

Jun Oto  
Katsunori Yamamoto  
Shigefumi Koike  
Mutsuo Onodera  
Hideaki Imanaka  
Masaji Nishimura

## Sleep quality of mechanically ventilated patients sedated with dexmedetomidine

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J. Oto (✉) · M. Onodera · M. Nishimura  
Department of Emergency and Critical Care  
Medicine, The University of Tokushima  
Graduate School, 3-18-15 Kuramoto-cho,  
Tokushima 770-8503, Japan  
e-mail: joto@clin.med.tokushima-u.ac.jp  
Tel.: +81-88-6339347  
Fax: +81-88-6339339

M. Onodera  
e-mail: m-onodera@clin.med.tokushima-u.ac.jp

M. Nishimura  
e-mail: nmasaji@clin.med.tokushima-u.ac.jp

K. Yamamoto · S. Koike  
Sleep Disorder Center, Toyohashi Mates  
Clinic, Toyohashi, Japan

K. Yamamoto  
e-mail: kyamamoto@mates.or.jp

S. Koike  
e-mail: skoike@mates.or.jp

H. Imanaka  
Emergency and Disaster Medicine,  
The University of Tokushima Graduate  
School, Tokushima, Japan  
e-mail: imanakah@clin.med.tokushima-u.ac.jp

**Abstract Purpose:** Dexmedetomidine is thought to activate an endogenous pathway that naturally promotes non-rapid eye movement (NREM) sleep. Dexmedetomidine may induce restorative sleep, that is, NREM stage 3 and 4 (slow wave sleep; SWS) or sleep continuity in mechanically ventilated patients. Few data have been published, however, on the sleep characteristics of mechanically ventilated patients during dexmedetomidine infusion.

**Methods:** We recorded polysomnography (PSG) for 24 h in mechanically ventilated patients sedated with dexmedetomidine. Dexmedetomidine (0.2–0.7 µg/kg/h) was administered intravenously to maintain the Richmond Agitation–Sedation Scale between –1 and –4 only during the nighttime (9:00 p.m. to 6:00 a.m.). During the daytime, we interrupted the sedatives and analgesics unless the patient complained of discomfort. When this occurred midazolam or opioids were administered intermittently. Sleep stages and the frequency of arousal/awakening during the nighttime were analyzed

using Rechtschaffen and Kales criteria. **Results:** For the ten mechanically ventilated adult patients recruited into the study, the median total sleep time (TST) during the night was 4.7 h (IQR, 4.2–8.1 h), and 78 % of sleep occurred during the night (median 78 %, IQR: 69–88 %). Sleep architecture was exclusively NREM sleep stage 1 (median 28.9 % of TST) and stage 2 (median 71.2 % of TST). Neither SWS (median 0 % of TST) nor rapid eye movement (REM) sleep (median 0 % of TST) was observed. Median frequency of arousals/awakenings was 9.3/h (IQR, 3–19.5/h). **Conclusions:** In mechanically ventilated patients, nighttime infusion of dexmedetomidine preserved the day-night cycle of sleep but induced severely disturbed sleep architecture without evidence of SWS or REM sleep.

**Keywords** Dexmedetomidine · Sleep stage · Mechanical ventilation · Sedation

### Introduction

Sleep disturbance is a common complication of mechanically ventilated intensive care unit (ICU) patients

[1–4]. About half of ICU patients report sleep disturbance in the ICU, and one-third continue to have poor quality of sleep for 6–12 months even after discharge [5]. In the ICU, patients show severe sleep fragmentation, sleep–

wake disorganization and abnormal sleep architecture with increased stage 1 and stage 2 non-rapid eye movement (NREM) sleep, decreased slow wave sleep (SWS) and rapid eye movement (REM) sleep [1–4]. Although the effects of sleep deprivation on critically ill patients have not been well studied, sleep disorders may negatively affect physiological functions, particularly neurocognitive functions, immune mechanisms [1–4] and respiratory functions [6, 7]. Sleep disruption of critically ill patients may be caused by the ICU environment, underlying medical illness, mechanical ventilation and sedation [1–4].

