

# Sleep Arousal after Lower Abdominal Surgery and Relation to Recovery from Respiratory Obstruction

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**Background:** Hypoxemic episodes occur during sleep after abdominal surgery, possibly caused by airway obstruction. The authors found arousals from sleep more often than respiratory disturbances, so they related changes in sleep state (short arousals from sleep and longer periods of waking) to the sudden increase in respiratory flow that indicates relief from complete or partial respiratory obstruction.

**Methods:** Sleep state and nasal flow were studied in 16 patients receiving patient-controlled morphine and oxygen by facemask on the night after routine gynecologic surgery. Traces were analyzed separately for sleep events and for sudden increases in respiratory flow. The authors noted sleep events (arousals from sleep and transition from sleep to wake) that occurred within 12 s of relief of obstruction.

**Results:** Sleep quality was poor, with only stage 2 sleep in most patients. Median sleep duration was 70% of the study period, with 15 arousals and 6 awakenings per hour of sleep. Only 30% of arousals and awakenings were associated with relief of obstruction. Relief of obstruction also occurred without arousal from sleep, with a median frequency of 38 (30–62) in each night. Relief of obstruction was more frequently associated with arousal from sleep after benzodiazepine premedication (33% vs. 28%;  $P = 0.012$ ), but this allocation was not randomized.

**Conclusions:** Arousals from sleep are frequent after abdominal surgery and mostly not related to respiratory disturbance. Relief of respiratory obstruction can occur during sleep without sleep arousal and during wakefulness.

SLEEP is often disturbed in patients recovering from major<sup>1</sup> and minor surgery,<sup>2</sup> but disturbance is less when opioid analgesia is not used.<sup>3</sup> Opioid analgesics may cause sleep disturbance,<sup>4</sup> and this sleep disturbance is associated with impaired oxygenation.<sup>5,6</sup>

In sleep apnea syndrome, episodes of airway obstruction and hypoxemia impair daytime function<sup>7</sup> and may have harmful cardiovascular effects.<sup>8–10</sup> It is tempting to suppose that similar associations are present after surgery because patients sleep poorly after surgery, have

airway obstruction, and have repeated arousals from sleep and episodes of hypoxemia.<sup>5,11</sup> An arousal from sleep is defined as a short increase in electroencephalographic frequency, from a period of at least 10 s of sleep, that does not necessarily lead to a longer period of wakefulness. However, the frequency of arousals is greater than the frequency of episodic obstruction.<sup>12</sup> Although there is no doubt that changes in sleep state are associated with changes in respiration<sup>13,14</sup> and that repeated changes in sleep state affect respiratory reflexes,<sup>15–17</sup> the explanation that arousals from sleep are caused by episodes of airway obstruction does not fit our observations adequately. To find how sleep and respiratory changes are linked, we studied patients receiving morphine *via* patient-controlled administration. We noted the episodes of relief of partial obstruction, arousals from sleep, and changes of sleep state. We chose relief of obstruction as an index of respiratory disturbance because it is an abrupt respiratory change that can be recognized easily and exactly timed to within a breath or two. In contrast, the onset of partial respiratory obstruction is often gradual and difficult to define. We considered that changes in respiration were linked with sleep events if they decreased within 12 s of a change in electroencephalographic state. Ventilatory changes occur 4–8 s after changes in sleep,<sup>13,14</sup> so we used twice this time difference to include most breathing changes that could be related to a change in electroencephalographic state.

