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Continuous Positive Airway Pressure Mitigates Opioid-induced Worsening of Sleep-disordered Breathing Early after Bariatric Surgery

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This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Bariatric surgery patients are vulnerable to sleep-disordered breathing (SDB) early after recovery from surgery and anesthesia. The authors hypothesized that continuous positive airway pressure (CPAP) improves postoperative oxygenation and SDB and mitigates opioid-induced respiratory depression.

Methods: In a randomized crossover trial, patients after bariatric surgery received 30% oxygen in the postanesthesia care unit (PACU) under two conditions: atmospheric pressure and CPAP (8 to 10 cm H₂O). During 1 h of each treatment, breathing across cortical arousal states was analyzed using polysomnography and spirometry. Arousal state and respiratory events were scored in accordance with American Academy of Sleep Medicine guidelines. Data on opioid boluses in the PACU were collected. The primary and secondary outcomes were the apnea hypopnea index (AHI) and apnea after self-administration of opioids in the PACU. Linear mixed model analysis was used to compare physiologic measures of breathing.

Results: Sixty-four percent of the 33 patients with complete postoperative polysomnography data demonstrated SDB (AHI greater than 5/h) early after recovery from anesthesia. CPAP treatment decreased AHI ($8 \pm 2/h$ vs. $25 \pm 5/h$, $P < 0.001$), decreased oxygen desaturations ($5 \pm 10/h$ vs. $16 \pm 20/h$, $P < 0.001$), and increased the mean oxygen saturation by 3% ($P = 0.003$). CPAP significantly decreased the respiratory-depressant effects observed during wakefulness–sleep transitions without affecting hemodynamics. The interaction effects between CPAP treatment and opioid dose for the dependent variables AHI ($P < 0.001$), inspiratory flow ($P = 0.002$), and minute ventilation ($P = 0.015$) were significant.

Conclusions: This pharmacophysiologic interaction trial shows that supervised CPAP treatment early after surgery improves SDB and ameliorates the respiratory-depressant effects of opioids without undue hemodynamic effects. (ANESTHESIOLOGY 2016; 125:92-104)

OBSTRUCTIVE sleep apnea (OSA), the most common type of sleep-disordered breathing (SDB), occurs in more than 75% of patients undergoing bariatric surgery.¹ Data suggest that OSA increases the risk of postoperative respiratory complications, including reintubation,² as a consequence of an increased vulnerability to upper airway collapse in the perioperative period. Opioids are commonly administered both intra- and postoperatively for pain control³ and induce a dose-dependent decrease in respiratory drive and upper airway dilator muscle activity.⁴ Practice guidelines suggest that attempts should be made to minimize the use of opioids for postoperative pain treatment in OSA patients. However, studies have shown OSA patients to have a lower pain threshold⁵ and to require high doses of analgesics and opioids to accomplish adequate analgesia, compared to patients without OSA.⁶

What We Already Know about This Topic

- Continuous positive airway pressure effectively reduces nocturnal obstructive respiratory events in patients with obstructive sleep apnea
- Its effectiveness for early postoperative period remains uncertain particularly in obstructive sleep apnea patients receiving opioids for analgesia

What This Article Tells Us That Is New

- This prospective, randomized, crossover trial compared the apnea hypopnea index (AHI) with and without continuous positive airway pressure (CPAP) in 38 morbidly-obese patients and found that the CPAP reduced the AHI by 69% and was more effective during non-rapid eye movement sleep than during wakefulness
- The AHI was worsened by self-administered opioid for pain and CPAP application effectively mitigated the AHI deterioration

Dr. Zaremba and Shin participated equally in preparing the manuscript.

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The most effective treatment for OSA is continuous positive airway pressure (CPAP). CPAP significantly reduces the number of respiratory events during sleep and improves hemoglobin oxygen saturation (SpO_2)⁷ by increasing upper airway diameter and preventing upper airway collapse. However, it is not entirely clear if CPAP is similarly effective during the early postoperative period with lingering effects of anesthetics, neuromuscular blockade, and analgesics.⁸ While some studies found beneficial effects of early postoperative CPAP on arterial oxygen concentration partial pressure (Pao_2) and early respiratory complications after extubation,^{9,10} other studies indicate that postoperative CPAP does not always improve breathing.^{11,12} No information is available on the effect of CPAP on sleep- and opioid-induced respiratory depression in patients with high risk of sleep apnea in the recovery room.

