

Effects of Dexmedetomidine on Sleep Quality in Critically Ill Patients

A Pilot Study

Christina Alexopoulou, M.D., Eumorfia Kondili, M.D., Eleni Diamantaki, M.D., Charalambos Psarologakis, M.D., Sofia Kokkini, M.D., Maria Bolaki, M.D., Dimitris Georgopoulos, M.D., Ph.D.

ABSTRACT

Background: Dexmedetomidine, a potent α -2-adrenergic agonist, is widely used as sedative in critically ill patients. This pilot study was designed to assess the effect of dexmedetomidine administration on sleep quality in critically ill patients.

Methods: Polysomnography was performed on hemodynamically stable critically ill patients for 57 consecutive hours, divided into three night-time (9:00 PM to 6:00 AM) and two daytime (6:00 AM to 9:00 PM) periods. On the second night, dexmedetomidine was given by a continuous infusion targeting a sedation level -1 to -2 on the Richmond Agitation Sedation Scale. Other sedatives were not permitted.

Results: Thirteen patients were studied. Dexmedetomidine was given in a dose of $0.6 \mu\text{g kg}^{-1} \text{h}^{-1}$ (0.4 to 0.7) (median [interquartile range]). Compared to first and third nights (without dexmedetomidine), sleep efficiency was significantly higher during the second night (first: 9.7% [1.6 to 45.1], second: 64.8% [51.4 to 79.9], third: 6.9% [0.0 to 17.1], $P < 0.002$). Without dexmedetomidine, night-time sleep fragmentation index (7.6 events per hour [4.8 to 14.2]) and stage 1 of sleep (48.0% [30.1 to 66.4]) were significantly higher ($P = 0.023$ and $P = 0.006$, respectively), and stage 2 (47.0% [27.5 to 61.2]) showed values lower ($P = 0.006$) than the corresponding values (2.7 events per hour [1.6 to 4.9], 13.1% [6.2 to 23.6], 80.2% [68.9 to 92.8]) observed with dexmedetomidine. Without sedation, sleep was equally distributed between day and night, a pattern that was modified significantly ($P = 0.032$) by night-time dexmedetomidine infusion, with more than three quarters of sleep occurring during the night (79% [66 to 87]).

Conclusion: In highly selected critically ill patients, dexmedetomidine infusion during the night to achieve light sedation improves sleep by increasing sleep efficiency and stage 2 and modifies the 24-h sleep pattern by shifting sleep mainly to the night. (ANESTHESIOLOGY 2014; 121:801-7)

SLEEP in critically ill patients has been recently recognized as an important aspect of the modern intensive care. It has been shown that the quality of sleep in critically ill patients is low, characterized by severe sleep fragmentation, excessive stage 1 of sleep (light sleep) and substantial reduction in rapid eye movement (REM) and slow-wave sleep (SWS).^{1,2} In addition, some patients may exhibit atypical patterns, consisting of absence of typical stage 2 of sleep. Thus, although the total sleep duration may be normal or even increased,³ critically ill patients are considered to be qualitatively sleep disrupted. The impaired sleep quality may on long-term cause cardiopulmonary, neurological, immunological, and metabolic consequences, leading to increased morbidity.⁴⁻⁸

A widely held belief is that sedation in critically ill patients promotes sleep and thus reduces the detrimental effect of sleep deprivation or poor sleep quality. Indeed, it

What We Already Know about This Topic

- Dexmedetomidine is used as a sedative for perioperative use and in the intensive care unit setting
- This agent is thought to best mimic natural sleep patterns as a therapeutic agent

What This Article Tells Us That Is New

- In selected critically ill patients, dexmedetomidine infusions at night to achieve light levels of sedation increases sleep efficiency and modifies 24-h sleep patterns by shifting sleep to nights

has been shown that in approximately 50% of mechanically ventilated patients, the dose of γ -aminobutyric acid receptor (GABA) agonists (propofol and benzodiazepines) is increased during the night (11:00 AM to 7:00 PM).⁹ Recent data, however, suggest that this strategy may not be beneficial. In critically ill patients ventilated on assisted modes,

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propofol administration, to achieve the recommended level of sedation, does not increase sleep efficiency, whereas suppressing the REM sleep stage further worsens the poor sleep quality of these patients.¹⁰ These results do not support the use of GABA agonists to facilitate sleep in critically ill patients ventilated on assisted modes.