## Materials and Methods

With approval from the Lothian Health Board Ethics Committee (Edinburgh, United Kingdom), we observed patients after surgery. We did not change clinical management other than to apply monitoring equipment. We asked women who were about to have abdominal surgery for nonmalignant gynecologic conditions to participate, and we obtained written informed consent. We excluded patients who were already taking opioid analgesic agents or other centrally acting medication, such as antidepressants, anxiolytics, and night sedatives. All patients came to the hospital on the morning of surgery. Because this was an observational study, anesthetic management was not standardized and was given according to clinical routine. However, management was similar in all cases: either no premedication or premedication with temazepam or diazepam by mouth between 1 and 2 h before surgery, followed by propofol intravenous for anesthetic induction, nitrous oxide, and isoflurane to

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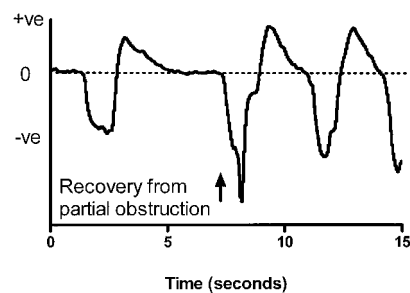
maintain anesthesia, and neuromuscular blockade with either atracurium or vecuronium. Opioid supplements during surgery were given either as morphine or, in one case, diamorphine. Some patients were given nonsteroidal analgesic agents, such as diclofenac rectally or piroxicam sublingually. After surgery, all patients were given patient-controlled analgesia (2 mg intravenous morphine with a 5-min lockout period between demands). All patients received prophylactic antiemetic treatment with 50 mg cyclizine intravenous at the end of surgery and 2.5 mg cyclizine with each morphine dose.

During anesthesia and surgery, the following electrodes and sensors were applied. For electroencephalogram recording, we inserted subcutaneous scalp electrodes in the C3-C4, Cz-Pz positions and fastened them in place with collodion. We applied disposable gel electrodes above and lateral to the eyes for electrooculography and submentally for electromyographic measurement.

After the patient had returned to the ward after the operation, we taped a pulse oximeter probe to a finger (Embla; Flaga hf, Reykjavik, Iceland) and placed a nasal pressure cannula (Pro-Tech airflow sensor; Woodinville, WA), similar to a very narrow nasal oxygen cannula, in the nostrils. This cannula was connected to a differential pressure transducer (type 3EA; Gaeltec, Skye, United Kingdom) and generates a signal that is proportional to nasal flow.<sup>18,19</sup> The devices were taped firmly in place, and the cables and tubing were lead in a single bundle from the patient's shoulder to a miniature data logging harness. The patients recovered from anesthesia in a dedicated recovery area where they were given intravenous morphine until comfortable, and patient-controlled analgesia was established. They were then nursed in a large gynecologic ward containing 20 beds. When the patient was stable and comfortable in the ward, we connected a miniature data-logging system (Embla) set to start recording from 10 PM until 6 AM the next morning. The submental electromyogram was filtered between 22 and 90 Hz with a 50-Hz notch, and other signals were filtered between 0.3 and 35 Hz.

No special precautions were taken to ensure that the ward was quiet or to adjust the level of lighting. However, the usual ward routine is to dim the lights between 22:00 and 06:00 h, and ward activity between these times is limited. Oxygen therapy using a simple variable function mask with a flow of 4 l/min is standard for our patients receiving patient-controlled analgesia, and this was given over the study period. Patients were not monitored clinically for pulse oxygen saturation, and the measurements that we recorded were not displayed. The next morning, the recording apparatus was removed, and the patients were asked about their quality of sleep, using semistructured questions.

The signals were transferred to a laboratory display unit (Somnologics; Flaga hf) and coded so that the traces could be studied without knowing their source. The



**Fig. 1. Nasal cannular pressure.** An example of recovery from partial respiratory obstruction: At the arrow, there is an abrupt change in signal amplitude, associated with an increase in frequency and a change in waveform. The preceding waveform is flattened.

