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Effects of propofol on sleep quality in mechanically ventilated critically ill patients: a physiological study

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Abstract *Purpose:* To access the effect of propofol administration on sleep quality in critically ill patients ventilated on assisted modes. *Methods:* This was a randomized crossover physiological study conducted in an adult ICU at a tertiary hospital. Two nights' polysomnography was performed in mechanically ventilated critically ill patients with and without propofol infusion, while respiratory variables were continuously recorded. Arterial blood gasses were measured in the beginning and at the end of the study. The rate of propofol infusion was adjusted to maintain a sedation level of 3 on the Ramsay scale. Sleep architecture was analyzed manually using predetermined criteria. Patient–ventilator asynchrony was evaluated breath by breath using the flow–time and airway pressure–time waveforms. *Results:* Twelve patients were studied. Respiratory variables, patient–ventilator asynchrony, and arterial blood gasses did not differ between experimental conditions. With or without propofol all patients demonstrated abnormal sleep architecture, expressed by lack of sequential progression through sleep stages and their abnormal distribution. Sleep efficiency, sleep fragmentation, and sleep stage distribution (1, 2, and slow wave) did not differ with or without propofol. Compared to without propofol, both the number of patients exhibiting REM sleep ($p = 0.02$) and the percentage of REM sleep ($p = 0.04$) decreased significantly with propofol. *Conclusions:* In critically ill patients ventilated on assisted modes, propofol administration to achieve the recommended level of sedation suppresses the REM sleep stage and further worsens the poor sleep quality of these patients.

Keywords REM sleep · Sleep efficiency · Respiratory variables · Patient–ventilator asynchrony

Introduction

Sleep abnormalities are extremely common in critically ill patients [1]. These patients exhibit considerable reduction in rapid eye movement (REM) and slow-wave sleep (SWS) and more frequent arousals and awakenings than normal [2, 3]. Although the total sleep time may be normal or even increased, the quality of sleep is poor. As a result, these patients are considered to be qualitatively sleep deprived. The impaired sleep quality may cause cardio-respiratory, neurological, immunological, and metabolic consequences, leading to increased morbidity [4–9].

Mechanically ventilated critically ill patients often receive sedatives to facilitate care [10]. Propofol, a $GABA_A$ agonist, is commonly used in these patients because of its predictable pharmacokinetics [11]. Although this strategy has been advocated to promote sleep [12] and, thus, reverse the detrimental consequences

of sleep deprivation, the effects of propofol on sleep quality in critically ill patients are not well established. Studies have shown that prolonged sedation with propofol in rats is associated with a restorative effect similar to sleep [13]. Propofol administration in sleep-deprived animals results in recovery from sleep deprivation that is not different from that obtained with normal sleep [14]. In normal humans as well as in critically ill patients propofol-induced loss of consciousness is accompanied by the appearance of EEG slow waves that resemble the slow waves of non-REM (NREM) sleep [15, 16]. Nevertheless, in all these studies the doses of propofol were much higher than those recommended in critically ill patients [10]. Indirect data in the literature indicate that at lower dose propofol may adversely affect sleep [17]. The aim of this physiological study was to assess the effects of propofol on sleep quality in a group of critically ill patients ventilated on assisted modes. The rate of propofol infusion was adjusted to maintain a sedation level of 3 on the Ramsay scale (response to commands) [18], as recommended for this group of patients [10].

