with caution in a general population of critically ill patients. Finally, sleep was evaluated only during the night, and it is well known that critically ill patients exhibit abnormal sleep/awake state over 24 hours due to pronounced temporal disorganization or disturbances in melatonin secretion (2, 48).

CONCLUSIONS

In conclusion, the current study found that stable critically ill patients spend little time in stable or deep sleep, whereas most of the time are either awake or in a transitional state characterized by frequent wake intrusions. This study also showed that in most patients, light sedation has a favorable effect on sleep quality. These findings point to an approach to normalizing sleep and avoiding the complications of sleep deprivation in these vulnerable patients.

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Drs. Georgopoulos, Kondili, and Younes conceived this work. Dr. Younes performed the odds ratio product analysis. All authors drafted and reviewed the article; all authors read and approved the final article. Drs. Georgopoulos, Kondili, and Alexopoulou participated in the data collection and data analysis.

Dr. Younes developed the odds ratio product used in this study and has a patent on this technology. The technology is licensed to Cerebra Health (Winnipeg). He owns shares in Cerebra and receives royalties from this license. The remaining authors have disclosed that they do not have any conflicts of interest.

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REFERENCES

1. Younes M: To sleep: Perchance to ditch the ventilator. *Eur Respir J* 2018; 51:1800624
2. 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
3. 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
4. Parthasarathy S, Tobin MJ: Sleep in the intensive care unit. *Intensive Care Med* 2004; 30:197–206
5. Beecroft JM, Ward M, Younes M, et al: Sleep monitoring in the intensive care unit: Comparison of nurse assessment, actigraphy and polysomnography. *Intensive Care Med* 2008; 34:2076–2083
6. White DP, Douglas NJ, Pickett CK, et al: Sleep deprivation and the control of ventilation. *Am Rev Respir Dis* 1983; 128:984–986
7. Chen HI, Tang YR: Sleep loss impairs inspiratory muscle endurance. *Am Rev Respir Dis* 1989; 140:907–909
8. Bryant PA, Trinder J, Curtis N: Sick and tired: Does sleep have a vital role in the immune system? *Nat Rev Immunol* 2004; 4:457–467
9. Faraut B, Boudjeltia KZ, Vanhamme L, et al: Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. *Sleep Med Rev* 2012; 16:137–149
10. Khan MS, Aouad R: The effects of insomnia and sleep loss on cardiovascular disease. *Sleep Med Clin* 2017; 12:167–177
11. Davies SK, Ang JE, Revell VL, et al: Effect of sleep deprivation on the human metabolome. *Proc Natl Acad Sci U S A* 2014; 111:10761–10766
12. Spiegel K, Leproult R, Van Cauter E: Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; 354:1435–1439
13. Babkoff H, Sing HC, Thorne DR, et al: Perceptual distortions and hallucinations reported during the course of sleep deprivation. *Percept Mot Skills* 1989; 68:787–798
14. 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
15. Dres M, Younes M, Rittayamai N, et al: Sleep and pathological wakefulness at the time of liberation from mechanical ventilation (SLEEWE). A prospective multicenter physiological study. *Am J Respir Crit Care Med* 2019; 199:1106–1115
16. Thille AW, Coudroy R, Reynaud F, et al: Impact of sleep alterations on weaning duration of mechanically ventilated patients: How much is bad? *Eur Respir J* 2018; 52:1800979
17. 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
18. 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
19. Seymour CW, Pandharipande PP, Koestner T, et al: Diurnal sedative changes during intensive care: Impact on liberation from mechanical ventilation and delirium. *Crit Care Med* 2012; 40:2788–2796
20. 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; 381:640–646
21. Alexopoulou C, Kondili E, Diamantaki E, et al: Effects of dexmedetomidine on sleep quality in critically ill patients: A pilot study. *Anesthesiology* 2014; 121:801–807
22. Treggiari-Venzi M, Borgeat A, Fuchs-Buder T, et al: Overnight sedation with midazolam or propofol in the ICU: Effects on sleep quality, anxiety and depression. *Intensive Care Med* 1996; 22:1186–1190
23. Engelmann C, Wallenborn J, Olthoff D, et al: Propofol versus flunitrazepam for inducing and maintaining sleep in postoperative ICU patients. *Indian J Crit Care Med* 2014; 18:212–219
24. Lewis SR, Schofield-Robinson OJ, Alderson P, et al: Propofol for the promotion of sleep in adults in the intensive care unit. *Cochrane Database Syst Rev* 2018; 1:CD012454
25. Younes M, Ostrowski M, Soiferman M, et al: Odds ratio product of sleep EEG as a continuous measure of sleep state. *Sleep* 2015; 38:641–654
26. Qanash S, Giannouli E, Younes M: Assessment of intervention-related changes in non-rapid-eye-movement sleep depth: Importance of sleep depth changes within stage 2. *Sleep Med* 2017; 40:84–93
27. Kuna ST, Tanayapong P, Maislin G, et al: Odds ratio product: A measure of sleep homeostasis following prolonged wakefulness. *Sleep* 2018; 41:A83
28. Smith MG, Younes M, Aeschbach D, et al: Traffic noise and its impact on sleep depth measured by the odds ratio product. *Sleep* 2019; 42: A54
29. Younes M, Schweitzer PK, Griffin KS, et al: Comparing two measures of sleep depth/intensity. *Sleep* 2020; 43:zsaa127
30. Quan SF, Howard BV, Iber C, et al: The sleep heart health study: Design, rationale, and methods. *Sleep* 1997; 20:1077–1085
31. Iber C, Ancoli-Israel S, Chesson AL, et al: The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, IL, American Academy of Sleep Medicine, 2007
32. Younes M, Giannouli E: Mechanism of excessive wake time when associated with obstructive sleep apnea or periodic limb movements. *J Clin Sleep Med* 2020; 16:389–399
33. Uchida S, Maloney T, Feinberg I: Beta (20-28 Hz) and delta (0.3-3 Hz) EEGs oscillate reciprocally across NREM and REM sleep. *Sleep* 1992; 15:352–358
34. Merica H, Blois R: Relationship between the time courses of power in the frequency bands of human sleep EEG. *Neurophysiol Clin* 1997; 27:116–128