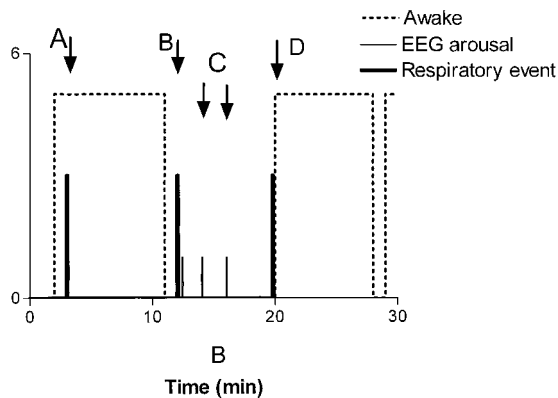
respiratory signal and signals for sleep staging were analyzed separately by a single trained investigator (A. W.). Respiratory and sleep signals were analyzed using the same 30-s epochs. Using the standard scoring system used since 1968,<sup>20</sup> sleep was classified into the following states: alert or relaxed wakefulness, non-rapid eye movement (REM) stages 1-4, and REM. Each epoch was considered either wake or sleep if either state occupied more than 15 s. The time of start and the duration of wake periods were noted.

Electroencephalographic arousals were recognized using the method of Cheshire *et al.*,<sup>21</sup> and the times were noted. Using this method, an arousal is at least 1.5 s of alpha or theta electroencephalogram rhythm and a concurrent increase in submental electromyographic activity, after a period of at least 10 s of sleep. The nasal flow signal was scored for events that we classified as relief of obstruction, and the times were noted. A relief of obstruction had occurred if one or more of the following criteria were present:

1. an obvious increase in respiratory frequency, within three respiratory cycles
2. a change in the inspiratory flow pattern from a flattened to a more rounded shape<sup>19</sup>
3. a sudden increase in flow amplitude<sup>22</sup> (fig. 1)

Generally, two or three of these features were present. After episodes of relief of obstruction had been identified, we retrospectively noted the features that had been used for identification.

After the signals used for sleep and respiratory events had been separately classified, the code was broken, and the data were exported to a spreadsheet (Excel 2000, version 9.0; Microsoft Corp., Seattle, WA) to determine the times between the electroencephalographic features (arousal or wake) and relief of obstruction. Relief of respiratory obstruction and sleep events were considered related if they occurred within 12 s of each other (fig. 2). They were classified as relief of obstruction in relation to either electroencephalographic arousal (the short-term appearance of the wake state) or transition to



**Fig. 2.** Analysis allowing association between events. Each event (recovery from obstruction, arousal from sleep, and transition from sleep to wake) is coded by a bar given a different arbitrary amplitude. Sleep state is shown by awake as 5, asleep as 0, a recovery from obstruction as 3, and an arousal as 1. Arrows indicate the possible separate classifications. (A) Recovery from obstruction alone; (B) recovery from obstruction associated with arousal; (C) arousal alone; (D) recovery from obstruction and transition from sleep to wake. EEG = electroencephalographic.

wakefulness (when an epoch of sleep is followed by at least 1 min of waking). We noted whether electroencephalographic arousal or transition to wakefulness was either preceded or followed by a relief of obstruction or whether sleep events occurred alone. Oxygenation during the study period was summarized as the mean and SD of oxygen saturation values at 1-s intervals.

#### Statistical Management

Data analysis was predominantly descriptive, using median and upper and lower quartile values (Minitab release 12, 1998; Westwood Business Park Coventry, United Kingdom). The frequencies of events were compared with analysis of variance. *Post hoc* observations were interpreted with the Mann-Whitney U test.

**Table 1.** Patient Details

Type of Surgery	Premedication Agent, mg	Age, yr	Height, cm	Weight, kg	PCA Morphine, mg
Hysterectomy	None	55	155	60	10
Hysterectomy	None	64	168	97	30
Hysterectomy	None	40	167	60	32
Hysterectomy	None	38	156	70	30
Myomectomy	None	38	168	97	28
Laparotomy	None	44	165	68	40
Median (range)		42 (26)	166 (13)	69 (37)	30 (30)
Hysterectomy	Temazepam, 20	42	163	72	54
Hysterectomy	Temazepam, 20	51	170	75	32
Hysterectomy	Temazepam, 20	38	154	57	30
Hysterectomy	Temazepam, 10	49	156	93	16
Hysterectomy	Temazepam, 20	56	171	70	26
Hysterectomy	Temazepam, 20	58	162	86	26
Hysterectomy	Temazepam, 20	48	160	66	28
Laparotomy	Diazepam, 10	60	160	59	34
Median (range)		50 (22)	161 (17)	71 (36)	29 (38)

PCA = patient-controlled analgesia.