Methods

Patients

The study, performed between October 2009 and October 2011, was approved by the human studies subcommittee and informed consent was obtained from patients and surrogates. Critically ill patients who had been receiving mechanical ventilation for at least 48 h and who were anticipated to be on assisted modes for two consecutive days were studied. At the time of the study, the patients were hemodynamically stable without vasoactive drugs and ventilated on assisted modes of support through cuffed endotracheal or tracheostomy tubes. We think that it was mandatory for proper interpretation of the results to perform sleep studies in patients not receiving any sedative or opioid, because both may affect sleep architecture; this study design made it possible to compare sleep with and without propofol. Thus, patients not requiring sedation or analgesia with opioids were selected. Exclusion criteria were (1) Glasgow coma scale less than 11; (2) acute physiology score portion of the APACHE II greater than 15 [19]; (3) presence of delirium at the time of the study, as defined by the confusion assessment method for ICU; (4) administration of any sedative drugs or opioids over the last 24 h; (5) detectable plasma levels of sedative drugs (i.e., benzodiazepine, propofol) or opioids (i.e., morphine) before the study; (6) history of epilepsy or any other neurological disease that may potentially have significant effect on the quality of sleep; (7) history of sleep apnea; and (8) ongoing sepsis. The mode of support, level of assist, positive end-expiratory pressure (PEEP), and fractional concentration of inspired O_2 (FIO_2) were determined by the primary physician, who was not involved in the study. Changes either in the mode of support or in the ventilator settings based on the primary physician's judgment resulted in patient withdrawal from the study. Administration of opioids and/or neuroleptic (antipsychotic) medications during the entire study period was also a reason for patient withdrawal. Where necessary, nonsteroidal anti-inflammatory drugs (NSAIDs) were used for analgesia.

Measurements

Polysomnography was performed on each patient as previously described [1]. Sleep architecture was scored manually using standard criteria [20]. Total sleep fragmentation index (TSFI) was calculated as the sum of arousals and awakenings per hour of sleep [20]. Periodic breathing was identified visually [16]. Respiratory variables were measured on a breath-by-breath basis during NREM sleep and in a similar fashion during wakefulness. Major asynchrony, such as ineffective efforts, double triggering, and autotriggering, was evaluated by inspection of flow–time and pressure–time waveforms [21]. Asynchrony index (expressed in percentage) was calculated as the number of asynchrony events divided by the total respiratory rate computed as the sum of the number of ventilator cycles (triggered or not) and of ineffective efforts [22].

Study protocol

All studies were performed between 10:00 p.m. and 7:00 a.m. in a single room in the ICU with the window blinds closed. Noise, nursing, and other interventions were minimized during the night of the study. Light was decreased to a minimum level that did not interfere with patient's assessment. Care was taken to ensure similar environmental conditions between the two study nights.

Each patient was studied during two consecutive nights with or without propofol in a random order. On the propofol night, a bolus of 0.01–0.05 mg/kg of propofol was given over 2 min at 10.00 p.m. followed by continuous infusion at a rate that was adjusted to maintain a sedation level of 3 on the Ramsay scale [18]. In order to prevent bias in propofol administration, only two highly experienced physicians were responsible for propofol titration (EK and CA, senior intensivists) and did not have access to EEG. Continuous infusion was stopped at 7.00 a.m. Apart from this time interval the patients did not receive any sedation throughout the study. If there was need for sedation as judged by the primary physician, the patient was withdrawn from the study. On both experimental conditions arterial blood gasses were measured in the beginning and at the end of the study.

Data were analyzed using non-parametric tests. Continuous variables were expressed as medians (interquartile

ranges, IQR) and compared using the Wilcoxon test. Categorical variables were compared using the Fisher exact test. A *p* value less than 0.05 was considered statistically significant.

Results

Thirteen patients were studied. Ten patients were ventilated with pressure support (PS), 2 with proportional assist ventilation with load-adjustable gain factors (PAV+), and one with continuous positive airway pressure (CPAP) (Purritan-Benett 840, Tyco, Gosport, UK). With propofol one patient ventilated with PAV+ exhibited severe respiratory acidosis ($PaCO_2$ 80 mmHg, pH <7.30) necessitating a mode change and thus was excluded from further analysis. Baseline characteristics of the remaining 12 patients are shown in Table 1 (see also Table S1 in ESM). Apart from propofol all other medications were similar (in terms of type and dose) between the two study periods. The median propofol infusion rate was 0.86 mg/kg/h (IQR 0.67–1.25). In all but one patient (no. 12) the requirements for sedation remained constant throughout the study night.