Critically ill patients are often given sedatives and analgesics to increase comfort, decrease anxiety and promote sleep. The two most commonly used classes of ICU sedatives are those that interact with the gamma-aminobutyric acid (GABA) receptor, such as benzodiazepine and propofol, and those that bind to alpha-2 receptors in the locus ceruleus [1], such as dexmedetomidine. Even though infusing propofol and midazolam at night increases total sleep time and improves the perception of having slept [4, 8], pharmacological sedation with these GABA agonists is not the same as normal physiological sleep and results in significant disturbance of sleep architecture, including suppression of SWS and REM sleep [1–4]. Such loss of SWS sleep may impair memory formation and increase delirium [9]. Meanwhile, REM sleep deprivation has been associated with impaired attention, memory alteration and delirium [2, 9]. It has been well established that administration of GABA agonists, especially benzodiazepine, causes delirium and prolongs mechanical ventilation and ICU stay [10, 11]. In devising an adequate sleep-promotion strategy, physicians have to avoid excessive sedation and prescribe sleep-promoting drugs that minimally affect sleep architecture. At the same time, daily sedative interruption reduces unnecessary use of sedatives and avoids excessive sedation, resulting in improved prognoses for mechanically ventilated patients [12, 13]. In addition, there is evidence that such interruption, compared with continuous infusion of benzodiazepine, increases the duration of SWS and REM sleep [14].

Dexmedetomidine has sedative–analgesic properties and is approved for ICU use. It has been shown to inhibit the release of norepinephrine in the locus ceruleus and has been shown to enhance SWS by mimicking the endogenous NREM sleep pathway [15]. It has been reported that dexmedetomidine infusion ensures adequate sedation levels and preserves rearousability, physiological sleep and cognitive brain functions [16]. Two recent clinical trials have demonstrated that dexmedetomidine-sedated patients experienced significantly more delirium-free days in the ICU than those receiving benzodiazepines [17, 18]. Accurate measurement of the quality and quantity of sleep during mechanical ventilation can be obtained polysomnographically [4]. However, we could find no

published data for sleep characteristics during administration of dexmedetomidine to critically ill patients. Consequently, we investigated the effects of dexmedetomidine combined with daily sedative interruption on the sleep characteristics of mechanically ventilated patients. Considering the above evidence, we hypothesized that dexmedetomidine combined with daily sedative interruption preserves restorative sleep, SWS, normal sleep/wake cycles and sleep continuity in mechanically ventilated patients.

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## Patients and methods

In this study conducted in the ICU at Tokushima University Hospital, qualified adult patients who received mechanical ventilation (assist-control (A/C) mode with pressure control ventilation) for longer than 48 h, along with sedative infusions, were sequentially enrolled in the study. Exclusion criteria were the presence of psychiatric illness, anoxic brain injury, suspected encephalopathy (drug overdose, hepatic failure or renal failure), history of sleep disturbance and taking sleep medicine on a daily basis, seizure disorder and severe hemodynamic instability with systolic blood pressure <90 mmHg despite vasopressor support. The study protocol was approved by the ethics committee of Tokushima University Hospital (Institutional Review Board no. 883). Written informed consent was obtained from all participating patients or their families.

### Sedation protocol

The sedation of all patients included daily sedative interruption. In general, midazolam or propofol was used for sedation, supplemented with morphine or fentanyl for analgesia. The study period had two major divisions, daytime (6:00–21:00) and nighttime (21:00–6:00). Sedatives and analgesics were discontinued at 6:00 until patients were awake enough to respond to requests [12]. If patients showed signs of intolerable anxiety or agitation, midazolam was intermittently administered as required. During the daytime, dexmedetomidine was not used for acute agitation because of the risk of adverse cardiovascular side effects if administered in a rapid single shot [19]. Agitation was characterized as frequent unpurposeful movement, patient–ventilator dissynchrony, pulling on the catheter or aggressive behavior toward medical staff. Apparent pain was treated by morphine or fentanyl. At 21:00, intravenous administration of dexmedetomidine with a loading dose of 1.0 µg/kg for 20 min, followed by 0.2–0.7 µg/kg/h to maintain a Richmond Agitation–Sedation Scale (RASS) of –1 to –4 [20]; if patients showed agitation, the dose was increased to 0.7 µg/kg/h.