## Results

We asked 23 patients to participate. Four declined, and recordings were technically inadequate in three subjects. Two additional subjects were excluded: one because of a variation in anesthetic technique (epidural analgesia); the other did not have a transverse lower abdominal incision. In one subject, recording of oxygen saturation was not successful, but the other data from this patient were used.

Details of the patients analyzed are given in table 1, separated according to premedication. There was no significant difference in characteristics between those who did and did not receive premedication.

Generally, the patients did not report good sleep. The median proportion of sleep in the study period from 22:00 to 06:00 h was 70%. No patients had any stage 3 or 4 sleep, and only four patients had any REM sleep, ranging between 8 and 86 min. The characteristics of the sleep for each patient are shown in table 2. There were many arousals (short periods) and awakenings (longer changes) from sleep. The median number of awakenings in the 8-h study period was 35 (22-45), and the frequency of arousals per hour of sleep was 15 (10-20). The number of electroencephalographic events (transient arousal or waking) associated with relief of obstruction was 36 (20-50) per night. This was significantly less than the total number of arousals and awakenings (78 [55-106];  $P < 0.001$ ). A typical example of an arousal from sleep, with no change in respiratory pattern, is shown in figure 3, and an episode of relief from respiratory obstruction, in a conscious subject, is shown in figure 4.

An episode of relief from respiratory obstruction generally showed all three of the criteria used (median frequency of all three criteria occurring in these events, for all the subjects, was 53% [34-58%]). A loss of flattening of the waveform was seen in 80% (60-98%), and



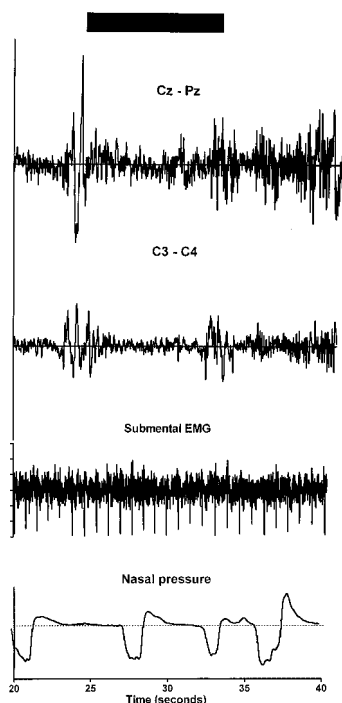
**Table 2. Sleep Pattern, Arousals and Awakenings, and Relation with Recovery from Obstruction (Respiratory Events)**

Premedication Agent	Duration, min			Mean SpO <sub>2</sub> , %	No. of EEG Arousals			No. of Awakenings			Respiratory Events without EEG Events	
	Awake	Asleep	REM		Resp First	Resp After	Alone	Resp First	Resp After	Alone	Total	During Sleep
None	95	386	86	—	14	4	98	2	1	8	31	19
None	119	354	0	90	48	7	152	7	13	43	51	31
None	109	332	0	97	7	3	36	2	1	15	22	17
None	149	332	13	100	30	7	94	8	5	26	50	23
None	112	369	0	95	1	2	17	8	5	21	33	27
None	75	405	0	99	3	9	46	9	1	12	23	5
Median	112	354	0	97	10	5	70	7	3	18	32	21
Q1-Q3	109-119	332-369	0-13	92-99	4-26	3-7	38-97	3-8	1-5	13-25	23-50	14-28
Benzodiazepine	172	309	0	98	26	14	65	6	14	39	84	50
Benzodiazepine	135	345	8	95	18	7	73	12	4	21	35	18
Benzodiazepine	71	410	0	100	25	5	58	4	7	28	59	36
Benzodiazepine	262	219	48	98	10	1	25	2	2	10	41	7
Benzodiazepine	223	126	0	97	1	12	21	18	1	35	164	160
Benzodiazepine	213	267	0	98	3	9	39	14	6	27	72	43
Benzodiazepine	82	398	9	99	34	3	55	4	3	16	34	21
Benzodiazepine	150	331	0	99	42	3	91	4	2	17	28	11
Median	160	219	0	98	21	6	57	5	4	24	50	28
Q1-Q3	122-215	255-358	0-8	97-99	8-28	3-10	45-67	4-12	2-6	17-30	34-81	13-48