None of the patients exhibited either atypical (EEG features of SWS and absence of typical stage 2 sleep as indicated by no recognition of K complexes and sleep spindles) or burst suppression EEG pattern [23]. With propofol sleep efficiency was not different from that without propofol (Table 2; Fig. 1). In all patients and on both study nights abnormal sleep architecture was observed consisting of a lack of sequential progression through sleep stages. Independent of the experimental condition SWS was infrequently observed, occurring in two patients without and in four with propofol (Fig. 2). Without propofol 6 out of 12 patients exhibited REM sleep. Propofol infusion virtually abolished the REM sleep ($p = 0.04$), which was observed only in one patient

Table 1 Patients' characteristics

Male sex, *n* (%)	6 (50)
Age (years)	73 (63–75)
APACHE II at admission (points)	23 (16–34)
MV length (days)	18 (16–25)
MV modes, *n* (%)	
PS	10 (84)
CPAP	1 (8)
PAV+	1 (8)
PEEP (cmH_2O)	6 (5–6)
FIO_2	0.4 (0.3–0.5)

Values are median (IQR)

PEEP positive end-expiratory airway pressure, *MV* mechanical ventilation, *PS* pressure support, *CPAP* continuous positive airway pressure, *PAV+* proportional assist ventilation with load adjustable gain factors. *FIO_2* fractional concentration of inspired O_2

Table 2 Sleep architecture without and with propofol

	Without propofol	With propofol	*p* value
TST (min)	214 (40–285)	260 (113–417)	0.37
Sleep efficiency (% TST)	62.6 (13.1–85.9)	76.3 (28.4–96.9)	0.37
Stage 1 (% TST)	30.7 (4.6–66.7)	20.8 (5.6–80.6)	1.00
Stage 2 (% TST)	46.1 (3.0–80.4)	48.9 (4.8–84.0)	0.66
SWS (% TST)	0 (0–0)	0 (0–5.8)	0.75
REM (% TST)	1.4 (0–13.0)	0 (0–0)	0.04
TSFI (events/h)	8.1 (2.9–16.2)	4.8 (1.3–14.6)	0.33
Stage shifts	21 (7–48)	22 (11–28)	0.69
Intersleep awake (% TST)	11.4 (3.1–42.9)	6.8 (1.2–43.5)	0.79

Values are median (IQR)

TST total sleep time, *REM* rapid eye movement, *SWS* slow wave sleep, *TSFI* total sleep fragmentation index
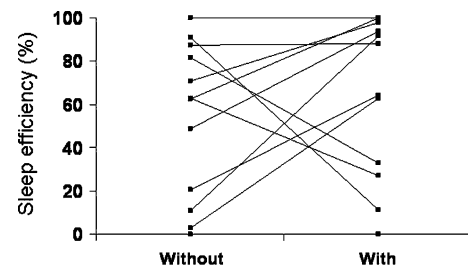

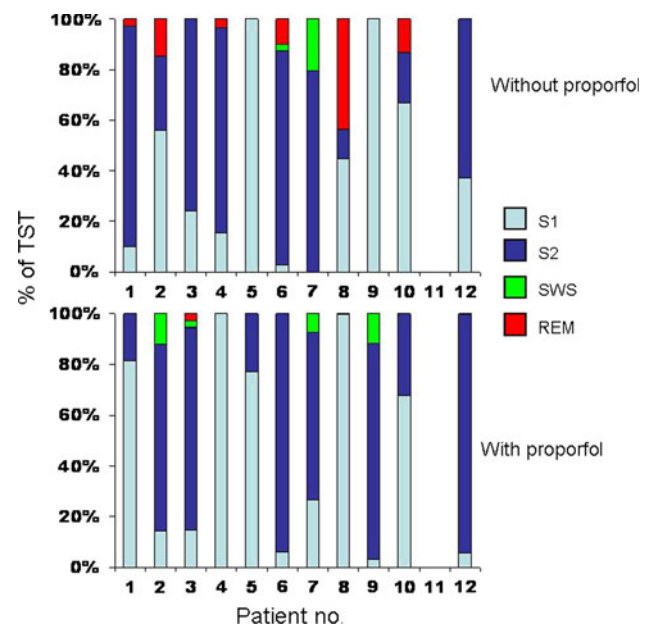**Fig. 1** Sleep efficiency in each patient with and without propofol