If this was not sufficient to control agitation, midazolam would be administered with an intermittent dose of 1–5 mg as a rescue sedative. Apparent pain was treated with intermittent doses of fentanyl (25–50 µg) or morphine (1–5 mg) based on physiological parameters such as blood pressure, heart rate and respiratory rate in addition to facial expression, limb movement and patient–ventilator asynchrony [17]. Administration of sedatives or analgesics beyond the base protocol was at the discretion of the attending physician. Neuromuscular agents were not administered.

By either the attending physicians or staff nurses, sedation was evaluated using RASS criteria at 2-h intervals or when nursing care was provided. During the nighttime, staff nurses decreased environmental stimulation by minimizing noise and illumination and scheduled nursing care. RASS, dexmedetomidine dosage, and administration of midazolam and opioids during daytime and nighttime were recorded. Patient–care interactions with nurses or physicians, including assessment of vital signs, nursing care, respiratory care and medical examinations during daytime and nighttime, were also recorded.

### Polysomnography

All subjects were monitored with continuous 24-h polysomnography (PSG) (Sandman Elite ver. 7.2, Covidien, MO). Electrodes were placed on the subject's head at the left and right parietal lobe and left and right occipital lobe positions according to the international 10/20 system of electrode placement. Positioning was relative to two electrodes, A1 (left) and A2 (right), placed on the mastoid region of each subject. To differentiate REM sleep from NREM sleep and wakefulness, two extraocular (EOG) electrodes were utilized to monitor eye movements, and two submaxillary electromyogram (EMG) electrodes were applied to monitor muscle tone. The PSG was calibrated using 50-µV signals at a sensitivity of 5 µV/mm. If skin impedance exceeded 10 kΩ, the electrodes were reapplied. Two PSG sleep technicians later scored the polysomnograms, according to the criteria of Rechtschaffen and Kales, in 30-s epochs [21]. Arousal and awakening from sleep were scored according to the American Sleep Disorders Association criteria [22]. Arousal and awakening were indexed as the number of arousals plus awakenings per hour of sleep. Total sleep time (TST) was defined as the sum of time spent in any sleep stage during the monitoring period. Sleep efficiency was defined as TST in proportion to a defined period (e.g., 100 % sleep efficiency during the nighttime would be represented as  $100 \times \text{TST} / 9 \text{ h}$ ). Duration of each sleep stage is expressed in total hours during the monitoring period. Arousal was indexed as the number of arousals

per hour during the monitoring period. Primary endpoints of this study were total sleep time, sleep efficiency, arousal/awakening index, total amount of each sleep stage including NREM stage 1–4 and REM sleep during the nighttime and the portion of sleep time during the nighttime versus daytime.

### Statistical analysis

Data are presented as the mean  $\pm$  standard deviation or, if not normally distributed, as median values (interquartile range). Relationships between the mean dosage of dexmedetomidine and total sleep time (TST), arousal index and the duration of sleep stages were assessed using Spearman's rho (rs). All statistical tests were two-sided, and a *P* value <0.05 was considered statistically significant.

## Results

Clinical features of the ten patients enrolled in the study are summarized in Table 1. Items include age, gender, body weight, body mass index, acute physiology and chronic health evaluation (APACHE) II scores, duration of mechanical ventilation prior to the study, sedatives used prior to the study, diagnosis, vasopressor use and serum creatinine data.

### Polysomnographic study

Figure 1a, b shows sample hypnograms of patients sedated with dexmedetomidine. There was variability in the sleep efficiency and structure of sleep stages; one patient showed preserved sleep continuity with predominantly stage 2 NREM sleep, and fragmented sleep with predominance of stage 1 or 2 NREM sleep in others. Figure 2 shows polysomnograph tracings of spontaneous arousal (Fig. 2a) and nursing care-related arousal (Fig. 2b). The features of the EEG were almost the same in both types of arousal.

