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Sleep during proportional-assist ventilation with load-adjustable gain factors in critically ill patients

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Abstract *Background:* Proportional-assist ventilation with load-adjustable gain factors (PAV+) automatically adjusts the flow and volume assist to represent constant fractions of resistance and elastance of the respiratory system, respectively. Resistance and elastance are calculated at random intervals of 4–10 breaths, by applying a 300 ms pause maneuver at the end of selected inspirations. *Objectives:* To determine whether the large number of end-inspiratory occlusions during PAV+ operation influences sleep quality in critically ill patients who exhibited good patient–ventilator synchrony during pressure support (PS, baseline). *Methods:* One and two nights' polysomnography was performed in sedated (protocol A, $n = 11$) and non-sedated (protocol B, $n = 9$) patients, respectively, while respiratory variables were continuously recorded. In each protocol the patients were ventilated with PAV+ and PS at two levels of assist (baseline and high). *Results:* In both protocols sleep quality did not differ between the modes of support or the assist levels. In sedated patients sleep efficiency was slightly but significantly higher with PAV+ than with high PS, while it did not differ between modes in non-sedated patients. The two modes of support had comparable effects on respiratory variables. Independent of the mode of support and particularly at high assist, a significant proportion of patients developed periodic breathing during sleep (27% in protocol A and 44% in protocol B). *Conclusion:* In patients exhibiting good patient–ventilator synchrony during PS, the large number of short-term end-inspiratory occlusions with PAV+ operation did not adversely influence sleep quality. With both modes high assist may cause unstable breathing during sleep.

Keywords End-inspiratory occlusion · Assisted modes · Pressure support

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 and more frequent arousals and awakenings than normal [2, 3]. Although largely ignored in ICU, sleep disturbances may adversely affect patient outcome through various pathways [1].

The mode of ventilatory support and patient-ventilator interaction may influence sleep quality. Meza et al. showed in normal humans that pressure-support ventilation (PS) may cause central apneas [4]. Parthasarathy and Tobin observed in critically ill patients greater sleep fragmentation during PS than during assist-volume control ventilation with backup rate slightly lower than the patient's spontaneous breathing frequency [5].

Proportional-assist ventilation (PAV) is a mode of support in which the ventilator pressure is proportional

to instantaneous flow and volume and hence to pressure generated by the respiratory muscles [6]. Numerous studies have shown that PAV improves the synchrony between patient and ventilator [7–10] and may, at least in normal humans, decrease sleep disruption compared with PS [4]. The necessity of regular measurements of respiratory system mechanics, however, imposes a major obstacle to the widespread use of this mode. For this reason methods of non-invasive determination of resistance and elastance of the respiratory system when patients are ventilated with PAV have been described [11, 12]. Based on these methods, a software has been developed (PAV+) which automatically adjusts the flow assist and volume assist such that they always represent constant fractions of the measured values of resistance and elastance of the respiratory system [13]. Calculation of respiratory system mechanics is performed by applying, at random intervals of 4–10 breaths, a 300 ms pause maneuver at the end of selected inspirations [11, 12].

The large number of brief end-inspiratory occlusions may affect the sleep quality in critically ill patients, thus counterbalancing to some extent the advantages of PAV+ in terms of patient–ventilator synchrony. Although studies in both normal humans and patients with sleep apnea indicate that arousals occur when the duration of upper airway obstruction is several-fold longer than 300 ms [14, 15], the type (end-inspiratory) and site (trachea) of occlusion and the critical illness itself may result in different response. In addition, Younes et al. [11] have shown that in critically ill patients behavioral response or phasic activation of expiratory muscles may occur during the 300 ms of occlusion [on line data supplement of ref. 11]. Thus, it is possible that PAV+ might adversely affect sleep in critically ill patients. The aim of this study was to determine whether PAV+ influences sleep quality in critically ill patients already receiving PS. Because it has been shown that neuroventilatory coupling (the ratio between tidal volume and inspiratory effort) (1) may influence sleep quality [4] and (2) is largely affected by the assist level with PS but not with PAV [4, 10], both modes were studied at two levels of assist, while the breathing pattern was continuously monitored. Finally, since nowadays a not inconsiderable proportion of critically ill patients receive sedative drugs during assisted modes of support, due to the fact that the early reinstitution of spontaneous breathing has become an important therapeutic option [16], sleep and breathing patterns during both modes of support were evaluated in two groups of patients, one with and the other without sedation. Some of the results of this study have been previously reported in the form of an abstract [17].

Methods

Additional details on the methods are provided in the Electronic Supplementary Material (ESM).