Dexmedetomidine is a potent α -2-adrenergic agonist, with widespread action on the brain that includes sedation, anesthetic-sparing, analgesia, and sympatholytic properties.¹¹ It has been shown that compared to GABA agonists, dexmedetomidine more closely resembles natural non-REM sleep.^{12–15} However, polysomnographic data on critically ill patients are scanty. The only study that performed polysomnography to assess sleep with dexmedetomidine sedation was that of Oto *et al.*,¹⁶ which concluded that, in mechanically ventilated patients, night-time infusion of dexmedetomidine induced severely disturbed sleep architecture since there was no evidence of SWS and REM sleep. Nevertheless, the absence of the control group and the fact that sedation depth was not tightly controlled ranging from light to severe (–1 to –4 on Richmond Agitation Sedation Scale [RASS]) complicate the interpretation of these results. The aim of this pilot study was to examine sleep quality in critically ill patients with and without dexmedetomidine sedation, titrated to achieve RASS –1 to –2.

Materials and Methods

Patients

The study, performed between October 2011 and November 2013, was approved by the human studies subcommittee (Ethics Committee, University Hospital of Heraklion, Greece), and informed consent was obtained from patients and surrogates. Critically ill patients who had been receiving mechanical ventilation for at least 48 h before study entry and who were anticipated to be in the intensive care unit (ICU) for at least 5 days after study entry were enrolled. At the time of the study, the patients were hemodynamically stable without vasoactive and sedative drugs and were either ventilated on assisted modes of support (pressure support or proportional assist ventilation) or breathed spontaneously (t-piece) through cuffed endotracheal or tracheostomy tubes. In all patients, before the study, a morning blood sample was obtained to measure plasma levels of propofol and midazolam. Exclusion criteria were (1) Glasgow Coma Scale less than 11, (2) acute physiology score portion of the Acute Physiology and Chronic Health Evaluation II (APACHE II) greater than 15,¹⁷ (3) administration of any sedative drugs during the last 24 h, (4) detectable plasma levels of propofol

or midazolam, (5) heart rate less than 50 min⁻¹, (6) second- or third-degree atrioventricular block (unless pacemaker installed), (7) severe liver failure (bilirubin >100 μ mol/l), (8) use of centrally acting α -2 agonists or antagonists within 24 h before start of the study, (9) history of epilepsy, (10) history of any other neurological disease that may potentially have significant effect on sleep quality, (11) history of sleep apnea, (12) ongoing sepsis, and (13) presence of delirium at the time of the study, as defined by the confusion assessment method for ICU.¹⁸ The mode of support and ventilator settings were determined by the primary physician, who was not involved in the study. Patients who received opioids for analgesia were not excluded, provided that there was no change in the dose throughout the study. Where necessary, nonsteroidal anti-inflammatory drugs were used for additional analgesia. Administration of neuroleptic (antipsychotic) medications during the entire study period was a reason for patient withdrawal.

Study Protocol

Polysomnography was performed on each patient as previously described.¹⁹ Sleep data were processed automatically (Alice; Respironics, Pittsburgh, PA) according to established rules²⁰ and stored in a computer disc for later analysis. Sleep architecture was scored manually using standard criteria.²⁰ Sleep efficiency was calculated as the ratio between the total sleep time and the total recording time and expressed as percentage.²⁰ Sleep fragmentation index was calculated as the sum of arousals and awakenings per hour of sleep²⁰ (additional details are shown in Supplemental Digital Content 1, <http://links.lww.com/ALN/B62>). Each patient was studied for a total of 57 h, divided into three night-time (9:00 PM to 6:00 AM) and two daytime (6:00 AM to 9:00 PM) periods (fig. 1). The entire study started at 9:00 PM and ended 57 h later at 6:00 AM. At 9:00 PM on the second night, a loading dose of dexmedetomidine was given (0.5 μ g/kg over 20 min), followed by a continuous infusion at a rate adjusted (0.2 to 0.7 μ g kg⁻¹ h⁻¹) to maintain a sedation level –1 to –2 on RASS. To prevent bias in dexmedetomidine administration, only two senior intensivists (C.A. and E.K.) were responsible for dexmedetomidine titration and did not have access to electroencephalogram. Continuous infusion was stopped at 6:00 AM. Apart from this time interval, the patients did not receive any sedation throughout the study (fig. 1). If there was need for sedation, as judged by the primary physician, the patient was withdrawn from the study. 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'



Fig. 1. Study design. Dex = Dexmedetomidine.

assessment. Care was taken to ensure similar environmental conditions among the 3 study nights. In addition, the mode of ventilation and assist level remained unaltered during the study nights. Changes in the mode of ventilation or assist level based on the primary physician's judgment resulted in patient withdrawal from the study. Patients who required a change in the mode of ventilation during the daytime periods were not excluded from the study but were analyzed only during the night-time.