We aimed to investigate if CPAP treatment early after surgery in the postanesthesia care unit (PACU) improves apnea hypopnea index (AHI), and if the use of postoperative opioids increases AHI in the PACU. In addition, we hypothesized that CPAP treatment mitigates respiratory-depressant effects of opioids given for postoperative pain therapy, with a specific emphasis taken on respiratory-depressant effects in transitions from wakefulness to sleep.¹³

Materials and Methods

Study Design and Hypothesis

This study was approved by the Institutional Review Board of Partners Healthcare, Boston, Massachusetts, under the protocol number 2011P001333. After approval, we performed this prospective, blinded, randomized, crossover study to test if CPAP applied in the PACU after bariatric surgery improves SDB and ameliorates the respiratory-depressant effects of postoperative opioids. We hypothesized that CPAP, when applied in the PACU after bariatric surgery, would decrease AHI (primary outcome measure) compared to the current standard of care. The secondary hypothesis was that CPAP decreases the respiratory-depressant effects of opioids given *via* patient-controlled analgesia (PCA) in the PACU. This trial was registered with ClinicalTrials.gov identifier: NCT01697878 (principal investigator: Dr. Eikermann; date of registration: September 21, 2012).

Patient Selection

Forty-five patients aged 18 yr or older scheduled for laparoscopic Roux-en-Y gastric bypass, laparoscopic partial vertical gastrectomy, laparoscopic sleeve, or revision of gastric band to gastric bypass at Massachusetts General Hospital, Boston, Massachusetts, between March 2012 and July 2014 were approached for recruitment before their surgery, and written informed consent was obtained by study staff. Patients with known impairment of cognitive function, decision-making capacity, and/or muscle weakness were excluded from this study.

Study Treatment

Patients were fitted with an oronasal CPAP mask during their preanesthesia interview. After surgery, patients were transferred to a private PACU room where two members of the study team were present. After hand-off between the anesthesia provider and the PACU nurse, patients were connected to the study equipment and polysomnography device within a median of 24 (9 to 83, interquartile range) minutes after PACU admission. During their PACU stay, patients received treatment with 30% supplemental oxygen (fraction of inspired oxygen [F_{IO_2}] of 0.3) applied under atmospheric pressure (AP) or CPAP. AP and CPAP were applied for 1 h each in a randomized crossover design using a high-flow CPAP circuit with a custom-made open circuit to prevent rebreathing (fig. 1). Inspiratory gas was mixed from a high-pressure room air and oxygen source using an oxygen blender (Hans Rudolph Inc., USA) to provide a constant F_{IO_2} of 0.3 to the circuit during CPAP and AP treatments. The outlet of the oxygen blender was connected to a reservoir balloon and the CPAP facemask without an expiration valve (Respironics Inc., USA), while the open end of the circuit was either left open to the atmosphere during AP or connected to a 10 cm H_2O positive end-expiratory pressure valve during CPAP. Inhaled gas was warmed and humidified by a humidifier connected downstream of the flowmeter to avoid drying and bleeding of the nasal mucosa.¹⁴ All study patients spent the entire PACU stay in supine position with the upper body elevated to approximately 30 degrees.

Study Measures

Polysomnography data were obtained using a Type 2 out-of-center polysomnography device (Alice PDx, Philips Respironics Inc.).¹⁵ This polysomnography device includes electroencephalography, electrooculography, and submental and limb electromyography, as well as measures of abdominal and thoracic respiratory efforts using impedance plethysmography belts, nasal respiratory airflow, and body position. Sleep stages, arousals, and respiratory events were scored in accordance with the 2007 American Academy of Sleep Medicine Guidelines.¹⁶

Baseline severity of SDB was assessed based on recent (within 6 months before surgery) sleep lab-based polysomnography testing or home-based polysomnography testing initiated by the study team. For patients with recent polysomnography results, we obtained and reviewed their complete sleep study reports. If records were not available or were more than 6 months old, patients underwent home-based sleep testing using our out-of-center device before surgery.