Table 2 shows the median duration of TST, distribution of sleep stages and patient–care interactions. Although sleep efficiency was about 50 % of the nighttime period, 78 % of sleep occurred during the nighttime (median 78 %, IQR: 69–88 %). Stage 1 and 2 NREM sleep was predominant, and during the nighttime SWS was only detected in three and REM sleep only in two patients. Although the arousal/awakening index figures during daytime were higher than the normal range, the nighttime periods were within the normal range. Patient

**Table 1** Demographic data

Age (years)	68 ± 9
Gender (male/female)	3/7
Body weight	55 ± 14
Body mass index	22 ± 6
APACHE II score	17.7 ± 6.9
Days of MV prior to the study (day)	4.1 ± 3.0
Sedatives prior to the study	
Propofol (n)	1
Cumulative dose of propofol (mg/kg)	80
Midazolam (n)	9
Cumulative dose of midazolam (mg/kg)	2.2 (2.0, 2.4)
ICU diagnosis, n (%)	
Medical	
Heart failure	1 (10)
Pneumonia	1 (10)
Sepsis	3 (30)
Others	2 (20)
Surgical	
Cardiovascular surgery	2 (20)
Abdominal surgery	1 (10)
Vasopressors, n (%)	5 (50)
Serum creatinine (mg/dl)	0.7 ± 0.4

Data were presented as mean ± SD, median (inter-quartile range) or No (%) unless otherwise noted

APACHE II score Acute Physiology and Chronic Health Evaluation II score, MV mechanical ventilation

care interactions occurred 1.0–1.3 times per hour throughout the nighttime.

#### RASS findings with sedatives and opioids

Table 3 shows the RASS related to dexmedetomidine dosage. The mean maintenance dose of dexmedetomidine was 0.61 µg/kg/h (0.43–0.7 µg/kg/h). Six of ten patients required dexmedetomidine infusion at 0.7 µg/kg/h. No patients received midazolam during the study period. Four patients required fentanyl or morphine during the nighttime. No patient received antidepressant or psychotropic medication. Daytime and nighttime RASS values

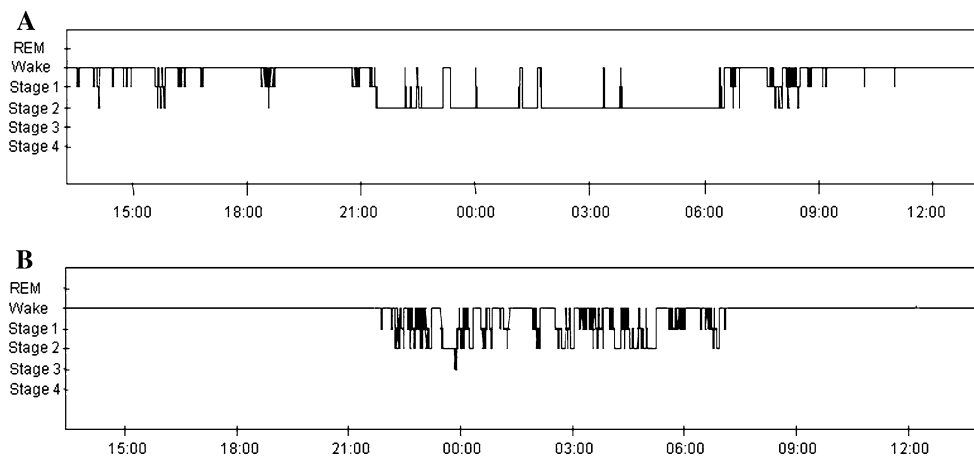
were statistically significantly different ( $P < 0.001$ ). During the nighttime, 92 % of RASS scores were –1 to –4, and no statistically significant correlations were found between dexmedetomidine dosage and TST ( $rs = 0.32$ ,  $P = 0.37$ ), arousal index ( $rs = 0.45$ ,  $P = 0.19$ ), duration of stage 1 ( $rs = 0.21$ ,  $P = 0.56$ ), stage 2 ( $rs = 0.19$ ,  $P = 0.6$ ), SWS ( $rs = 0.21$ ,  $P = 0.56$ ) and REM sleep ( $rs = 0.18$ ,  $P = 0.62$ ).