Patients

Seventeen patients who were receiving mechanical ventilation for at least 48 h were studied. In order to avoid the confounding factor of patient–ventilator dyssynchrony, frequently observed with PS but not with PAV [18], we studied only patients who exhibited good patient–ventilator synchrony with this mode at settings determined by the primary physician. Patients who exhibited significant patient–ventilator dyssynchrony during PS, as indicated by the occurrence of ineffective efforts, excessive triggering delay or apneas [19], were excluded. The institutional ethics committee approved the study and informed consent was obtained from each patient or next of kin.

Measurements

Flow (V'), volume (V), airway pressure (Paw), end-tidal CO_2 ($PETCO_2$), the motion of the rib cage and abdomen, inspiratory (T_I) and expiratory (T_E) time, total respiratory cycle time (T_{TOT}) and peak inspiratory airway pressure (Paw_{peak}) were measured on a breath-by-breath basis, while coefficient of variation of tidal volume (V_T) and T_{TOT} were calculated [5, 13]. Polysomnography was performed on each patient as previously described [5]. Sleep architecture was scored manually [20, 21]. Central apneas, arousals and awakenings were defined using standard criteria [21]. Total sleep fragmentation was calculated as the sum of arousals and awakenings per hour of sleep [5]. Breath components were measured during non-REM (NREM) sleep and in a similar fashion during wakefulness. Periodic breathing was identified visually [21, 22]. Ineffective efforts were evaluated by inspection of flow–time waveform [19]. The elastance (Ers) and resistance (Rrs) of the respiratory system were measured with PAV+ mode using the ventilator software (Puritan-Bennett 840) [11, 12].

Study protocol

The patients were connected to a ventilator (Puritan-Bennett 840), capable of ventilating them with PS and PAV+. All studies were done between 9:00 p. m. and 7:00 a. m. (protocol A) and 11:00 p. m. and 6:00 a. m. (protocol B) in single rooms in the intensive care unit with the window blinds closed. Noise, nursing and other interventions were minimized during the study night.

One and two nights' polysomnography studies were performed in sedated (protocol A, $n = 11$) and non-sedated (protocol B, $n = 9$) patients, respectively. Three patients were studied in both protocols.

In protocol A the patients were sedated with propofol as judged by the primary physician. The level of sedation was such as to achieve a score of 3 on Ramsay's scale with

no changes in the infusion rate during the study time. In protocol B all patients were alert before the study with no need for sedation.

During the study nights the patients were ventilated randomly either with PS or with PAV+ at two levels of assist, baseline and high. The pressure support at which the patient was ventilated before the study, served as baseline pressure support (PS_{base}). With PAV+, the baseline percentage of unloading ($PAV+_{base}$) was set such as to achieve mean inspiratory airway pressure similar to that with PS_{base}. High pressure support (PS_{high}) was obtained by increasing the pressure-assist level by 40–50% or until Paw reached 30 cmH_2O, whichever occurred first. High PAV+ ($PAV+_{high}$) was obtained by increasing the percentage of unloading by 40–50% or until it reached a value of 85%, whichever occurred first.

Data were analyzed by multi-factors analysis of variance for repeated measurements (ANOVA), followed by Tukey's test for multiple comparison if the F-value was significant and non-parametric Mann–Whitney U test where appropriate. A P value less than 0.05 was considered statistically significant. All values are expressed as mean ± SD.

Results

(For further details see the ESM.) Table 1 shows patients' characteristics.

Protocol A: sedated patients

PS_{base} and PS_{high} averaged 14.5 ± 3.9 cmH_2O and 19.5 ± 5.1 cmH_2O, respectively. The corresponding assist values with PAV+ were $44.5 \pm 14.5\%$ ($PAV+_{base}$) and $65.5 \pm 18.1\%$ ($PAV+_{high}$). Ers was 30.7 ± 8.3 and 30.6 ± 8.7 cmH_2O/l with $PAV+_{base}$ and $PAV+_{high}$, respectively. The corresponding values of Rrs were 14.6 ± 4.8 and 14.7 ± 4.4 cmH_2O/l/s. All patients completed the protocol, and the sedation requirements did not increase in any of them during the night (mean propofol infusion 185.5 ± 61.5 mg/h). Ramsay scale (evaluated at the beginning and at the end of the study) remained constant.

Sleep recordings

With PAV+, sleep efficiency was significantly higher than that with PS_{high} independent of the assist level (Table 2). Neither the mode of mechanical ventilation nor the level of assist affected the sleep staging (Table 2, Fig. 1). In all but one patient REM sleep was not observed.

