Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern

J. Rosenberg, G. Wildschiodtz, M. H. Pedersen, F. Von Jessen and H. Kehlet

**SUMMARY**

Ten patients undergoing major abdominal surgery under general anaesthesia were monitored with a pulse oximeter, electroencephalogram, electromyogram, electrocardiogram and eye and hand movement sensors two nights before and three nights after surgery. Episodic hypoxaemic events were increased significantly after surgery (P < 0.05). Rapid eye movement (REM) sleep decreased significantly on the first night after operation (P < 0.05). Seven patients had increased amounts of REM sleep (rebound) on the second, third or both nights compared with the preoperative night. Slow wave sleep was depressed significantly on the first two nights after operation (P < 0.05). REM sleep-associated hypoxaemic episodes for individual patients increased about three-fold on the second and third nights after operation compared with the night before operation (P < 0.05). We conclude that postoperative sleep pattern is disturbed severely with early depression of REM and slow wave sleep and with rebound of REM sleep on the second and third nights. Postoperative rebound of REM sleep may contribute to the development of sleep disordered breathing and nocturnal episodic hypoxaemia. (Br. J. Anaesth. 1994; 72: 145-150)

**KEY WORDS**


Late postoperative constant hypoxaemia is a well known phenomenon and superimposed episodic hypoxaemia has been demonstrated after major orthopaedic, abdominal and thoracic surgery [1-7]. Postoperative hypoxaemia may be a contributing factor in myocardial ischaemia [3,8] and infarction [9], wound infection [10] and mental confusion [11] after otherwise uncomplicated surgery. The pathogenesis of the episodic changes remains largely unknown, although preliminary data in six very obese patients showed episodic hypoxaemia to be associated with ventilatory arrhythmias during rapid eye movement (REM) sleep in the late postoperative period [12]. The aim of the present study was to investigate the relationship between sleep pattern and episodic hypoxaemia in low-risk patients after major abdominal surgery.

**MATERIAL AND METHODS**

The study was approved by the local Ethics Committee and the patients participated in the study after giving their informed consent. We studied 10 patients (six male; median age 54 (range 32-75) yr; weight 72 (46-87) kg; height 172 (158-183) cm) undergoing major abdominal surgery. None of the patients was receiving regular medication before operation and exclusion criteria were symptoms of neurological, cardiac or respiratory disease, including excessive daytime sleepiness. Oxygen therapy was not given during the first 3 days after surgery, other than a few hours (< 6 h) in the recovery unit. All patients underwent elective surgery with no recognized risk factors and received routine postoperative care.

Three patients underwent colonic resection, one Roux-en-Y anastomosis, four gastric resection and two colo-colostomy after Hartmann resection. All patients received oral diazepam for premedication (table I); anaesthesia was induced and maintained with thiopentone, midazolam, low-dose fentanyl, suxamethonium, pancuronium and nitrous oxide in oxygen. Postoperative analgesia comprised morphine or ketobemidone 5-10 mg i.m. on demand; opioid administration was monitored for the first 3 days after surgery (table I). Sedative drugs were not used in the surgical ward. All patients slept in a single-bed

| Table I. Perioperative medication (median (range)). Opioid doses are given as morphine equivalents. Day was defined as 07:00-19:00, night as 19:00-07:00 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Premedication (diazepam) (mg) | 10 (10-20) | Intraoperative fentanyl (µg) | 0.55 (0.4-0.8) | Opioids (morphine equiv.) |
| Day 0: Day | 10 (5-21) | | | |
| Night | 21 (8-30) | | | |
| Day 1: Day | 22 (10-50) | | | |
| Night | 22 (0-80) | | | |
| Day 2: Day | 17 (0-30) | | | |
| Night | 15 (0-45) | | | |
| Total, day 0-2 | 107 (28-192) | | | |

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room with the door closed and the nursing staff were allowed to enter the room only when called or to administer the i.v. fluid regimen. Thus routine hourly checks were not performed by the nurse. All patients were monitored in the bedroom with a continuous electrocardiogram (ECG) with an alarm for cardiac arrest. In this way, noise and disturbance were limited to a minimum. The bedroom was maintained at 20°C.

Arterial oxygen saturation (SpO₂) was measured with a pulse oximeter (Nellcor N-200) with an adhesive finger probe [13] on two consecutive nights before operation and on the first three nights after operation. Data were stored in the internal memory of the oximeter with subsequent data printout the following morning. The oxygen saturation tracings were analysed for mean all-night oxygen saturation by estimating average values for every 15-min period throughout the recording, followed by averaging of all the periods [3]. Episodic hypoxaemia was defined as a decrease in oxygen saturation of 5% or more within 2 min [3]. Episodic desaturations were classified on the basis of whether the nadir was greater than (or equal to) or less than 80% SpO₂ [2]. Minimum SpO₂ was defined as the minimum single value for SpO₂ observed during the study night. Analysis of oximetry data was performed without knowledge of the sleep data except when calculating the frequency of hypoxaemic episodes during REM sleep; this was performed after scoring of REM sleep periods (see below).