EEG = electroencephalographic; Q1 = first quartile value; Q3 = third quartile value; REM = rapid eye movement; Resp after = respiratory event after EEG arousal; Resp first = respiratory event before EEG arousal; SpO<sub>2</sub> = oxygen saturation measured by pulse oximetry.

amplitude changes were seen in 74% (5-100%). Waveform and amplitude changes were associated alone in 10% of events, and waveform and frequency were associated in 14%. In only two subjects were frequency changes seen in isolation.

The number of episodes of relief of respiratory ob-



**Fig. 3.** An example of a short period of arousal from sleep, indicated by the solid bar, with no change in breathing pattern. The traces are two electroencephalogram channels, a submental electromyogram (EMG), and nasal flow.

struction in the study period not linked with sleep events (either arousals or awakenings) was 38 (30-62). This was greater than the number of occasions when respiratory and sleep events were related (fig. 5). The populations in which recovery from respiratory obstruction was not related to sleep events and the population in which respiratory and sleep events were related were significantly different (analysis of variance,  $P < 0.001$ ). Sleep was fragmented. The rate of wakening was 4.8 (3.1-7.3) episodes per hour of sleep.

Patients who had received premedication spent less time asleep and had more respiratory-related arousals. After premedication, the proportion of respiratory-related arousals was 32% (31-36%), compared with 28% (22-29%) ( $P < 0.05$ ; fig. 6). Premedication had no apparent effect on the incidence of respiratory disturbances not associated with arousal.

If sleep events were related to relief of obstruction, this relief of obstruction occurred more frequently before than after the changes in sleep state, but the difference was not great. Premedication did not have a clear effect (fig. 7).

Oxygenation was satisfactory in all except one patient, who had a mean saturation of only 90%. The record showed a period of a lower saturation, later returning to a satisfactory value. The oxygen mask probably came off and was then replaced. In the remainder of the patients, the mean oxygen saturation measured by pulse oximetry (SpO<sub>2</sub>) was 98%, and the mean SD of the values in each patient was 1.2%, indicating that there were very few changes in SpO<sub>2</sub>. We found no relations between oxygen saturation and respiratory disturbances, morphine use