Independent of the mode of mechanical ventilation, two patients (no. 2 and 7) developed periodic breathing during NREM sleep (> 10% of NREM sleep) when the level of assist was increased. In one of these patients (no. 2) apneas were observed when the patient was ventilated with $PAV+_{high}$ (apnea index 8.9 apneas/h). One additional patient (no. 8) exhibited significant periodic breathing during PS_{high}. Total sleep fragmentation did not

Table 1 Patients' characteristics

Patient. no.	Sex	Age (years)	Days on MV	Diagnosis on admission
1 [A]	M	72	7	Postoperative ARF – sepsis
2 [A]	W	45	4	Sepsis
3 [A]	M	73	15	Sepsis
4 [A]	W	75	11	CRF – sepsis
5 [A]	W	77	14	Intestinal ischemia – sepsis
6 [A,B]	W	75	22	Abdominal aortic rupture – MODS
7 [A]	M	70	15	Heart failure
8 [A,B]	M	46	21	Heart failure
9 [A]	W	66	14	Pneumonia – sepsis
10 [A]	M	79	8	AECOPD
11 [A,B]	W	77	10	Heart failure
12 [B]	M	59	15	Cardiogenic shock
13 [B]	M	45	16	Spinal cord injury - ARF
14 [B]	M	71	8	AECOPD – heart failure
15 [B]	M	79	19	Central nervous system damage
16 [B]	M	18	9	Spinal cord injury – ARF
17 [B]	M	60	12	Sepsis
Mean		63.9	12.9	
SD		16.7	5.0	

The superscript letters A and B indicate the protocol(s) in which the patients were studied. *MV*, Mechanical ventilation; *ARF*, acute respiratory failure; *CRF*, chronic renal failure; *AECOPD*, acute exacerbation of chronic obstructive pulmonary disease; *MODS*, multiple organ dysfunction syndrome

Table 2 Protocol A: sleep architecture at different experimental conditions

	$PAV+_{base}$	$PAV+_{high}$	PS_{base}	PS_{high}
Sleep efficiency (% TST)	98.9 ± 2.3	98.1 ± 4.7	93.3 ± 10.8	87.7 ± 16.4 [a]
Stage 1 (% TST)	40.5 ± 41.5	39.4 ± 35.8	50.6 ± 40.5	55.2 ± 41.3
Stage 2 (% TST)	50.5 ± 42.3	48.1 ± 35.5	39.4 ± 37.7	35.0 ± 34.9
SWS (% TST)	9.9 ± 29.5	12.9 ± 28.3	11.01 ± 29.9	10.6 ± 24.3
REM (% TST)	N.O.	0.88 ± 2.7 [b]	N.O.	N.O.
Arousals per hour	4.6 ± 4.9	7.4 ± 10.7	5.4 ± 3.6	6.5 ± 6.7
Awakenings per hour	0.6 ± 1.4	0.8 ± 1.5	1.3 ± 1.4	2.7 ± 3.1
TSF (events/h)	5.2 ± 5.1	8.3 ± 11.1	6.8 ± 4.5	9.2 ± 8.5

TST, Total sleep time; *SWS*, slow-wave sleep; *REM*, rapid eye movement; *TSF*; total sleep fragmentation (arousals + awakenings); *N.O.*, not observed.[a] Significantly different from PAV+ mode.[b] REM was observed in one patient