Fig. 2 Sleep architecture in each patient without (*upper panel*) and with (*lower panel*) propofol. *REM* rapid eye movement; *S1*, *S2* sleep stage 1 and 2, respectively; *SWS* slow wave sleep. With and without propofol patient no. 11 did not achieve sleep

Table 3 Respiratory variables during wakefulness ($n = 12$) and NREM sleep ($n = 11$)

	Wakefulness		p value	NREM sleep		p value
	Without propofol	With propofol		Without propofol	With propofol	
TV (L)	0.44 (0.34–0.54)	0.43 (0.33–0.48)	0.66	0.40 (0.32–0.48)	0.40 (0.35–0.45)	0.87
T_{TOT} (s)	2.45 (2.01–3.00)	2.51 (1.85–2.83)	0.70	2.50 (2.28–3.35)	2.55 (2.00–2.70)	0.26
Paw_{peak} (cmH_2O)	11.5 (7.0–19.0)	11.5 (7.0–19.0)	0.32	11.0 (7.0–15.0)	11.0 (7.0–15.0)	0.32
$P_{ET}CO_2$ (mmHg)	40.4 (33.0–43.0)	41.5 (35.0–45.0)	0.11	41.3 (34.0–45.0)	43.0 (37.0–46.5)	0.13

Values are median (IQR)

TV tidal volume, T_{TOT} total breath duration, Paw_{peak} peak airway pressure, $P_{ET}CO_2$ end-tidal CO_2 partial pressure

Table 4 Difference in blood gasses between the end and beginning of each study night

	Without propofol	With propofol	p values
ΔPaO_2	−1.5 (−8.8/+12.5)	−4.5 (−9.0/+10.0)	0.64
$\Delta PaCO_2$	1.0 (−2.3/+5.0)	1.0 (0.0/+4.0)	0.70
ΔpH	0.00 (−0.03/+.01)	0.00 (−0.04/+0.01)	0.52

Values are median (IQR)

PaO_2, $PaCO_2$ partial pressure of arterial O_2 and CO_2, respectively

($p = 0.02$), accounting for 3 % of total sleep time (Table 2; Fig. 2). TSFI did not differ between the two experimental conditions (Tables 2 and S2).

Both during wakefulness and NREM sleep respiratory variables did not differ with or without propofol (Table 3). Without propofol the incidence of major asynchronies was low and remained unaffected by the propofol infusion [0.3 % (0.1–1.1) vs. 0.3 % (0.2–1.2), respectively]. One patient exhibited significant periodic breathing (more than 10 % of NREM sleep) in both experimental conditions. Arterial blood gasses remained relatively stable throughout the night (Table 4) and did not differ between experimental conditions (Table S3 in ESM).

Discussion

The main findings of our study were that in critically ill patients mechanically ventilated on assisted modes, propofol infusion titrated to achieve the recommended sedation depth suppressed the REM sleep stage and further worsened the poor sleep quality of these patients. These adverse effects of propofol on sleep cannot be explained either by increasing patient–ventilator dyssynchrony or by deteriorating gas exchange, which remained relatively stable during the two study nights.

The Ramsay sedation scale was used for titration of propofol administration [18]. Although this scale has not been validated properly and lacks a sufficient measure of agitation, it is very simple and used extensively in ICUs worldwide. In addition, this scale has excellent inter-rater

reliability and demonstrates strong correlation with validated sedation scales such as the Richmond agitation sedation scale [24, 25]. Furthermore in our study in order to avoid errors in sedation level, the titration of propofol was performed by two senior intensivists (EK, CA). The fact that in all but one patient the requirements for sedation remained constant throughout the study night indicates adequate goal-directed sedation. In addition the physicians responsible for titration did not have access to EEG and this guarantees that the titration of propofol followed the usual clinical practice (i.e., use of sedation scale) and was not influenced by EEG.