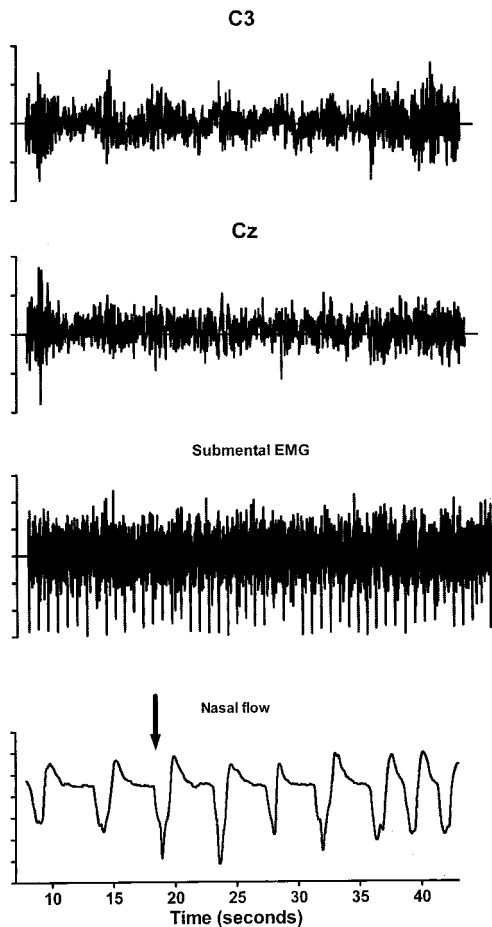


Fig. 4. An example of relief of obstruction (arrow), in a patient who was awake. EMG = electromyogram.

and the other measurements, or sleep quality and subjective reports from the patients. Most patients reported poor sleep and no dreams, and no patient wished to have measurements for a further night.

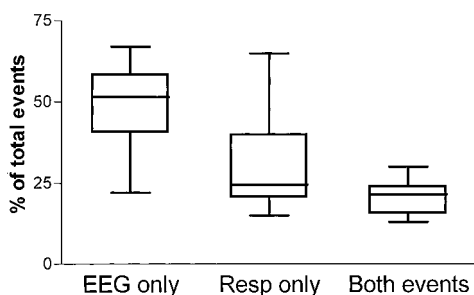


Fig. 5. Distribution of the total events recorded in the patients over the observation period. Associated = occasions when relief from respiratory obstruction and sleep state change occurred within 12 s; EEG = electroencephalogram; EEG only = either arousal or transition to wake, without association with a recovery from obstruction; resp only = relief of respiratory obstruction, not associated with change in sleep state.

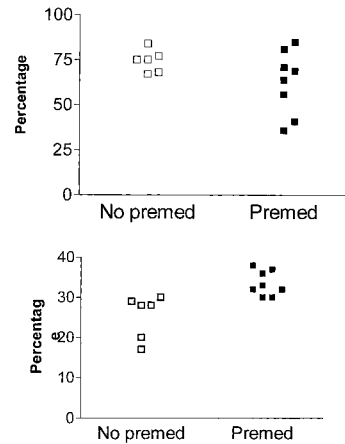


Fig. 6. Proportion of study time asleep and proportion of arousal and wake events that were related to relief of respiratory obstruction in patients who had received benzodiazepine premedication (filled symbols) and those who did not receive premedication (open symbols).

Discussion

In a previous study of patients receiving morphine analgesia after abdominal surgery, we found that hypoxic events and airway obstruction<sup>23</sup> were more frequent when the patients were awake. Perhaps respiratory disturbances or hypoxemia start when the patient falls asleep and then cause arousal, so that the epoch in which they were noted is classified as wakefulness. In this way, an event might seem to have occurred in the awake state, but it could have started when the patient was asleep.

We studied this possibility and sought to clarify the relation between relief of respiratory obstruction and arousals or awakenings. Sleep was generally poor, usually stage 2, with frequent awakenings and even more frequent arousals. Only approximately half of these sleep events were in relation to respiratory disturbances. Although they were less frequent, we also found relief of respiratory obstruction that was not associated with awakenings or arousals, and only 57% of these occurred during sleep. Our findings do not support the possibility that relief of airway obstruction precedes arousal from sleep or that relief of obstruction can be classified as occurring in a period of wakefulness when in fact it may have started during sleep.

The criteria to define arousal that we used were standard but may not detect small changes in sleep state. For example, playing a sound to a sleeping patient with obstructive sleep apnea can shorten a period of obstruction, even though no electroencephalographic arousal is evident.<sup>24</sup> Electroencephalographic frequencies change during the progress of obstructive apneas, irrespective of whether the obstruction ends in an arousal.<sup>25</sup> This suggests that arousal is gradual and not a categorical event. Our method of identifying arousal from sleep may not identify lesser degrees of arousal.