In the PACU, polysomnography was applied and supervised by a study staff member trained in sleep medicine. Measurements of airway pressure and airflow (Pneumotach, Hans Rudolph Inc.) were performed continuously. AHI, mean and nadir SpO_2 , and oxygen desaturation index (ODI) were derived from the polysomnography. Peak inspiratory flow (PIF), minute ventilation (MV), tidal volume (V_T), and

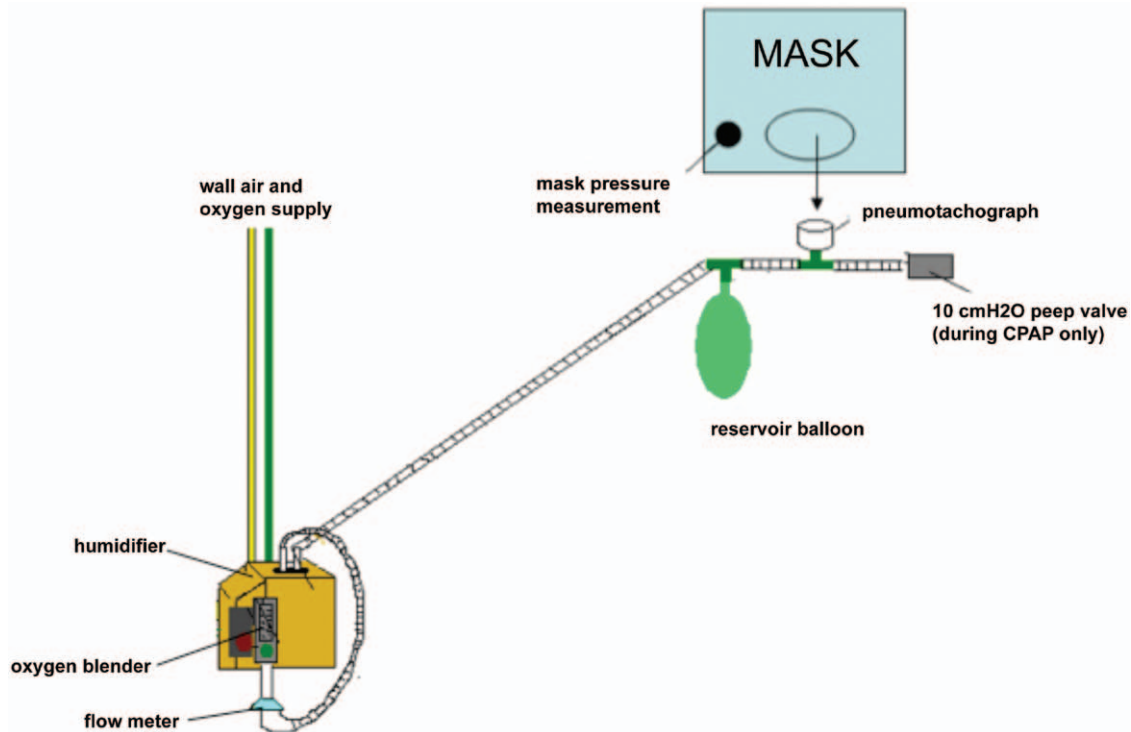


Fig. 1. Schematic of the high-flow continuous positive airway pressure (CPAP) circuit as described by Hess *et al.*¹⁴ Inspiratory gas was mixed from a high-pressure room air and oxygen source using an oxygen blender (Hans Rudolph, USA) to provide a constant fraction of inspired oxygen of 0.3 to the circuit. The outlet of the oxygen blender was connected to a reservoir balloon and the CPAP facemask without an expiration valve (Respironics Inc., USA). Inhaled gas was warmed and humidified by a humidifier connected downstream of the flowmeter. The open end of the circuit was either left open to the atmosphere during atmospheric pressure treatment or connected to a 10 cm H₂O positive end-expiratory pressure valve during CPAP treatment. A pneumotachograph (Hans Rudolph) was connected serial between tubing and oronasal CPAP mask. Pressure probe of the polysomnography equipment was connected to the CPAP mask in parallel to the CPAP tubing.

respiratory rate (RR) were calculated from the flow tracings of the pneumotach. Timing, frequency, and dose of opioids administered by a PCA pump were documented. Blood pressure and heart rate were recorded every 5 min throughout the study and PACU stay.