Contrary to general belief propofol administration at the doses studied did not significantly increase the sleep efficiency. On the other hand in three patients sleep efficiency was considerably lower with propofol than that without. In addition with and without propofol one patient did not achieve sleep at all. Paradoxical excitation, a well-described phenomenon observed with relatively low doses of propofol and consisting of an increase in beta activity on the EEG (13–25 Hz) and purposeless movements [26, 27], may underlie the low sleep efficiency, although none of the studied patients exhibited the clinical picture of this phenomenon. Nevertheless, the inability of propofol at doses studied to increase the sleep efficiency does not guarantee that this sedation depth is associated with sleep pattern in EEG.

Our study reconfirmed previous studies showing that critically ill patients exhibit disorganized and poor quality sleep as evidenced by the lack of sequential progression through sleep stages and low percentages of SWS and REM sleep [2, 3, 17]. Propofol infusion at doses titrated to achieve the recommended sedation depth in critically ill patients not only failed to improve the sleep architecture but worsened the sleep quality because the drug virtually eliminated REM sleep. One could argue that the REM suppression we observed with propofol was due to relatively short sleep duration; with propofol REM may be delayed and would have occurred later if patients had been observed for a greater duration. Although we cannot entirely exclude this possibility, it is highly unlikely because propofol exerts its pharmacological effects within minutes [11, 27]. In addition there is no evidence in the

literature indicating that the effects of propofol on EEG are time-dependent [27].

The clinical implication of propofol-induced suppression of REM sleep in critically ill patients is not known. Notwithstanding that the role of REM sleep in humans has not been clarified [28, 29], studies have shown that REM suppression causes insomnia, and might affect memory formation [30–33]. These effects may predispose to delirium and post-traumatic stress disorder (PTSD). Indeed studies in critically patients have shown that propofol administration (as well as other GABA agonists) is an independent risk factor for delirium [34, 35]. In addition indirect evidence in the literature indicates that the inability of critically ill patients to recall memories may be linked to PTSD [36]. Therefore, propofol infusion by depressing REM sleep might be associated with short-term (delirium) and long-term (PTSD) effects in critically ill patients.

It has been shown in critically ill patients that patient–ventilator dyssynchrony adversely affects sleep quality [37]. Propofol administration, mainly by decreasing respiratory drive, could influence patient–ventilator dyssynchrony [21], and thus sleep quality. In our study, however, this was not the case. Propofol, at the doses studied, did not decrease respiratory drive, as indicated by the constant $PaCO_2$ and respiratory variables, while the incidence of major patient–ventilator asynchronies remained unaffected. It follows that neither derangement of arterial blood gasses nor increased patient–ventilator dyssynchrony may explain the observed effects of propofol on sleep. Although pontothalamic and hypothalamic pathways might be involved in REM suppression [28, 29], the design of our study does not permit further clarification of the responsible mechanism.

The inability of propofol to improve sleep quality seems to contradict results of studies in rat models showing that propofol may mimic the restorative effects of normal sleep [13, 14]. Although the apparent discrepancy between these results and ours could be explained by species differences and the critical illness, we believe that the different dosing regimen mainly underlies the discrepancy. Tung et al. [13, 14] used doses of propofol several fold higher than those used in the current study. In humans high doses of propofol are associated with loss of consciousness and appearance of delta activity in EEG closely resembling SWS [15]. Collectively these studies and the current one indicate that the effects of propofol on sleep might be dose-dependent.

It is common practice to sedate difficult to wean patients during the night in order to obtain the restorative effects of sleep and thus facilitate the weaning process. Our findings do not support this practice. It is unknown whether an increase in dose in humans can cause restorative effects of sleep, as animal studies indicate [13, 14]. However, higher doses may depress respiratory drive leading in patients ventilated on assisted modes to hypoventilation and inefficient gas exchange.

Our study demonstrated that the amount of total sleep fragmentation was comparable to that reported in normal subjects in an ICU environment [38]. On the other hand some studies reported considerable sleep fragmentation in critically ill patients [2, 39]. We believe that in our patients the relative normal magnitude of sleep disruption may be due to selection criteria, the minimization of noise, nursing, and other interventions, and the use of a single room to study the patients. Nevertheless, in our patients the magnitude of sleep fragmentation was comparable to that observed by Gabor et al. [38] and Alexopoulou et al. [17] who selected critically ill patients for sleep studies using quite similar patient selection criteria to those in our study.