Arterial blood gasses were measured at the beginning and end of each study night. Heart rate, invasive arterial blood pressure, tidal volume (V_T), and respiratory rate were recorded during the night at half-hour intervals. V_T was recorded only in mechanically ventilated patients as measured by the ventilator.

During the entire study, the patients were attended by dedicated research assistants (ICU nurse). In addition, the proper placement of the polysomnography leads was inspected periodically by one of the researchers.

Statistical Analysis

No *a priori* power analysis was conducted. The number of studied patients was a compromise between the difficulty in recruitment (due to study design) and meaningful statistical analysis. Data were analyzed using nonparametric tests (SPSS version 17; IBM, Armonk, NY). Continuous variables were expressed as medians (25th to 75th interquartile range). Variables were compared using the Friedman test for repeated measurements followed, when indicated, by a pairwise comparison with the Wilcoxon signed-rank test using Bonferroni *post hoc* correction. Categorical variables were compared using the Fisher exact test. Statistical tests were two sided, and a *P* value less than 0.05 was considered statistically significant.

Results

General

Sixteen patients were studied. All met the definition of difficult or prolonged weaning, having been on mechanical ventilation for several days before the study. None of the patients had detectable levels of midazolam (or any other benzodiazepine) or propofol. Three patients did not complete the study and were excluded from the analysis. The reasons for study interruption were bradycardia (<50 beats/min) during dexmedetomidine infusion in one patient and decision of the primary physician to use sedation with GABA agonists and mode change in the others. Baseline characteristics of the remaining 13 patients are shown in table 1. By study design, all had sleep data during the 3 study nights, and 10 patients had also sleep data during the daytime periods (*i.e.*, no mode change during the daytime periods was performed in these 10 patients). Three out of 13 patients received opioids (transdermal fentanyl 25 $\mu\text{g}/\text{h}$ [$n = 1$], morphine 0.5 mg/h [$n = 1$], and tramadol hydrochloride 50 mg every morning [$n = 1$]) for analgesia and/or respiratory distress.

Night Data ($n = 13$)

The starting maintenance infusion dose of dexmedetomidine was 0.2 $\mu\text{g kg}^{-1} \text{h}^{-1}$ (0.2 to 0.2) and increased to 0.6 $\mu\text{g kg}^{-1} \text{h}^{-1}$ (0.4 to 0.7) to achieve a score of -1 to -2 on RASS. APACHE II score (calculated before study nights) did not differ significantly among nights (14 [13 to 17], 15 [13 to 18], 14 [12 to 17], $P = 0.161$). Throughout the entire night, arterial blood gasses, V_T , respiratory rate, and arterial blood gasses remained stable and without significant differences among nights (see these results in tables 1 and 2, Supplemental Digital Content 2, <http://links.lww.com/ALN/B63>). The maximum dose of dexmedetomidine was associated with a significant decrease in heart rate (see table

Table 1. Patients' Characteristics

	Sex	Age (yr)	Admission APACHE II	Admission Diagnosis	Days on MV	Mode of MV	Assist Level (cm H ₂ O%)
1	F	54	21	AECOPD/pneumonia	14	PS	5
2	M	67	26	Multiple trauma/ARDS	10	CPAP	None
3	M	34	11	Multiple trauma	8	PS	5
4	M	78	21	Pneumonia/ARDS	9	PS	5
5	F	81	24	Acute on CRF/pneumonia	15	PAV+	30%
6	M	47	23	ARDS	32	SB	None
7	M	60	16	ARDS	10	SB	None
8	M	55	25	Multiple trauma/sepsis/ARDS	40	SB	None
9	M	78	25	AECOPD	80	PS	10
10	M	55	25	GI-respiratory chemical injury	16	PAV+	35%
11	M	62	22	Spinal cord injury-respiratory failure	14	PS	8
12	F	65	24	AECOPD	14	PS	11
13	M	69	18	AECOPD	15	PS	5
Median (IQR)		62 (55-69)	23 (21-25)		14 (10-16)		