Data Processing

To evaluate the effect of CPAP on breathing during different arousal states in the PACU, we defined specific electroencephalography-derived arousal states for (1) wakefulness, (2) sleep onset (*i.e.*, transitions from wakefulness to non-rapid eye movement [non-REM] sleep), and (3) stable non-REM stage 2 sleep (NREM2) in accordance with previous reports.¹⁷

To further evaluate the effect of opioid application (*i.e.*, 1 mg morphine intravenously equivalent dose per bolus) *via* PCA on breathing during AP *versus* CPAP, the spectral electroencephalography power for the beta, alpha, and theta frequency bands was calculated using fast Fourier transformation as previously used by our and other groups.^{18–21} Briefly, electroencephalography raw signal (C3-A2) tracing derived from the polysomnography monitor was band limited using a 55-Hz low-pass and a 0.8-Hz high-pass filter. Fast Fourier transformation (nonoverlapping Hann 256 bit windows) was

then used on 5-s epochs of the filtered electroencephalography signal. The power content for each 20-s epoch was determined as the average power across four 5-s segments of the electroencephalography. The spectral distribution was categorized into the following frequency bands: beta (15 to 21 Hz), alpha (8 to 13 Hz), and theta (3 to 7 Hz). The power in each frequency bandwidth was expressed as a percentage of total power in each 20-s epoch.

Based on the measured electroencephalography power spectrum, two 20-s epochs of similar beta, alpha, and theta electroencephalography activity flanking a single opioid application were identified in the following manner: we first identified the earliest 20-s epoch with theta-dominant electroencephalography activity (non-REM sleep stage 1) after a single opioid application, and then we identified the last theta-dominant electroencephalography episode with similar electroencephalography profile preceding the opioid application. In addition, the last 20-s epoch of alpha-dominant electroencephalography activity (*i.e.*, wakefulness) based on visual examination preceding these episodes was identified. We analyzed ventilation (PIF, V_T, MV, and RR) for the first three consecutive breaths during each of these 20-s epochs. Pre- and postopioid episodes were defined as the last 10 min before opioid application and the first 10 min after an opioid

application, respectively. Mean and nadir SpO_2 and AHI were derived from the polysomnography measurements and averaged for all pre- and postopioid episodes during CPAP and AP treatments. Data recorded during the 10 min before and after treatment switch (CPAP to AP or *vice versa*) were excluded from analysis to prevent any overlapping effect between treatments.

To address the primary aim of the study, data were analyzed as averages across each cortical arousal state (wakefulness, stable non-REM sleep, and right before and after sleep onset) during AP and CPAP treatments in each individual patient. Subsequently, sequential arousal state-specific analyses were conducted. To address our secondary aim, data were averaged over 10 min before and after opioid episodes. In order to analyze breathing during the transition from wakefulness to sleep, PIF, MV, V_T , and RR were averaged over three consecutive breaths during 20-s epochs of similar cortical arousal states before and after opioid application.

Statistical Analysis

To evaluate the effect of CPAP on sleep apnea in the PACU (primary aim), we used a mixed linear model (MLM) with an identity link function for normally distributed probability and defined the intercept, treatment order, and lapsed PACU time as random effects. We tested for a fixed main effect of CPAP administration on the mean individual AHI (primary outcome) as well as on number of oxygen desaturations, the mean and nadir SpO_2 , and the exploratory endpoints V_T , PIF, MV, and RR. Comparisons of effect size (ES) were made between CPAP and AP. Random effects were excluded from the final model if they did not explain any variance of our fixed effects ($P > 0.05$).

To evaluate a potential mitigating effect of CPAP on opioid-associated respiratory depression (secondary aim), we used the same model as for our primary aim extended by the random effects, time to first opioid administration within study, morphine-equivalent dose of opioids administered within study, and morphine-equivalent dose of prestudy administered opioids. We tested for the fixed interaction effect of CPAP and opioid administration ("treatment group" × "before or after opioid use") on AHI, oxygen desaturation, and mean and nadir SpO_2 , as well as the exploratory endpoints V_T , PIF, MV, and RR.