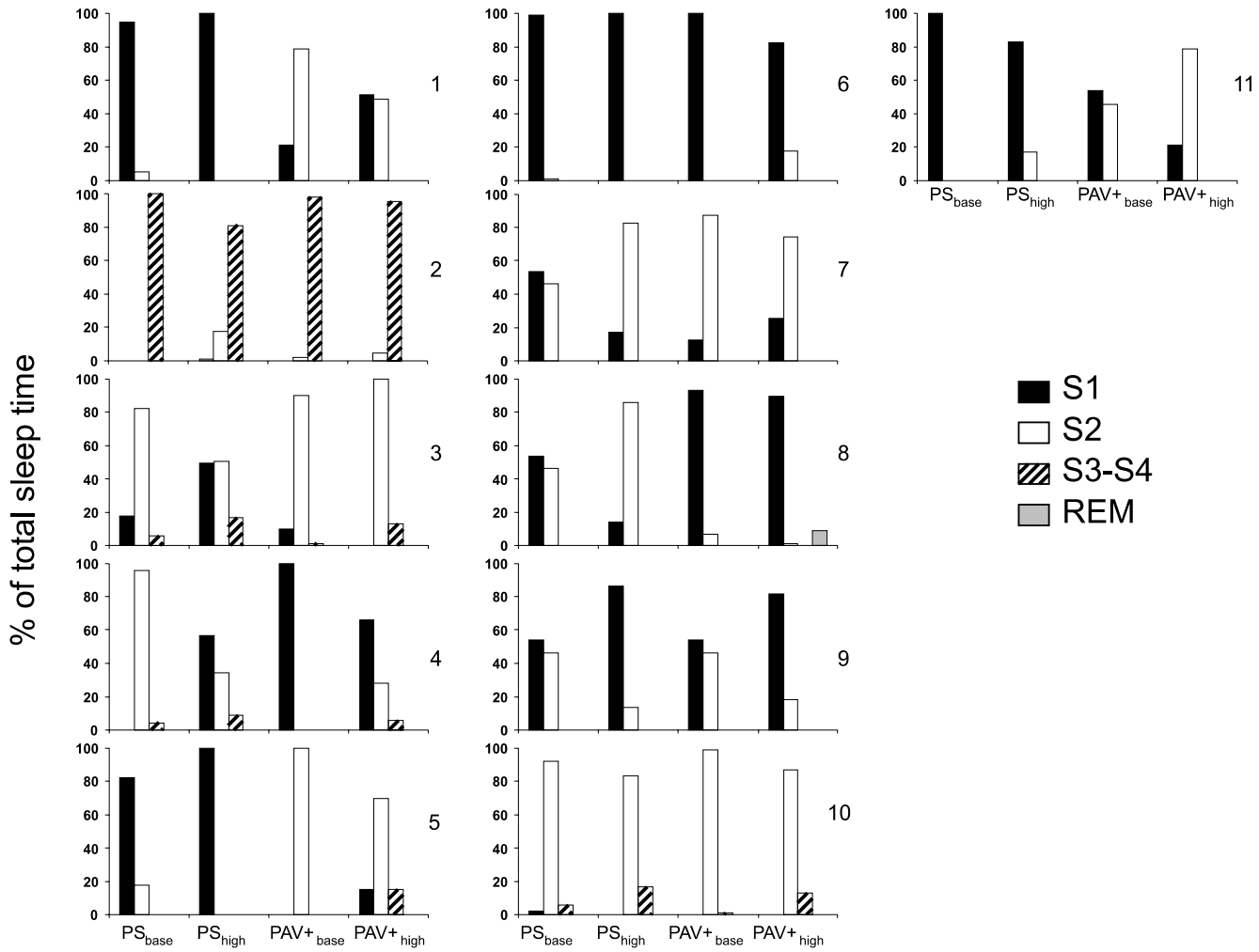

Fig. 1 Individual sleep staging in protocol A (sedated patients). The number in the upper right corner of each panel denotes the patient

differ between modes and was unaffected by the assist level (Table 2). However, total sleep fragmentation in patients with periodic breathing was significantly higher than in those without (20.5 ± 13.4 vs 4.9 ± 4.7 events/h, Mann–Whitney U test, $P < 0.05$).

Respiratory variables

Since only 1 out of 11 patients had reliable data during wakefulness during all experimental conditions studied (due to high sleep efficiency with propofol), respiratory

Table 3 Protocol B: sleep architecture at different experimental conditions

	PAV_{+base}	$PAV+_{high}$	PS_{base}	PS_{high}
Sleep efficiency (% TST)	75.6 ± 10.8	70.7 ± 21.0	68.1 ± 19.2	71.6 ± 14.9
Stage 1 (% TST)	55.0 ± 38.1	33.0 ± 30.4	52.0 ± 39.9	35.3 ± 34.7
Stage 2 (% TST)	36.3 ± 32.1	61.2 ± 27.6	42.5 ± 34.9	43.6 ± 31.6
SWS (% TST)	2.6 ± 7.4	4.1 ± 9.4	2.1 ± 3.9	1.8 ± 4.9
REM (% TST)	6.2 ± 13.9	1.7 ± 4.2	3.5 ± 6.2	19.3 ± 23.3
Arousals per hour	12.2 ± 8.0	11.4 ± 7.6	8.4 ± 4.8	10.5 ± 9.9
Awakenings per hour	4.0 ± 3.0	4.3 ± 3.2	3.6 ± 3.1	3.9 ± 3.4
TSF (events/h)	17.5 ± 8.2	16.8 ± 8.9	13.0 ± 5.5	15.3 ± 10.6

See Table 2 for explanation of abbreviations.