#### Discussion

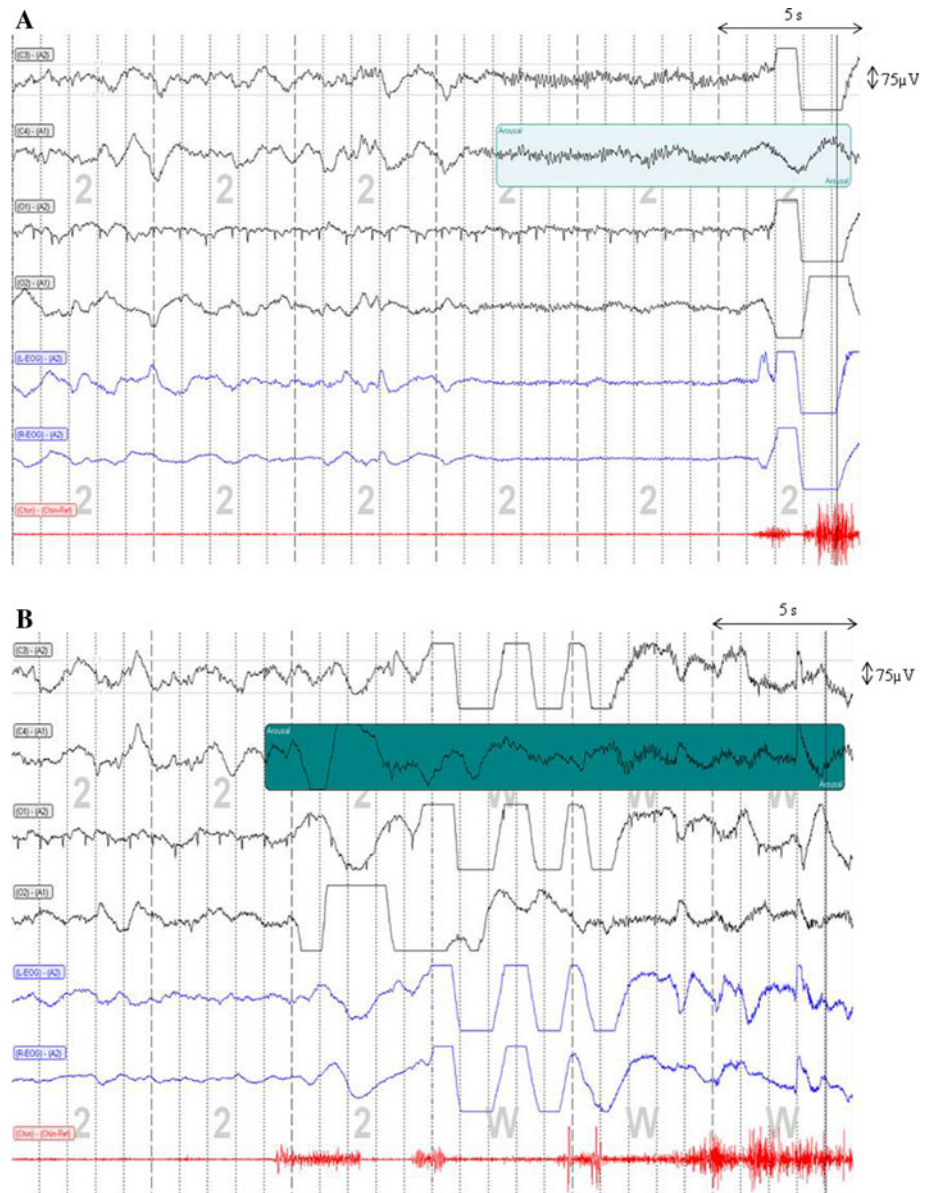
This is the first polysomnographic study of mechanically ventilated patients to investigate the effects on sleep characteristics of dexmedetomidine combined with daily interruption of sedative administration. We found that even though the sleep efficiency during the nighttime was about 50 %, the shift of sleep to the nighttime versus daytime was remarkable, and the arousal/awakening index was normal during the nighttime. Sleep that occurred during the nighttime period was predominantly stage 2 NREM sleep, and few showed evidence of any SWS or REM sleep during the nighttime period.