With an exploratory intention, we evaluated the fixed effect of treatment (CPAP *vs.* AP) on PIF, MV, and V_T during the electroencephalography-defined arousal states of wakefulness, sleep onset, and stable NREM2 sleep. We further tested for a fixed interaction effect between treatment (CPAP *vs.* AP) and arousal state (wakefulness *vs.* NREM2).

Goodness of fit of all models in relation to the intercept-only model was determined using the likelihood ratio test (LRT).

Our power calculation was based on our previous report.²² We expected a mean difference in AHI of 4 with a SD of 7/h. Taking into account a two-sided significance

level of 0.05 and power of 80%, we determined the required sample size to be 30 patients. Previous studies of noninvasive ventilation in postsurgical patients have reported a high rate of insufficient adherence to the CPAP treatment.²³ Thus, we aimed to include 45 patients in order to arrive at the desired sample size.

Statistical analyses were performed using SPSS version 22 (SPSS Inc., USA).

Results

On the day of surgery, 44 patients (see table 1 for demographics) were randomized to receive first AP or CPAP treatment. Thirty-eight of the 44 randomized study patients (18 received CPAP first and 20 received AP first) completed both treatments of the study and thus were included in the analyses of the effects of opioid and CPAP treatment on respiration and sleep. A summary of recruitment and study flow is illustrated in figure 2.

Table 1. Demographics and Intraoperative Management of Study Population

	Enrolled (N = 45)	Completed Study (n = 38)
Demographics		
Sex		
Men	14 (31%)	12 (32%)
Women	31 (69%)	26 (68%)
Age (yr)	44 ± 13	43 ± 13
BMI (kg/m ²)	46 ± 7	46 ± 8
Preoperative diagnosis of OSA	16 (36%)	12 (32%)
Previous CPAP treatment	11 (24%)	10 (26%)
ASA risk classification		
2	26 (58%)	23 (61%)
3	19 (42%)	15 (40%)
Intraoperative management		
Surgery type		
Laparoscopic Roux-en-Y gastric bypass	16 (36%)	13 (34%)
Laparoscopic partial vertical gastrectomy	21 (48%)	19 (50%)
Laparoscopic sleeve	6 (14%)	6 (16%)
Revision of gastric band to gastric bypass	1 (2%)	0 (0%)
Neuromuscular blocking agent administered		
Cisatracurium	29 (66%)	25 (66%)
Rocuronium	10 (23%)	8 (21%)
Vecuronium	5 (11%)	5 (13%)
NMBA dose (mg/kg)	29 ± 27.5	28 ± 27.3
Neostigmine-based reversal	39 (89%)	34 (89%)
Opioids applied intraoperatively	44 (100%)	38 (100%)
Morphine intravenous equivalent dose per weight (μg/kg)	125 ± 115	121 ± 121

All values are presented as n (%) or mean ± SD.

ASA = American Society of Anesthesiology; BMI = body mass index; CPAP = continuous positive airway pressure; NMBA = neuromuscular blocking agent; OSA = obstructive sleep apnea.