35. Mann K, Röschke J: Different phase relationships between EEG frequency bands during NREM and REM sleep. *Sleep* 1997; 20:753–756
36. Malhotra A, Younes M, Kuna ST, et al: Performance of an automated polysomnography scoring system versus computer-assisted manual scoring. *Sleep* 2013; 36:573–582
37. Goldschmied JR, Lacourse K, Maislin G, et al: Spindles are highly heritable as identified by different spindle detectors. *Sleep* 2020; 44:zsaa230
38. Jiang-Xie LF, Yin L, Zhao S, et al: A common neuroendocrine substrate for diverse general anesthetics and sleep. *Neuron* 2019; 102:1053–1065.e4
39. Gorgoni M, Ferlazzo F, Ferrara M, et al: Topographic electroencephalogram changes associated with psychomotor vigilance task performance after sleep deprivation. *Sleep Med* 2014; 15:1132–1139
40. Finelli LA, Baumann H, Borbély AA, et al: Dual electroencephalogram markers of human sleep homeostasis: Correlation between theta activity in waking and slow-wave activity in sleep. *Neuroscience* 2000; 101:523–529
41. De Gennaro L, Marzano C, Veniero D, et al: Neurophysiological correlates of sleepiness: A combined TMS and EEG study. *Neuroimage* 2007; 36:1277–1287
42. Clawson BC, Durkin J, Aton SJ: Form and function of sleep spindles across the lifespan. *Neural Plast* 2016; 2016:6936381
43. De Gennaro L, Ferrara M: Sleep spindles: An overview. *Sleep Med Rev* 2003; 7:423–440
44. Younes M, Soiferman M, Thompson W, et al: Performance of a new portable wireless sleep monitor. *J Clin Sleep Med* 2017; 13:245–258
45. 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
46. Sessler CN, Gosnell MS, Grap MJ, et al: The Richmond agitation-sedation scale: Validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; 166:1338–1344
47. Devlin JW, Skrobik Y, Gélinas C, et al: Executive summary: Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018; 46:1532–1548
48. Gehlbach BK, Chapotot F, Leproult R, et al: Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. *Sleep* 2012; 35:1105–1114