It is well described that the circadian rhythm is abolished in sedated critically ill patients. Total sleep time over a 24-h period is relatively normal, but about half of sleep occurred during the daytime [23, 24]. In the present study, we applied nocturnal infusion of dexmedetomidine, and 78 % of sleep occurred during the nighttime; the arousal/awakening index was reduced to within the normal range. Daytime interruption of sedatives may contribute to the normalization of circadian rhythms and prevent the shift of sleep to daytime. Continuous sedation disrupts circadian rhythm by reducing melatonin secretion [25, 26], and unnecessary sedatives should be avoided to maintain the circadian rhythms in mechanically ventilated patients. Dexmedetomidine is a short-acting drug; it possesses features of easy arousal and awakening with

**Fig. 1** Sample hypnograms of patients sedated with dexmedetomidine. **a** This patient slept for 90 % of the 24-h monitoring period, predominantly in stage 2 NREM sleep. SWS and REM sleep were not observed during the nighttime period (*top*). **b** The patient had isolated episodes of stage 1 and 2 NREM sleep, but was awake for most of the 24-h monitoring period (*bottom*)



**Fig. 2** Polysomnograph tracings of spontaneous arousal (a) and nursing care-related arousal (b). The features of the EEG were almost the same in both types of arousal. **a** Scored in 30-s epochs, polysomnograph showing stage 2 and arousal. An abrupt shift of more than 16 Hz in the EEG frequency was observed. **b** Scored in 30-s epochs, polysomnograph showing stage 2 and arousal. After verbal stimuli, an abrupt shift of more than 16 Hz in the EEG frequency was observed



mild stimuli. Daytime interruption of sedatives and the use of dexmedetomidine may have less effect on circadian rhythm and provide some benefit in promoting sleep/wake cycles in mechanically ventilated patients.

Mechanically ventilated patients experience severe sleep fragmentation with arousals/awakenings. These patients demonstrate up to 63 arousals/awakenings per hour of sleep [27, 28]. Although the arousal/awakening index was within normal values in our patients, it is difficult to compare our results with previous studies because multiple factors influence the arousal/awakening index. Sleep is disturbed by a variety of factors: noise, hospital staff access, patient-ventilator interaction, acute illness, pain, light and the endotracheal tube. We have been trying to decrease

these factors as much as possible, especially during the nighttime. The ventilator mode was A/C, and sleep quality was reportedly better with A/C than with other modes. We infused dexmedetomidine just during the nighttime. We are not sure daytime interruption of dexmedetomidine would improve sleep quality, because dexmedetomidine is usually infused continuously. While our results indicate that sedation with dexmedetomidine was more susceptible to arousal by mild stimuli compared with benzodiazepine, dexmedetomidine can maintain sleep continuity as well as benzodiazepine in mechanically ventilated patients.

In this study, sleep architecture during dexmedetomidine sedation was severely disrupted, as revealed by the predominance of stage 2 NREM sleep and almost

**Table 2** Sleep characteristics and patient care interactions during the study period

Daytime period (6:00–21:00)	
Total sleep time (h)	1.7 (0.8, 2.0)
Sleep efficiency (%)	11.3 (5.0, 13.7)
Stage 1 (min)	46 (13, 57)
Stage 2 (min)	54 (16, 67)
Stage 3, 4 (min)	0 (0, 0)
REM (min)	0 (0, 0)
Arousal/awakening index (n/h)	20.2 (11.3, 34.2)
Patient–care interactions (n/h)	1.5 (1.3, 1.7)
Nighttime period (21:00–6:00)	
Total sleep time (h)	4.7 (4.2, 8.1)
Sleep efficiency (%)	52.3 (47.0, 89.7)
Stage 1 (min)	76 (32, 145)
Stage 2 (min)	188 (136, 449)
Stage 3, 4 (min)	0 (0, 1.3)
REM (min)	0 (0, 0)
Arousal/awakening index (n/h)	9.3 (3, 19.5)
Patient–care interactions (n/h)	1.2 (1.0, 1.3)

Data were presented as median (quartile) unless otherwise noted  
REM rapid eye movement