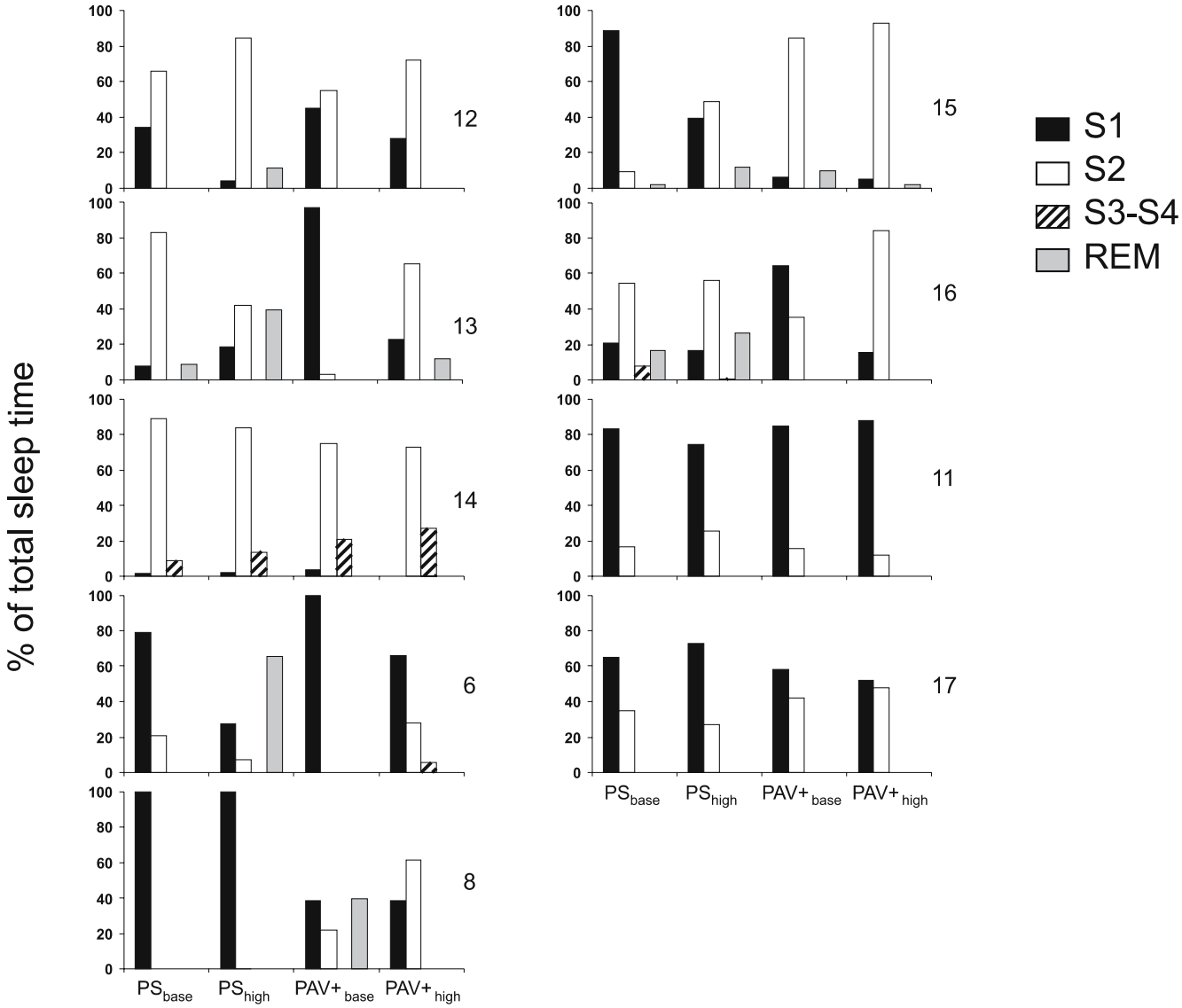

Fig. 2 Individual sleep staging in protocol B (non-sedated patients). The number in the upper right corner of each panel denotes the patient

data during wakefulness are not reported in this protocol. Both modes of support had comparable effects on respiratory variables during sleep (see ESM). Ineffective efforts were sporadically observed in two patients: in one during PS_{high} (3.5 efforts/min) and in another during $PAV+_{high}$ (1.2 efforts/min).