AECOPD = acute exacerbation of chronic obstructive pulmonary disease; APACHE II = Acute Physiology and Chronic Health Evaluation II; ARDS = acute respiratory distress syndrome; CPAP = continuous positive airway pressure; CRF = chronic respiratory failure; F = female; GI = gastrointestinal; IQR = 25th-75th interquartile range; M = male; MV = mechanical ventilation; PAV+ = proportional assist ventilation with load-adjustable gain factors; PS = pressure support; SB = spontaneous breathing.

3, Supplemental Digital Content 2, <http://links.lww.com/ALN/B63>).

Sleep efficiency differed significantly among the 3 study nights; compared to nights without dexmedetomidine infusion, sleep efficiency was significantly higher during the night with dexmedetomidine (fig. 2). Six patients during the first night and seven patients during the third night had sleep efficiency less than 10%, whereas in none during the second night (dexmedetomidine infusion) sleep efficiency was less than 10% ($P = 0.006$, Fisher exact test). One patient did not achieve sleep during the second or third night. Overall, three and four patients, during the first and third night, respectively, did not achieve sleep (see table 4, Supplemental Digital Content 2, <http://links.lww.com/ALN/B63>, for sleep architecture during the three study nights).

Because in patients who achieved sleep both during the first and third night ($n = 7$), sleep architecture did not differ between these 2 nights, sleep architecture data were analyzed as follows. The sleep stages, expressed as percentage of total sleep time, and sleep fragmentation index were averaged during the 2 nights (first and third) in patients in whom sleep was observed on both nights ($n = 7$), whereas in patients in

whom sleep occurred only on one of these nights ($n = 5$) the corresponding single value was used for analysis. Thus, each patient ($n = 12$) had sleep architecture data pertained to nights without dexmedetomidine, which was compared to that with dexmedetomidine. With dexmedetomidine, sleep fragmentation index and stage 1 of sleep (N1) were significantly lower, whereas stage 2 (N2) was higher than the corresponding values observed during the nights without dexmedetomidine (figs. 3 and 4). SWS (N3) and REM sleep did not differ with or without dexmedetomidine.

Day Data ($n = 10$)

In 10 of 13 patients polysomnography was performed for two consecutive 24-h periods (first and second periods). Sleep efficiency did not differ during the daytime periods before and after dexmedetomidine (14.3% [6.5 to 25.5] vs. 17.3% [5.8 to 28.0], $P = 0.695$). All patients achieved sleep during the daytime period before (first day) and nine of them achieved sleep after dexmedetomidine (second day). Compared to the previous night (first night), sleep efficiency during the first day did not differ significantly. Sleep

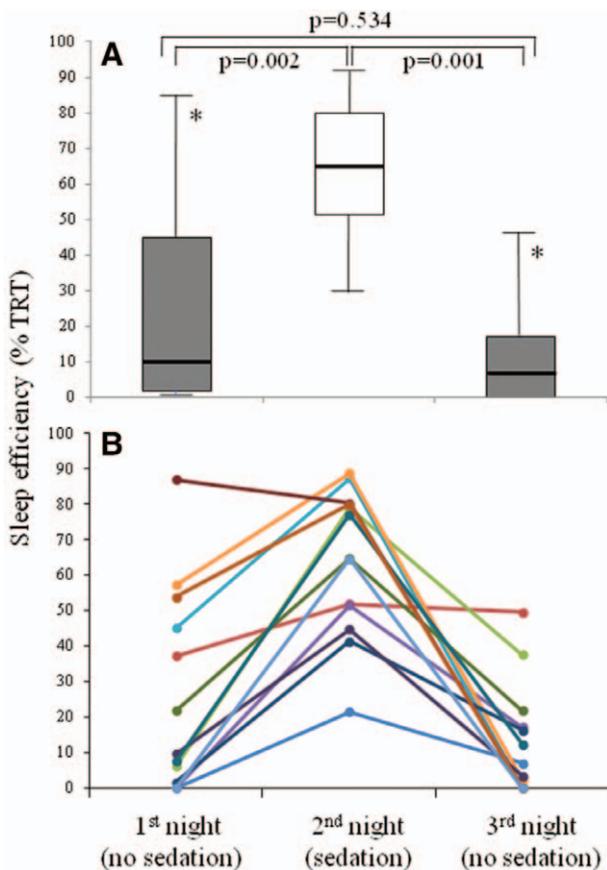


Fig. 2. (A) Box-whisker plot of sleep efficiency during the 3 study nights. Data pertain to 13 patients. (B) Individual sleep efficiency during the three study nights. Each color denotes an individual patient. *Significantly different from sleep efficiency during the second night. TRT = total recording time.