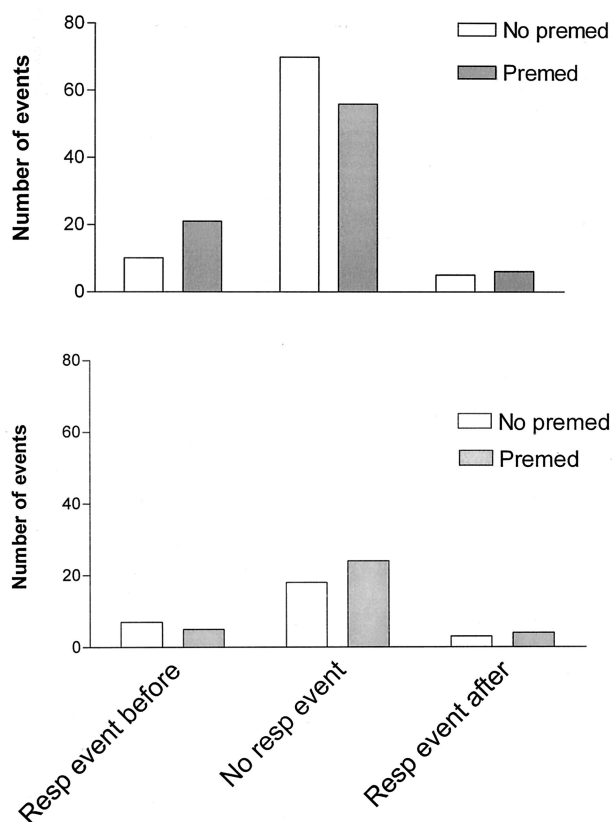


Fig. 7. Relation between arousals from sleep (*top*) and transition from sleep to wake (*bottom*) with episodes of recovery from obstruction. In most cases (*center columns*), there was no association with recovery from obstruction. In fewer cases, relief of respiratory obstruction could precede or follow arousal or awakening (*left and right columns*). There was no clear effect of premedication (*open columns* = no premedication; *shaded columns* = patients who received benzodiazepine premedication).

Several definitions are used for an arousal.<sup>26</sup> The most frequent, defined by the American Sleep Disorders Association,<sup>27</sup> is only moderately repeatable, particularly when judging arousal from light sleep.<sup>28</sup> We used a well-accepted and relatively stringent definition, which includes an increase in chin electromyogram, however brief, and a return to theta or alpha rhythm for more than 1.5 s.<sup>21</sup> A very similar definition (Université Catholique de Louvain, Brussels, Belgium) has comparable agreement and repeatability to the American Sleep Disorders Association definition but is easier to use because of the associated electromyographic changes required.<sup>29</sup>

Other workers have related arousal to changes in respiration, such as obstructive nonapneic events, similar to the majority of the events we studied. For example, esophageal and pharyngeal pressures were measured in patients with mild obstructive sleep apnea to identify respiratory effort-related arousals.<sup>30</sup> Most reductions in breathing were associated with cortical "microarousal," but the definition incorporated both electromyographic and respiratory features.

The onset of partial airway obstruction is associated with a reduction in flow, perhaps diversion of expiratory flow away from the nose, and characteristic changes in the waveform of inspiratory flow.<sup>19</sup> Because respiratory flow decreases gradually over a number of breaths, the exact time of onset of these changes in respiration is often not clear-cut. However, recovery from obstruction is characteristically prominent, abrupt, and easy to define. Generally, our patients showed all three criteria of recovery from partial obstruction that we had set. However, a small proportion of patients had respiratory events that were characterized by changes of amplitude and frequency only, with no detectable changes in inspiratory waveform. Because the pattern of distribution of these events was similar in other respects, we consider that these events were biologically similar to the events seen in other patients who had all three features. It is possible that the features of recovery from respiratory obstruction may be characteristic for particular individuals. We are confident that we were detecting recovery from obstructive, nonapneic events and not arousal from sleep that could alter the breathing pattern. However, even if this small proportion of events were misclassified, as they did not have all the features of relief of obstruction, this would not explain the limited association between relief of obstruction and arousal or awakening that we report here.