This study has several limitations. Firstly, in order to facilitate sleep classification using the standard criteria [20] a highly selected group of critically ill patients was studied. These criteria have not been developed for critically ill patients in whom atypical sleep pattern such as EEG features of SWS and absence of typical stage 2 sleep (i.e., absence of K complexes and sleep spindles) may be observed [23]. In our study patients with conditions known to be associated with this pattern (i.e., ongoing sepsis) were excluded [2, 3]. Thus, the results of this study should be applied with caution to a general population of critically ill patients in whom acute critical illness may cause encephalopathy and atypical sleep patterns [23]. Secondly, because of the study design, patients not requiring sedation were studied. In patients needing sedatives for various reasons (i.e., agitation, patient–ventilator dyssynchrony) the results might be different and this is also certainly a limitation. Thirdly, because of the strict selection criteria we applied, the number of patients studied over the 2-year period was small. Nevertheless, the effect of propofol on sleep was rather consistent between patients, partly overcoming this limitation. Fourthly, on both study nights sleep duration was approximately 4 h. This time interval may not reflect the sleep architecture adequately well, particularly in critically ill patients in whom the circadian rhythm is diminished because of disturbances in melatonin secretion [1]. However, long-term (24 h) polysomnography studies in critically ill patients have shown that sleep architecture and quality did not differ between day and night, indicating that night studies are sufficient to characterize the sleep pattern in these patients [2, 3]. We think that it is unlikely that long-term sleep studies may modify the results, at least qualitatively.

In conclusion this physiological study shows that propofol administration to achieve the recommended level of sedation in critically ill patients suppresses the REM sleep stage and further worsens the already impaired sleep quality of these patients. These results do not support the use of propofol to facilitate sleep in critically ill patients ventilated on assisted modes.