Table 4 Protocol B: respiratory variables during NREM sleep and wakefulness at different experimental conditions

	Awake				NREM			
	$PAV+_{base}$	$PAV+_{high}$	PS_{base}	PS_{high}	$PAV+_{base}$	$PAV+_{high}$	PS_{base}	PS_{high}
V_T (L)	0.48 ± 0.2	0.52 ± 0.3	0.42 ± 0.2	0.45 ± 0.2	0.43 ± 0.2 [a]	0.48 ± 0.3 [a]	0.40 ± 0.1	0.43 ± 0.2
T_I (s)	0.91 ± 0.3	0.96 ± 0.2	0.81 ± 0.2 [b]	0.82 ± 0.2 [b]	0.95 ± 0.2	0.97 ± 0.2	0.82 ± 0.2 [b]	0.83 ± 0.2 [b]
T_{TOT} (s)	2.54 ± 0.9	2.72 ± 0.9	2.40 ± 0.4	2.61 ± 0.6	2.62 ± 0.8	2.74 ± 0.9	2.57 ± 0.4	2.67 ± 0.5
T_I/T_{TOT}	0.37 ± 0.1	0.37 ± 0.1	0.34 ± 0.1	0.32 ± 0.1 [b]	0.37 ± 0.1	0.37 ± 0.1	0.32 ± 0.1 [b]	0.31 ± 0.1 [b]
MV (l/min)	11.47 ± 3.7	10.85 ± 3.7	10.40 ± 3.4	10.22 ± 3.8	9.88 ± 3.5 [a]	10.07 ± 3.3 [a]	9.37 ± 2.9 [a]	9.45 ± 3.3 [a]
Paw_{peak} (cmH_2O)	13.0 ± 6.8	15.9 ± 8.1	14.0 ± 4.1	17.1 ± 5.4	14.6 ± 2.9	17.7 ± 4.2	14.0 ± 4.8	17.2 ± 5.5
$PETCO_2$ (mmHg)	42.0 ± 10.2	40.8 ± 9.2	43.6 ± 9.8	42.5 ± 8.1	45.0 ± 10.3 [a]	42.6 ± 8.4	44.6 ± 9.8	42.7 ± 7.9
$V_T$coefficient (%)	15.1 ± 5.4	15.9 ± 7.0	14.6 ± 6.2	13.9 ± 5.5	12.4 ± 5.5	10.1 ± 3.8	10.4 ± 4.7	14.3 ± 7.4
T_{TOT}coefficient (%)	12.5 ± 5.8	17.1 ± 8.6	14.9 ± 8.9	16.7 ± 9.3	12.1 ± 6.1	12.1 ± 5.3	10.8 ± 5.6	11.2 ± 6.8 [a]

V_T, Tidal volume; T_I, inflation time; T_{TOT}, total respiratory cycle time; T_I/T_{TOT}, inflation to total respiratory cycle time ratio; *MV*, minute ventilation; Paw_{peak}, peak airway pressure; $PETCO_2$, partial pressure of end-tidal CO_2. [a] Significantly different from the corresponding values during wakefulness (state effect). [b] Significantly different from the corresponding values with PAV+ (mode effect)

Protocol B: non-sedated patients

PS_{base} and PS_{high} averaged $14.0 \pm 3.1\ cmH_2O$ and $18.3 \pm 4.4\ cmH_2O$, respectively. The corresponding support values with PAV+ were $48.8 \pm 12.5\%$ ($PAV+_{base}$) and $71.2 \pm 17.7\%$ ($PAV+_{high}$). Ers and Rrs were, respectively, $20.0 \pm 9.2\ cmH_2O/l/s$ and $13.5 \pm 3.3\ cmH_2O/l/s$ with $PAV+_{base}$ and $20.0 \pm 8.8\ cmH_2O/l/s$ and $13.2 \pm 3.3\ cmH_2O/l/s$ with $PAV+_{high}$.

Sleep recordings

Sleep efficiency and sleep stages did not differ between modes or between assist levels. REM sleep was observed in all but three patients (Table 3, Fig. 2).

Four patients developed periodic breathing (> 10% of NREM sleep) during at least one mode of mechanical ventilation: two patients exhibited periodic breathing during all four experimental conditions (no. 8 and 15), one developed periodic breathing during PS at both levels of assist (no. 16), and one during $PAV+_{high}$ (no. 13). Apneas were infrequently observed (apnea index < 5 apneas/h). Total sleep fragmentation did not differ between modes and was unaffected by the assist level (Table 3). Although total sleep fragmentation in patients with periodic breathing was higher than in those without, the difference was not significant (17.8 ± 9.5 vs. 13.8 ± 7.8 events/h, Mann–Whitney U test, $P > 0.05$).