We looked for a link between these respiratory events and transient arousal or longer-term awakening. Because others have found that respiration and sleep state change either simultaneously<sup>31</sup> or within 4–8 s,<sup>13,14,32</sup> we took 12 s as a generous time to link changes in respiration and sleep state. We considered the possibilities that either increasing drive with recovery from respiratory obstruction could trigger arousal or arousal could resolve obstruction. In fact, we found that most arousals were independent of recovery from airway obstruction. When recovery from obstruction and arousal were close together, the likelihood of arousal before or after the respiratory event was similar.

In sleep apnea syndrome, the likely mechanism is that arousal leads to recovery from airway obstruction.<sup>33</sup> However, our patients did not have this condition. Another factor, such as morphine administration, seems to affect the control of the airway. Previous work comparing morphine analgesia and regional analgesia reported frequent obstructive episodes during morphine administration, but in that study, obstructive episodes were only noted during sleep.<sup>5</sup>

During sleep, upper airway muscle activity is an important factor in the maintenance of airway patency. The neurons that control this muscle tone are controlled by the pontine reticular formation, whose activity is reduced during sleep. The activity of medullary raphe neurons is modulated by a cholinergic mechanism and can be reduced by intrapontine carbachol,<sup>34</sup> causing an

REM-like state. Serotonergic neurons in the medullary raphe<sup>35</sup> tonically activate the hypoglossal nucleus *via* 5HT<sub>2</sub> receptors. Pontine injections of carbachol reduce serotonin release at the hypoglossal neurons<sup>36</sup> and reduce genioglossal activity.

Opioids inhibit REM sleep by a  $\mu$ -opioid receptor mechanism.<sup>37</sup> Opioids inhibit acetyl choline release in the medial pontine reticular formation<sup>38,39</sup> and cause sleep disruption that can be antagonized by carbachol.<sup>40</sup> This sleep disruption is characterized by a decrease in REM sleep. Morphine may dissociate motor control of the upper airway from the sleep state so that airway control may be impaired even in subjects who are awake, leading to loss and return of airway patency such as the episode illustrated in figure 4. In addition, the reduction in respiratory drive by morphine (which is directed to the airway muscles as well as to the diaphragm) may allow loss of airway control of this type even when patients are awake. All the patients we studied also received cyclizine in addition to morphine, in proportion to the morphine doses given by PCA. Cyclizine, like other phenothiazines, can inhibit central cholinergic receptors and cause or accentuate confusion<sup>41</sup> and could possibly increase this effect of morphine.

Premedication with benzodiazepines seems to increase the association between respiratory obstruction and sleep arousal. Such an association was not found in a randomized trial of nitrazepam in patients with sleep apnea where hypoxemia or obstructive episodes were not increased.<sup>42</sup> However, our patients had undergone surgery and were given opiates, which interact with benzodiazepines, so different results are perhaps likely.

The effects of surgery on sleep have recently been summarized.<sup>43</sup> Poor sleep has been reported after surgery<sup>4</sup> and in high dependency<sup>44</sup> and intensive care units.<sup>45</sup> It goes unrecognized by nurses and is found in patients nursed in single rooms and after attempts to keep quiet.<sup>44</sup> Sleep disturbance is not known to be harmful,<sup>43</sup> and the effects of opioids on sleep quantity and pattern remain to be adequately defined. Although parallels can be drawn between patients after major surgery and patients with the sleep apnea/hypopnea syndrome, there do seem to be some fundamental differences. In the sleep apnea/hypopnea syndrome, the link between increased airway resistance, arousal, and recovery from airway obstruction is recognized and probably causal. After operation, the events of arousal, awakening, and recovery from airway obstruction are not clearly linked. Arousals occur without respiratory changes, and obstruction and recovery from airway obstruction occurs in patients who do not fulfill the standard criteria for sleep.

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