**Table 3** Richmond Agitation–Sedation Scale and drug dosages during the study period

Daytime (6:00–21:00)	
RASS	−0.5 (−0.1, −0.7)
Midazolam (n)	0
Morphine (n)	1
Dose (mg/kg)	0.18
Fentanyl (n)	1
Dose (µg/kg)	6.8
Nighttime (21:00–6:00)	
RASS	−2.2 (−1.3, −3.0)
Dexmedetomidine mean dose (µg/kg/h)	0.7 (0.5, 0.7)
Morphine (n)	2
Mean dose (mg/kg)	0.21
Fentanyl (n)	2
Mean dose (µg/kg)	2.4

Data were presented as median (quartile) unless otherwise noted  
RASS Richmond Agitation–Sedation Scale

complete absence of SWS and REM sleep. While there is no comparative data for mechanically ventilated patients, recent findings in a rat model have shown that dexmedetomidine increases NREM sleep and decreases REM sleep [15]. In an EEG study of healthy volunteers with a slight to moderate amount of slow-wave activity and abundant sleep spindle activity, patterns associated with dexmedetomidine sedation were similar to physiological stage 2 NREM sleep [29]. Dexmedetomidine binds to receptors in the locus ceruleus and inhibits norepinephrine release, which causes GABA output from the ventrolateral preoptic nucleus and as a result produces NREM sleep patterns [15]. Norepinephrine plays a permissive role during REM sleep [30]; thus, inhibition of its release by dexmedetomidine may make REM sleep difficult to achieve.

Several other factors may also have contributed to suppression of SWS and REM sleep in this study, including

preexisting poor sleep continuity, the advanced age of the patients, acute illness, vasopressor use, mechanical ventilation and frequent patient care interactions [3, 4]. These factors may plausibly explain why, for mechanically ventilated patients such as ours, dexmedetomidine might enhance stage 2 NREM sleep, but not preserve SWS and REM sleep. This might possibly be further investigated by examining whether withdrawal of dexmedetomidine provokes REM rebound, as do other REM-suppressive medications. While discontinuation, however, may be expected to result in acute medication withdrawal syndrome, there have been no reports of withdrawal effects associated with sudden discontinuation of dexmedetomidine [18, 31].

Our study had a number of limitations. First, this study is just a window on a 24-h sleep intrusion pattern and the overnight sleep quality of ten consecutive patients with a drug regimen not including midazolam, although not rigorously planned for midazolam wash out. The major limitation of the study is the absence of a control group. It would be more convincing if there were a control group for the comparison of dexmedetomidine and other hypnotics to no dexmedetomidine on sleep characteristics in mechanically ventilated patients. Second, we only measured sleep characteristics for 24 h and were unable to report any long-term effects of dexmedetomidine on sleep characteristics. Third, the sample size was too small to allow for logistic regression, and factors that may confound the results were not rigorously eliminated. For example, we used other hypnotics prior to the study, and these may have affected sleep characteristics. Fourth, because we did not measure other sedative or narcotic blood levels, we are unable to report the precise effects of these medications on sleep characteristics during the nighttime. Even so, we did adapt the daily regimen of sedative interruption to attenuate the effects of other sedatives and did not use midazolam during the study period. In addition, dexmedetomidine is indicated for light sedation and is often used in combination with other hypnotics. In a previous randomized study, when treated with dexmedetomidine to maintain sedation within the target range, 63 % of patients required another hypnotic [17]. Fifth, sleep fragmentation, in particular NREM stage shifts, is better described by the American Academy of Sleep Medicine (AASM) 2007 criteria than with the Rechtschaffen and Kales criteria [32]. Finally, other than patient–care interactions, we did not evaluate the effects of ICU environmental factors, such as noise and lighting, which could possibly affect sleep characteristics [3, 4], nor did we record information about sleep quality before the study.

In conclusion, mechanically ventilated patients who received dexmedetomidine in a regimen with daily sedative interruption showed a remarkable shift of sleep to the nighttime but experienced severely disturbed sleep architecture. Many factors contribute to sleep abnormality, and effective sedation strategies to promote the sleep of mechanically ventilated patients are required. To improve the quality and quantity of sleep, cognitive

functions and emotional well-being of mechanically ventilated patients, further clinical studies are required to evaluate the effects of different doses of dexmedetomidine or other sedative agents.

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**Conflicts of interest** None.

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