For sleep staging, the patients were monitored with a Somnolog System (Ventec Aps, Hellerup, Denmark) [14] on two consecutive nights before operation and on the first three nights after operation. The Somnolog stores continuously electroencephalogram (EEG) (α and δ activity by one-channel EEG—a modified F3-A2), electromyogram (EMG) (electrodes placed under the base of the mandible), ECG (two electrodes on the sternum), eye and hand movements (by movement sensors placed on the upper eyelid and dorsally to the proximal joint of the left index finger) and noise level placed on the upper eyelid and dorsally to the mandible), ECG (two electrodes on the sternum), eye and hand movements (by movement sensors placed on the upper eyelid and dorsally to the proximal joint of the left index finger) and noise level placed on the upper eyelid and dorsally to the mandible). Data were stored in the internal memory of the Somnolog with subsequent down-loading to a personal computer the following morning of the Somnolog with subsequent data printout the following morning. The oxygen saturation tracings were divided arbitrarily into stages 1, 2, 3 and 4 (stages 3 and 4 are termed slow wave sleep (SWS) and rapid eye movement (REM) sleep (stages 1, 2 and SWS comprise non-REM sleep)). Stage 1 = transient phase occurring usually at sleep onset; stage 2 = predominant sleep stage consisting of small amplitude brain waves together with sleep spindles and K complexes; stage SWS = associated with high-voltage, synchronized slow brain waves and accompanied usually by pulses of growth hormone secretion; stage REM = characterized by rapid bilaterally synchronous eye movements, desynchronized EEG and loss of skeletal muscle tone. = REM sleep.

Results

Median duration of surgery was 203 (range 95–270) min and intraoperative blood loss 700 (200–1500) ml. None of the patients developed postoperative complications, including febrile states requiring treatment.

There was a significant decrease in the duration of REM sleep on the first night after operation (table II). Seven of the 10 patients had increased durations of REM sleep (REM rebound) on the second or third (or both) nights after operation compared with the preoperative value for SpO₂ observed during the study night.

Table II. Sleep characteristics (median (range)). REM = rapid eye movement sleep; NREM = non-REM sleep; SWS = slow wave sleep (NREM stage 3 and 4). Sleep stages are given as percentage of total EEG monitoring time. * P < 0.05 compared with preoperative night, Wilcoxon signed rank test.

<table>
<thead>
<tr>
<th></th>
<th>Adaptation night</th>
<th>Preoperative night</th>
<th>After operation</th>
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<tbody>
<tr>
<td></td>
<td>Night 1</td>
<td>Night 2</td>
<td>Night 3</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>375 (119–468)</td>
<td>332 (233–440)</td>
<td>348 (269–442)</td>
</tr>
<tr>
<td>Awakenings and arousals (No.)</td>
<td>22 (7–38)*</td>
<td>18 (5–29)</td>
<td>21 (7–39)</td>
</tr>
<tr>
<td>Sleep stage (%)</td>
<td>NREM 1</td>
<td>8 (3–15)</td>
<td>4 (1–39)</td>
</tr>
<tr>
<td></td>
<td>NREM 2</td>
<td>43 (21–63)</td>
<td>38 (34–57)</td>
</tr>
<tr>
<td></td>
<td>NREM SWS</td>
<td>13 (0–23)</td>
<td>21 (4–30)</td>
</tr>
<tr>
<td></td>
<td>REM</td>
<td>17 (10–27)</td>
<td>17 (10–35)</td>
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</table>
LATE NOCTURNAL HYPOXAE/A

In order to assess the relationship between postoperative REM sleep and episodic hypoxaemia (fig. 2), we defined an index of hypoxaemic episodes during REM sleep for individual patients ([number of hypoxaemic episodes in REM sleep divided by total number of hypoxaemic episodes] divided by REM sleep time as a proportion of total sleep time). Thus an index of 1 indicates that the distribution of hypoxaemic episodes was equal between REM and non-REM sleep (corrected for the duration of REM sleep and an index > 1 indicates that episodic hypoxaemia was more concentrated in REM than in non-REM sleep for that night. If a patient had no REM sleep on a given night, the index was 0. An increase in the index after operation indicated that postoperative REM sleep differed from REM sleep before operation with respect to the accompanying risk of ventilatory arrhythmias and episodic hypoxaemia. Seven patients had an increased index of episodic hypoxaemia in REM sleep on the second night after operation compared with before operation (P < 0.05) and eight had an increased index on the third night after operation (P < 0.05) (table III).