References

1. Parthasarathy S, Tobin MJ (2004) Sleep in the intensive care unit. Intensive Care Med 30:197–206
2. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ (2000) Sleep in critically ill patients requiring mechanical ventilation. Chest 117:809–818
3. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ (2001) Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. Am J Respir Crit Care Med 163:451–457
4. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD (2000) Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-stokes respiration. Circulation 102:61–66
5. Leung RS, Bradley TD (2001) Sleep apnea and cardiovascular disease. Am J Respir Crit Care Med 164:2147–2165
6. McGuire BE, Basten CJ, Ryan CJ, Gallagher J (2000) Intensive care unit syndrome: a dangerous misnomer. Arch Intern Med 160:906–909
7. Irwin M, McClintick J, Costlow C, Fortner M, White J, Gillin JC (1996) Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. FASEB J 10:643–653
8. Irwin M, Rinetti G, Redwine L, Motivala S, Dang J, Ehlers C (2004) Nocturnal proinflammatory cytokine-associated sleep disturbances in abstinent African American alcoholics. Brain Behav Immun 18:349–360
9. Redwine L, Hauger RL, Gillin JC, Irwin M (2000) Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. J Clin Endocrinol Metab 85:3597–3603
10. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA Jr, Murray MJ, Peruzzi WT, Lumb PD (2002) Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 30:119–141
11. Kress JP, O'Connor MF, Pohlman AS, Olson D, Lavoie A, Toledano A, Hall JB (1996) Sedation of critically ill patients during mechanical ventilation. A comparison of propofol and midazolam. Am J Respir Crit Care Med 153:1012–1018
12. Mendel PR, White PF (1993) Sedation of the critically ill patient. Int Anesthesiol Clin 31:185–200
13. Tung A, Lynch JP, Mendelson WB (2001) Prolonged sedation with propofol in the rat does not result in sleep deprivation. Anesth Analg 92:1232–1236
14. Tung A, Bergmann BM, Herrera S, Cao D, Mendelson WB (2004) Recovery from sleep deprivation occurs during propofol anesthesia. Anesthesiology 100:1419–1426
15. Murphy M, Bruno MA, Riedner BA, Boveroux P, Noirhomme Q, Landsness EC, Brichant JF, Phillips C, Massimini M, Laureys S, Tononi G, Boly M (2011) Propofol anesthesia and sleep: a high-density EEG study. Sleep 34:283–291A
16. Klimathianaki M, Kondili E, Alexopoulou C, Prinianakis G, Georgopoulos D (2010) Effect of propofol on breathing stability in adult ICU patients with brain damage. Respir Physiol Neurobiol 171:232–238
17. Alexopoulou C, Kondili E, Vakouti E, Klimathianaki M, Prinianakis G, Georgopoulos D (2007) Sleep during proportional-assist ventilation with load-adjustable gain factors in critically ill patients. Intensive Care Med 33:1139–1147
18. Ramsay MA, Savege TM, Simpson BR, Goodwin R (1974) Controlled sedation with alphaxalone-alphadolone. Br Med J 2:656–659
19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
20. ASSM (2007) The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification. American Academy of Sleep Medicine, Westchester, IL
21. Georgopoulos D, Prinianakis G, Kondili E (2006) Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. Intensive Care Med 32:34–47
22. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L (2006) Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 32:1515–1522
23. Drouot X, Roche-Campo F, Thille AW, Cabello B, Galia F, Margarit L, d'Ortho MP, Brochard L (2012) A new classification for sleep analysis in critically ill patients. Sleep Med 13:7–14
24. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, Francis J, Speroff T, Gautam S, Margolin R, Sessler CN, Dittus RS, Bernard GR (2003) Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 289:2983–2991
25. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK (2002) The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 166:1338–1344
26. McCarthy MM, Brown EN, Kopell N (2008) Potential network mechanisms mediating electroencephalographic beta rhythm changes during propofol-induced paradoxical excitation. J Neurosci 28:13488–13504
27. Brown EN, Lydic R, Schiff ND (2010) General anesthesia, sleep, and coma. N Engl J Med 363:2638–2650
28. Siegel JM (2001) The REM sleep-memory consolidation hypothesis. Science 294:1058–1063
29. McCoy JG, Strecker RE (2011) The cognitive cost of sleep lost. Neurobiol Learn Mem 96:564–582
30. Fischer S, Hallschmid M, Elsner AL, Born J (2002) Sleep forms memory for finger skills. Proc Natl Acad Sci U S A 99:11987–11991
31. Laureys S, Peigneux P, Phillips C, Fuchs S, Degueldre C, Aerts J, Del Fiore G, Petiau C, Luxen A, van der Linden M, Cleeremans A, Smith C, Maquet P (2001) Experience-dependent changes in cerebral functional connectivity during human rapid eye movement sleep. Neuroscience 105:521–525
32. Karni A, Tanne D, Rubenstein BS, Askenasy JJ, Sagi D (1994) Dependence on REM sleep of overnight improvement of a perceptual skill. Science 265:679–682
33. Maquet P (2001) The role of sleep in learning and memory. Science 294:1048–1052
34. Frontera JA (2011) Delirium and sedation in the ICU. Neurocrit Care 14:463–474
35. Vasilevskis EE, Ely EW, Speroff T, Pun BT, Boehm L, Dittus RS (2010) Reducing iatrogenic risks: ICU-acquired delirium and weakness–crossing the quality chasm. Chest 138:1224–1233

36. Jones C, Griffiths RD, Humphris G, Skirrow PM (2001) Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med 29:573–580

37. Bosma K, Ferreyra G, Ambrogio C, Pasero D, Mirabella L, Braghiroli A, Appendini L, Mascia L, Ranieri VM (2007) Patient-ventilator interaction and sleep in mechanically ventilated patients: pressure support versus proportional assist ventilation. Crit Care Med 35:1048–1054

38. Gabor JY, Cooper AB, Crombach SA, Lee B, Kadikar N, Bettger HE, Hanly PJ (2003) Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. Am J Respir Crit Care Med 167:708–715

39. Parthasarathy S, Tobin MJ (2002) Effect of ventilator mode on sleep quality in critically ill patients. Am J Respir Crit Care Med 166:1423–1429