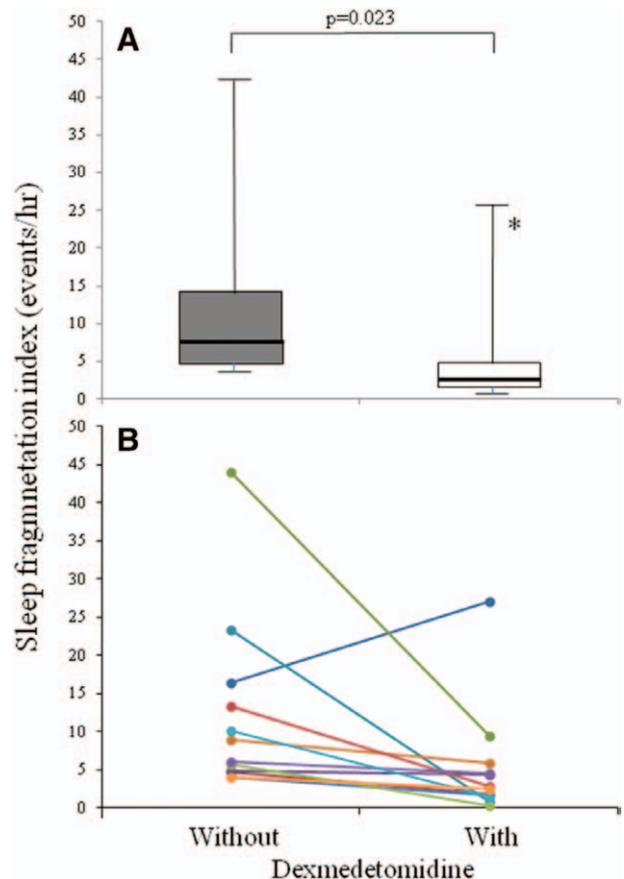


Fig. 3. (A) Box-whisker plot of sleep fragmentation index with and without dexmedetomidine infusion. Data pertain to 12 patients. (B) Individual sleep fragmentation index with and without dexmedetomidine infusion. Each color denotes an individual patient. *Significantly different from the corresponding values without dexmedetomidine.