Respiratory variables

Table 4 shows respiratory variables during NREM sleep and during wakefulness at different experimental conditions. The state (sleep or wakefulness) had a significant effect on V_T, minute ventilation, $PETCO_2$ and T_{TOT} variability. The mode of support (PAV+ or PS) had a significant effect only on T_I and T_I/T_{TOT}. Ineffective efforts were sporadically observed in one patient during sleep in all but PS_{base} experimental conditions (1.5 efforts/min with $PAV+_{base}$, 1.2 efforts/min with $PAV+_{high}$ and 2.0 efforts/min with PS_{high}).

Discussion

This study demonstrated that, in critically ill patients who exhibit good patient-ventilator synchrony when receiving pressure-support ventilation at settings determined by the primary physician, the sleep quality was not affected when the patients were ventilated with PAV+ titrated such as to achieve a similar mean inspiratory airway pressure. Furthermore, the two modes had relatively comparable effects on respiratory variables. These results did not change when the assist level was increased, although sleep efficiency in sedated patients was significantly higher with PAV+ than that with high PS. Independent of the mode and particularly at high assist, a significant percentage of patients developed periodic breathing during sleep.

It could be argued that, since the patients were ventilated with PS before the study (as part of the usual clinical management), they were better acclimatized to this mode than to PAV+. This might introduce an important bias in favor of PS and mask any beneficial effect of PAV+ on sleep. We believe that this is unlikely for the following reasons. Firstly, this type of acclimatization process mostly involves behavioral response and thus it should not play a significant role during sleep. Secondly, contrary to PS, where there is a boost of pressure assist, with PAV+ airway pressure increases gradually, reflecting the gradual increase in inspiratory muscle pressure [6, 7, 13]. In addition, with PAV+ expiratory asynchrony is not an important issue [6], whereas it is the rule with PS [13, 19]. It follows that PAV+ is a more patient-adapted mode, and better synchrony is expected between patient and ventilator, leading

to greater acceptability of this mode than of PS [23]. Thus, it is likely that patients receiving PS should adapt to PAV+ within a few breaths. Supporting this assumption, we compared, in a given experimental PAV+ period, sleep and respiratory data obtained during the first hour with those obtained during the last hour and did not observe any difference.

The patients were ventilated for 5 h with each mode of support (2.5 h at each assist level) in protocol A and for 6 h (3 h at each assist level) in protocol B. We believe that these periods may capture the sleep architecture reasonably well, since in critically ill patients circadian rhythm is diminished due to disturbances in melatonin secretion [24, 25]. This has been also supported by 24-h polysomnography studies in critically ill patients showing that sleep architecture and quality did not differ between day and night [2].

To our knowledge this is the first study showing sleep quality during propofol infusion in critically ill patients ventilated with assisted modes of support. We demonstrated that, independent of the mode and assist level, propofol infusion titrated to achieve a score of 3 on the Ramsay scale was associated with excellent sleep efficiency. Recent animal data indicate that propofol may induce sleep by affecting parts of the ascending cholinergic reticular activating system, which modulates the level of arousal [26]. Nevertheless, in ten patients total sleep fragmentation index was greater than 5 events per hour, whereas in five patients greater than 10 and in two patients greater than 20 events per hour were observed (see ESM, Fig. 2S). These findings indicate that sleep disruption, sometimes severe, may occur despite the use of sedatives. Since arousals rather than awakenings contribute most to total sleep fragmentation in these patients (Table 2), sleep disruption during sedation may be undetected. It follows that the bedside assessment of sedation using various sedation scales may not correlate with objective scoring of sleep. However, we should note that our work was not designed to investigate the effect of propofol on sleep in critically ill patients, and further studies are needed to resolve this issue.

Our study showed that, independent of the assist level, PAV+ and PS had comparable effects on sleep architecture. In both sedated and non-sedated patients sleep stages and sleep disruption did not differ between PAV+ and PS. In non-sedated patients sleep efficiency was also unaffected by the mode. Although in sedated patients sleep efficiency was slightly but significantly higher with PAV+ than that with high PS, the difference was too small to be of clinical significance. Therefore, in this group of patients, the large number of end-inspiratory airway occlusions during PAV+ operation (approximately between 150 and 360 occlusions/hour depending on respiratory rate) did not affect the sleep quality. These results indicate that the number of end-inspiratory occlusions of short duration is not a critical factor for sleep disruption in critically ill patients.