For all variables of oxygenation and sleep pattern, we were not able to demonstrate a statistically significant first night effect of monitoring and hospitalization (differences between the first and second nights before operation), except for the number of awakenings and arousals (table II).

FIG. 2. Episodic hypoxaemia (SpO2) and associated rebound of REM sleep on the second night after operation in a 36-yr-old woman undergoing gastric resection. The heart rate (HR) tracing originates from the ECG recording.

The present study had three major findings: late postoperative hypoxaemia, severely disturbed sleep after major surgery and an increased frequency of hypoxaemic episodes in periods of REM sleep in the late postoperative period.

Our patients suffered from constant and episodic hypoxaemia, with maximum changes on the second night after operation (table III). This confirms our previous findings in patients undergoing major abdominal surgery without supplementary oxygen therapy [2, 3, 6, 16]. One of our patients had more than 30 hypoxaemic episodes (37 episodes) on the night before operation suggesting a sleep apnoea syndrome; however, his EEG sleep pattern did not have the characteristic pattern of sleep apnoea syndrome (frequent movement arousals [17]) either before or after operation. He had a maximum of hypoxaemic episodes on the first night after operation (96 episodes), suggesting frequent pharyngeal obstructions resulting from the residual effects of anaesthesia [18, 19].

There is a possibility that some of the episodes recorded as hypoxaemia observed during pulse oximetry monitoring may have been artefacts caused by motion or probe displacement [20]. However, a study in non-surgical patients with sleep apnoea or lung disease showed that fewer than 1% of the observed desaturations were not reflected in transcutaneous oxygen tension monitoring [21], thus suggesting overnight pulse oximetry monitoring to give a reliable estimate of episodic hypoxaemia. Furthermore, in all our studies including the present one, the oximeter probe was secured with adhesive tape, making displacement and measurement artefact unlikely. Finally, we and others have found pre-

TABLE III. Pulse oximetry oxygen saturation characteristics (median [range]). An episodic hypoxaemic event was defined as a decrease in oxygen saturation (SpO2) of 5% or more which occurred within a 2-min period. The index of hypoxaemic episodes in REM sleep was defined ([No. of hypoxaemic episodes in REM sleep divided by total No. of hypoxaemic episodes] divided by percent REM sleep of total sleep time). *P < 0.05 compared with preoperative night, Wilcoxon signed rank test

<table>
<thead>
<tr>
<th>After operation</th>
<th>Night 1</th>
<th>Night 2</th>
<th>Night 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO2(%)</td>
<td>94 (82-97)*</td>
<td>91 (82-96)*</td>
<td>94 (90-97)*</td>
</tr>
<tr>
<td>Mean</td>
<td>96 (92-97)</td>
<td>96 (92-98)</td>
<td>94 (82-97)*</td>
</tr>
<tr>
<td>Minimum</td>
<td>89 (79-94)</td>
<td>87 (82-95)</td>
<td>84 (69-91)*</td>
</tr>
<tr>
<td>Hypoxaemic episodes</td>
<td>80 (57-86)*</td>
<td>80 (76-91)*</td>
<td>80 (76-91)*</td>
</tr>
<tr>
<td>Total No.</td>
<td>5 (0-45)</td>
<td>10 (0-37)</td>
<td>6 (1-96)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>9 of 10</td>
<td>8 of 10</td>
<td>10 of 10</td>
</tr>
<tr>
<td>No. to &lt; 80% SpO2</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Index of episodes in REM sleep</td>
<td>0 (0-2.1)</td>
<td>0.5 (0-1.4)</td>
<td>0 (0-7.8)</td>
</tr>
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</table>
viously [2,3,8] simultaneous occurrence of episodic hypoxaemia and ECG abnormalities when obtained by two different methods of measurement (pulse oximeter and ECG monitor), thus verifying that episodic hypoxaemia measured by pulse oximetry represents actual pathophysiological events rather than artefacts. Nevertheless, the issue of reliability of oximetry monitoring after major surgery needs further study.

Sleep studies have been performed in patients undergoing major abdominal surgery [22-24], inguinal herniotomy [23,25] and open heart surgery [25-27] and have shown suppression of REM and SWS after operation, with a subsequent rebound effect in the later postoperative period. Our study found changes comparable to those in previous studies in patients undergoing similar procedures [22-25]. The phenomenon of rebound of REM and SWS after initial suppression of normal sleep has been shown in many non-surgical studies in animals and human volunteers [28-31].