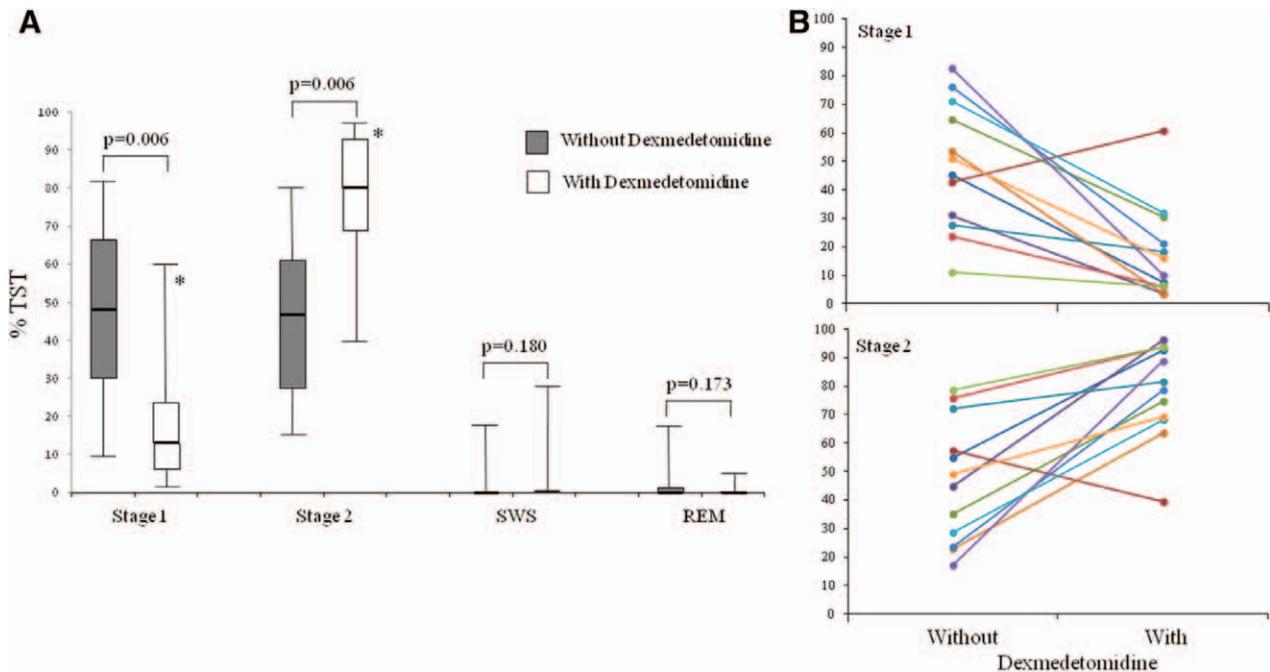


Fig. 4. (A) Box-whisker plot of night-time sleep architecture with and without dexmedetomidine infusion. Data pertain to 12 patients. (B) Individual percentage of total sleep time of stages 1 and 2 of sleep with and without dexmedetomidine infusion. Each color denotes an individual patient. *Significantly different from the corresponding sleep stage without dexmedetomidine. REM = rapid eye movement sleep; SWS = slow wave sleep (N3); TST = total sleep time.

efficiency during the second day was significantly lower than that during the previous night when dexmedetomidine was given (second night) (see these data in table 5, Supplemental Digital Content 2, <http://links.lww.com/ALN/B63>). Compared to sleep architecture during the first day (before dexmedetomidine infusion), sleep architecture during the second day (after dexmedetomidine infusion) was characterized by less stage 1 and more stage 2 and REM sleep, the difference, however, being nonsignificant (see fig. 1, Supplemental Digital Content 3, <http://links.lww.com/ALN/B64>). Sleep was equally distributed between day and night in the first period (no dexmedetomidine infusion during the night), while it mainly occurred during the night in the second period (dexmedetomidine infusion during the night); 48% (32 to 71) of total sleep time occurred during the night in the first period and 79% (66 to 87) in the second ($P = 0.032$).

Discussion

The main findings of our study were that in critically ill patients, dexmedetomidine infusion during the night titrated to achieve light sedation (RASS -1 to -2) significantly increased sleep efficiency and improved sleep architecture by reducing the sleep fragmentation and stage 1 and increasing the stage 2 of sleep. Furthermore, our study showed that without sedation, sleep was equally distributed between day and night, a pattern that was modified by night-time dexmedetomidine infusion with more than three quarters of sleep occurring during the night.

The RASS was used for titration of dexmedetomidine administration.^{21,22} This scale has been validated properly, has excellent interrater reliability, is relatively simple, and is used extensively in ICUs worldwide. Furthermore, in our study, to avoid errors in sedation depth, the titration of dexmedetomidine was performed by two senior intensivists (C.A. and E.K.). In addition, the physicians responsible for titration did not have access to electroencephalogram, which guarantees that the titration of dexmedetomidine followed the usual clinical practice (*i.e.*, use of sedation scale) and was not influenced by electroencephalogram.

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.^{2,3,10,19} Dexmedetomidine infusion at doses titrated to achieve the recommended sedation depth in critically ill patients increased sleep efficiency and improved the sleep architecture by decreasing the stage 1 and increasing stage 2 of sleep. Notwithstanding that few patients exhibited SWS and REM, dexmedetomidine did not affect SWS and REM sleep. In addition, sleep became less fragmented with dexmedetomidine. These results contradict those obtained with the GABA agonist propofol, which worsened sleep quality because the drug virtually eliminated REM sleep with no effect on sleep efficiency, sleep fragmentation, and stage 1 and 2 of sleep.¹⁰ Nevertheless, the fact that dexmedetomidine sedation does not increase the most restorative sleep stages (SWS and REM)²³ indicates that sleep quality of

critically ill patients remains low even during sedation with this agent. It is not known, however, if longer or more often (*i.e.*, every night) administration of this sedative might further influence sleep quality in these patients.