In both protocols, and independent of the mode and assist level, a reduced proportion of slow-wave and REM sleep compared to normal was observed. These results are in accordance with previous studies in critically ill patients [2, 5, 27]. Taking into consideration that REM and slow-wave sleep are the most restorative stages of sleep, it appears that critically ill patients are functionally sleep deprived. The critical illness itself and the use of propofol in protocol A may contribute to the observed reduction in REM and slow-wave sleep [1, 24, 28]. Nevertheless, we should note that our patients were lightly sedated with propofol. It has been shown in sleep-deprived animals that a higher dose of propofol may achieve normal sleep [29]. Thus, the REM sleep observed during sedation in one of our patients could be due to propofol dose, although the dose in this patient did not differ from the remaining. Although in critically ill patients a higher dose of propofol may restore sleep architecture, as suggested by animal studies [29], the concomitant decrease in respiratory drive [30] may cause hypoventilation during both PS and PAV+.

Our study demonstrated that, in non-sedated patients, the amount of total sleep fragmentation was comparable to that reported in normal subjects in an intensive care unit environment [27]. On the other hand, some studies have reported considerable sleep fragmentation in critically ill patients [2, 5]. We believe that in our patients the relatively normal magnitude of sleep disruption may be due to the selection criteria and to the use of a single room to study the patients and minimize noise [3, 31]. Indeed, Gabor et al. [27], whose criteria for selection of critically ill patients for sleep studies were quite similar to ours, observed a similar magnitude of sleep fragmentation.

Three patients in protocol A (27%) and 4 in protocol B (44%) (6 out of 17 patients studied) developed significant periodic breathing during sleep, particularly at high assist level (ESM, Fig. S5). Though the number of patients was small, the mode of support did not appear to influence the tendency to develop unstable breathing. Thus, contrary to studies in sleeping normal humans [4], inappropriately high assist with PAV+ may place a critically ill patient at risk of unstable breathing, similarly to PS. It seems that in these patients the underlying disease and not the mode of support is the significant contributing factor for unstable breathing. Indeed, conditions known to predispose to unstable breathing (heart failure and central nervous system damage) [32, 33] were more common among patients with periodic breathing during at least one experimental condition compared with patients with stable breathing (50% vs 20%). The occurrence of unstable breathing with PAV+ suggests that loop gain in these patients is very high (i. e. close to 1) and under this circumstance the increased controller gain (induced by PAV+) cannot be counterbalanced by lowering the inspiratory effort [34]. This is supported by the observed increase in V_T and decrease in $PETCO_2$ with increasing the assist with both modes. It is of interest

to note that in our study periodic breathing was associated with increased sleep disruption, particularly in sedated patients, in accordance with studies showing that unstable breathing may cause sleep fragmentation [5, 35]. These results suggest that periodic breathing during assisted modes of support may cause sleep disruption even in sedated patients, and is a sign of inappropriately high assist.

In non-sedated patients in whom adequate data during wakefulness were obtained, we observed that minute ventilation and $PETCO_2$ differed between sleep and wakefulness during both modes of support. This indicates that adjusting the assist level in PAV+ or PS may have different effects on minute ventilation and gas exchange depending on the sleep–wakefulness state. Similar results, at least qualitatively, have been reported by Parthasarathy and Tobin [5], who showed a significant effect of state on minute ventilation and $PETCO_2$ in patients ventilated with either assist-control ventilation or PS. Therefore, independent of the mode, when the physician decides to change the assist level based on current values of V_T, minute ventilation or $PETCO_2$, the state (sleep or wakefulness) should be taken into consideration.

We should note that, in order to avoid the confounding factor of patient–ventilator dyssynchrony observed frequently with PS but not with PAV [18], we studied only patients who exhibited good patient–ventilator synchrony with this mode. It is not known whether similar results would have been obtained in unselected critically ill patients exhibiting considerable patient–ventilator dyssynchrony. For example, in a patient with excessive intrinsic PEEP, PAV+ may result in significant hypoventilation and gas exchange disturbances [36], effects which may influence sleep. On the other hand, the gross dissociation between the ventilator rate and patient's breathing frequency, which are frequently observed with PS [18], may adversely affect sleep quality. This dissociation does not occur with PAV+ [18] and it is likely that in these patients mechanical ventilation with PAV+ may improve sleep quality. Further studies are needed to resolve these issues.

In conclusion, our study showed that, in carefully selected critically ill patients, the method of measurement of elastance and resistance used by the recent version of proportional-assist ventilation (PAV+) does not adversely affect sleep quality.

Conflict of interest: Dimitris Georgopoulos received in 2006 an amount of 4,500 euros as lecture fee (honoraria) from the company TYCO.

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