Several contributing factors may disturb sleep pattern in the surgical patient. It is likely that general anaesthesia per se does not play a major role, as a randomized study found equally disturbed sleep patterns in patients receiving regional or general anaesthesia for hernia repair [25]. Furthermore, 3 h of general anaesthesia in non-surgical volunteers produced only a modest reduction in SWS for one night and no changes in REM sleep [32]. Finally, patients with non-surgical physical stress, such as medical and trauma ICU patients [33,34], patients with acute myocardial infarction [35] and volunteers with exercise-induced stress [36], had suppression of REM and SWS similar to that in surgical patients. These data suggest that surgical stress is a major cause of disturbed sleep after operation and that anaesthesia per se plays only a minor role, if any. Use of an i.v. cannula may not be of importance, as it has been shown not to cause significant alterations in sleep pattern in volunteers [37]. Furthermore, our patients did not have significant postoperative fever and were not situated in an uncomfortably hot environment or disturbed by noise from other patients—all factors which could have altered sleep [38-41].

Surgical stress, including postoperative pain and endocrine changes, increases sympathetic activity [42] and may be involved in the pathogenesis of postoperative sleep disturbance, as these factors have been shown to cause sleep changes similar to those observed in the present study [43-45]. Interleukin-1, one of the key mediators of injury, may also be an important pathogenetic factor in postoperative REM sleep suppression, as administration of interleukin-1 to animals reduces REM sleep—an effect which is reversed after administration of an interleukin-1-receptor antagonist [46]. Furthermore, corticotrophin releasing hormone, which is involved in the cerebral surgical stress response [42], has been shown to inhibit sleep in animals [47]. However, as REM sleep is controlled by many regions (suggesting a dynamic interaction between cortex and other subcortical systems [48]) it may be a global effect of surgical stress on the brain which causes REM disturbance after major surgery, rather than selected endocrine markers of the surgical stress response.

Postoperative administration of morphine has been claimed to be a contributing factor in sleep disturbance [24] as doses of 0.2 mg kg$^{-1}$ in volunteers without pain produced REM and SWS suppression [49]. Our patients who experienced postoperative pain received doses of morphine 5-10 mg (corresponding to approximately 0.1 mg kg$^{-1}$), which has been shown in volunteers to produce only a slight decrease in SWS and no change in REM sleep [50]. Therefore we do not believe that postoperative administration of opioids in the doses used can explain the profound changes in sleep pattern observed in our study. The concomitant suppression of REM sleep and administration of opioids confirms earlier observations [24], but while the intensity of postoperative pain (which itself may suppress REM sleep) and the amount of opioid given are related, their relative independent effect on sleep disturbance cannot be inferred from our study. Our patients did not receive any other psychotropic drugs in the perioperative period.

We found an increase in the index of hypoxaemic episodes during REM sleep after surgery. REM sleep is known to be associated with hypventilation and ventilatory instability, with frequent apnoea in normal volunteers [51,52], one mechanism being loss of pharyngeal muscle tone [53,54]. The rebound of intense REM sleep after operation [24] may act with additional factors such as opioid administration [1,55] and supine posture [51,56] in aggravating sleep-disordered breathing, thus increasing the frequency of hypoxaemic episodes in the late postoperative period.

Besides the relationship between episodic hypoxaemia and REM rebound, the clinical importance of the suppression of REM and SWS after operation is unknown, but there are several potential implications. Deprivation of SWS in volunteers has been shown to precipitate depression and fatigue [28,30] and postoperative SWS suppression may therefore play a role in the pathogenesis of postoperative fatigue [57] although not studied specifically. Deprivation of REM sleep in volunteers produces irritability, impaired learning and impaired memory processing [29,58,59], thus making REM sleep suppression a possible contributing factor in postoperative delirium. REM sleep is associated normally with apnoea [51] and REM rebound after surgery has been shown to be associated with haemodynamic instability [60] and increased production of urinary catecholamines [61]. Reeder and colleagues have shown coherent fluctuations in systolic arterial pressure, episodic hypoxaemia and episodic tachycardia after major surgery [62]. The postoperative episodic increases in heart rate [2,3,62] may cause a reduction in coronary blood flow in patients with coronary stenosis, as demonstrated during REM sleep in non-surgical patients [63]. It is therefore likely that rebound of REM sleep on the second and third nights after operation may be associated with, or be pathogenetic factors in, episodic hypoxaemia, episodic tachycardia and haemodynamic instability. Subsequently, these
changes may lead to postoperative myocardial ischae-
mia [3, 8], infarction [9], arrhythmias [3] and eventu-
ally sudden unexpected death [64]. However, this
hypothesis requires further investigation.

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