Recently, Oto *et al.*¹⁶ infused dexmedetomidine during the night in mechanically ventilated patients and concluded that the drug induced severely disturbed sleep architecture without evidence of SWS and REM. However, in this study, night-time sleep without dexmedetomidine was not studied. In addition, daytime sleep before dexmedetomidine infusion was also characterized by the absence of SWS and REM. Our study did not show any evidence of dexmedetomidine-induced sleep disruption in critically ill patients; compared to no sedation, dexmedetomidine did not affect SWS and REM sleep, and on the other hand, sleep became deeper (increased stage 2, decreased stage 1) and less fragmented. Also, daytime and night-time data after dexmedetomidine infusion did not show any hard evidence of REM rebound phenomenon, although there was a trend for increased REM after sedation. Finally, it is of interest to note that sleep architecture with dexmedetomidine is quite similar to that reported by Oto *et al.* (relatively high sleep efficiency and stage 2 of sleep and low stage 1 and SWS, see table 2 in Oto *et al.*¹⁶ study).

It is well documented that circadian rhythm is abolished in critically ill patients due to pronounced temporal disorganization or disturbances in melatonin secretion.²⁴ Our study showed that dexmedetomidine may preserve the day–night cycle of sleep, partly restoring the normal circadian rhythm. Compared to a 24-h period with no sedation in which sleep was equally distributed between day and night, dexmedetomidine infusion during the night resulted in a night-time shift of sleep; when dexmedetomidine was infused during the night, less than one-quarter of the total 24 h of sleep occurred during the day. However, we believe that these findings are largely due to study design (*i.e.*, administration of dexmedetomidine during the night) since there is no known reason to expect different effect of dexmedetomidine on sleep if the medication would be given during daytime (although this issue should be formally studied).

Our results may have clinical implications. Studies have shown that delirium and posttraumatic stress disorder, common morbidities in critically ill patients and ICU survivors, may be linked to sleep abnormalities during the ICU stay.²³ In addition, GABA agonists, which worsen sleep in these patients,¹⁰ are an independent risk factor for both delirium and posttraumatic stress disorder.^{9,25,26} On the other hand, some studies have demonstrated that compared to GABA agonists, dexmedetomidine may be associated with a decreased incidence of delirium,^{27–29} and this might be partly explained by the achievement of better sleep, as our study demonstrated. Nevertheless, further studies are needed to clarify these issues.

This study has several limitations. First, in order to facilitate sleep classification using the standard criteria,²⁰

a highly selected group of critically ill patients were studied. These criteria have not been developed for critically ill patients in whom atypical sleep pattern, such as electroencephalogram features of SWS and absence of typical stage 2 sleep (*i.e.*, absence of K complexes and sleep spindles), may be observed.³⁰ In our study, patients with conditions known to be associated with this pattern (*i.e.*, ongoing sepsis) were excluded. 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.³⁰ Second, 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. Third, because of the strict selection criteria we applied, the recruitment rate was very low (annual rate of ICU admission approximately 500 patients), and thus, the number of patients studied over the 2-yr period was small. Nevertheless, the effect of dexmedetomidine on sleep was rather consistent between patients, partly overcoming this limitation.

In conclusion, this pilot study shows that night-time dexmedetomidine administration to achieve the recommended level of sedation in highly selected critically ill patients increases sleep efficiency and improves sleep quality by reducing the sleep fragmentation and shifting the sleep from stage 1 to stage 2. In addition, dexmedetomidine modifies the 24-h sleep pattern by shifting sleep mainly to the night, partly restoring normal circadian rhythm.

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Competing Interests

Dr. Georgopoulos received lecture fee (honoraria) from Orion Pharma (Espoo, Finland). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Georgopoulos: Intensive Care Medicine Department, University Hospital of Heraklion, Medical School, University of Crete, Heraklion, Crete 71110, Greece. georgop@med.uoc.gr. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Parthasarathy S, Tobin MJ: Sleep in the intensive care unit. *Intensive Care Med* 2004; 30:197–206

2. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ: Sleep in critically ill patients requiring mechanical ventilation. *Chest* 2000; 117:809–18
3. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ: 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; 163:451–7
4. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD: Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation* 2000; 102:61–6
5. Leung RS, Bradley TD: Sleep apnea and cardiovascular disease. *Am J Respir Crit Care Med* 2001; 164:2147–65
6. McGuire BE, Basten CJ, Ryan CJ, Gallagher J: Intensive care unit syndrome: A dangerous misnomer. *Arch Intern Med* 2000; 160:906–9
7. Irwin M, McClintick J, Costlow C, Fortner M, White J, Gillin JC: Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *FASEB J* 1996; 10:643–53
8. Redwine L, Hauger RL, Gillin JC, Irwin M: Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *J Clin Endocrinol Metab* 2000; 85:3597–603
9. Seymour CW, Pandharipande PP, Koestner T, Hudson LD, Thompson JL, Shintani AK, Ely EW, Girard TD: Diurnal sedative changes during intensive care: Impact on liberation from mechanical ventilation and delirium. *Crit Care Med* 2012; 40:2788–96
10. Kondili E, Alexopoulou C, Xirouchaki N, Georgopoulos D: Effects of propofol on sleep quality in mechanically ventilated critically ill patients: A physiological study. *Intensive Care Med* 2012; 38:1640–6
11. Gerlach AT, Murphy CV, Dasta JF: An updated focused review of dexmedetomidine in adults. *Ann Pharmacother* 2009; 43:2064–74
12. Coull JT, Jones ME, Egan TD, Frith CD, Maze M: Attentional effects of noradrenaline vary with arousal level: Selective activation of thalamic pulvinar in humans. *Neuroimage* 2004; 22:315–22
13. Sanders RD, Maze M: Contribution of sedative-hypnotic agents to delirium *via* modulation of the sleep pathway. *Can J Anaesth* 2011; 58:149–56
14. Nelson LE, Guo TZ, Lu J, Saper CB, Franks NP, Maze M: The sedative component of anesthesia is mediated by GABA(A) receptors in an endogenous sleep pathway. *Nat Neurosci* 2002; 5:979–84
15. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M: The α 2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *ANESTHESIOLOGY* 2003; 98:428–36
16. Oto J, Yamamoto K, Koike S, Onodera M, Imanaka H, Nishimura M: Sleep quality of mechanically ventilated patients sedated with dexmedetomidine. *Intensive Care Med* 2012; 38:1982–9
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–29
18. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK: Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; 29:1370–9
19. Alexopoulou C, Kondili E, Vakouti E, Klimathianaki M, Prinianakis G, Georgopoulos D: Sleep during proportional-assist ventilation with load-adjustable gain factors in critically ill patients. *Intensive Care Med* 2007; 33:1139–47
20. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specification, 1st edition. Westchester: American Academy of Sleep Medicine, 2007
21. 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: Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003; 289:2983–91
22. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK: The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; 166:1338–44
23. McCoy JG, Strecker RE: The cognitive cost of sleep lost. *Neurobiol Learn Mem* 2011; 96:564–82
24. Gehlbach BK, Chapotot F, Leproult R, Whitmore H, Poston J, Pohlman M, Miller A, Pohlman AS, Nedeltcheva A, Jacobsen JH, Hall JB, Van Cauter E: Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. *Sleep* 2012; 35:1105–14
25. Trompeo AC, Vidi Y, Locane MD, Braghiroli A, Mascia L, Bosma K, Ranieri VM: Sleep disturbances in the critically ill patients: Role of delirium and sedative agents. *Minerva Anestesiol* 2011; 77:604–12
26. Usuki M, Matsuoka Y, Nishi D, Yonemoto N, Matsumura K, Otomo Y, Kim Y, Kanba S: Potential impact of propofol immediately after motor vehicle accident on later symptoms of posttraumatic stress disorder at 6-month follow up: A retrospective cohort study. *Crit Care* 2012; 16:R196
27. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW: Effect of sedation with dexmedetomidine *vs* lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. *JAMA* 2007; 298:2644–53
28. Pandharipande PP, Sanders RD, Girard TD, McGrane S, Thompson JL, Shintani AK, Herr DL, Maze M, Ely EW; MENDS Investigators: Effect of dexmedetomidine *versus* lorazepam on outcome in patients with sepsis: An a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care* 2010; 14:R38
29. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group: Dexmedetomidine *vs* midazolam for sedation of critically ill patients: A randomized trial. *JAMA* 2009; 301:489–99
30. Drouot X, Roche-Campo F, Thille AW, Cabello B, Galia F, Margarit L, d'Ortho MP, Brochard L: A new classification for sleep analysis in critically ill patients. *Sleep Med* 2012; 13:7–14