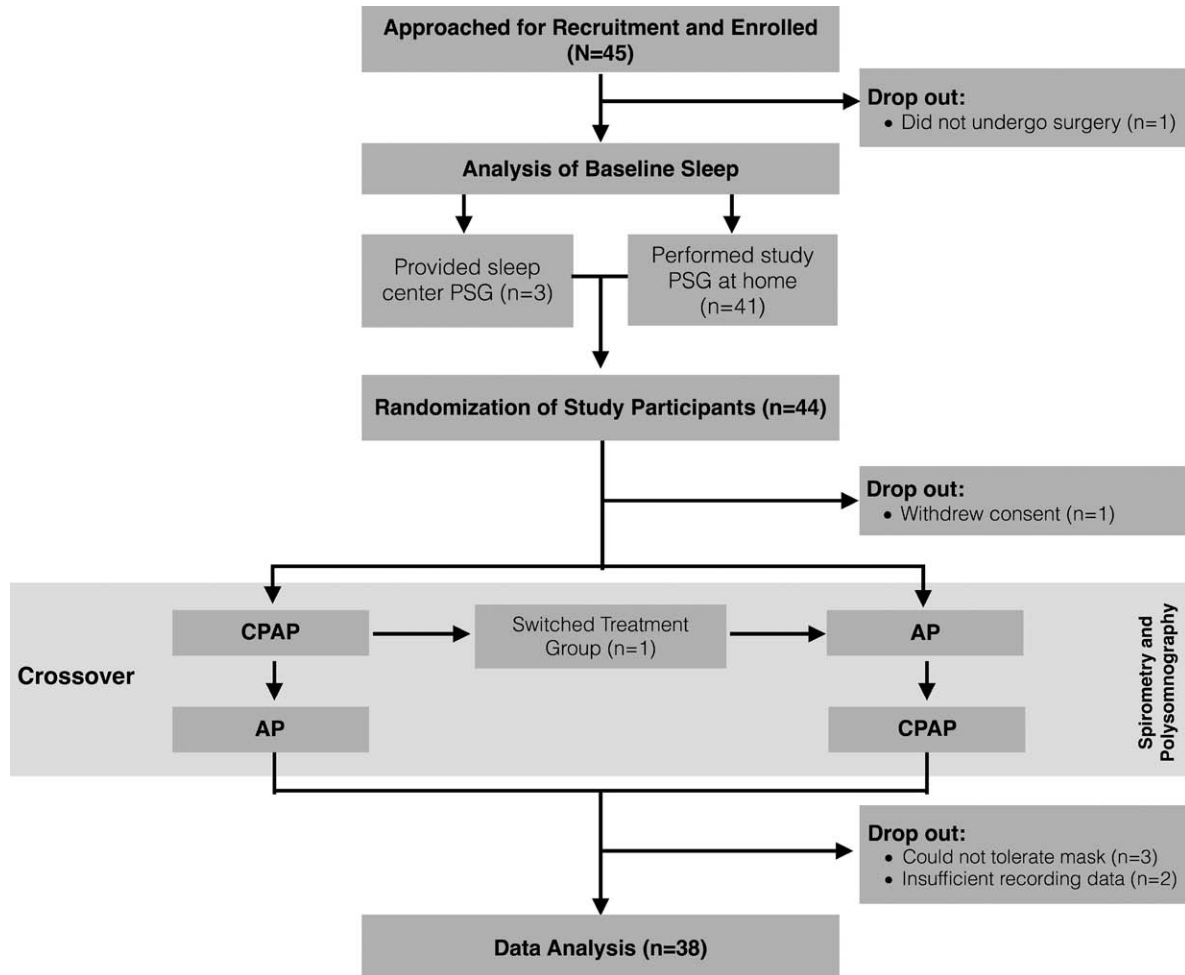


Fig. 2. Flow chart of study protocol. AP = atmospheric pressure; CPAP = continuous positive airway pressure; PSG = polysomnography.

Baseline Sleep Apnea

Twenty-six patients completed preoperative sleep testing, and 92% were found to have sleep apnea (AHI > 5/h). Among these patients, only 29% had a known diagnosis of OSA. In this group, mean preoperative AHI was 25 ± 22 /h, and 67% of the patients demonstrated predominantly obstructive events. Based on American Academy of Sleep Medicine criteria, the severity of sleep apnea was in the moderate to severe range (fig. 3).

Based on our polysomnography measurements in the PACU, 64% of the 33 patients with reliable polysomnography data for the entire treatment period demonstrated sleep apnea during daytime sleep immediately after surgery. The severity of sleep apnea measured by sleep study before admission and in the PACU was similar: mean AHI under AP in the PACU was 25 ± 28 /h and did not differ significantly from the AHI measured during home- or sleep lab-based testing before surgery ($P = 0.927$).

Effect of CPAP during Sleep and Wakefulness in the PACU

Compared to AP, CPAP treatment improved sleep apnea in the PACU by reducing both AHI and ODI by 69% (regular linear model [RLM]: LRT, $P < 0.001$; ES, 18.6; 95% CI, 7.3

to 29.8, $P = 0.002$, and MLM with random intercept [RI]: LRT, $P < 0.001$; ES, 12.1; 95% CI, 6.6 to 17.6; $P < 0.001$, respectively; fig. 4) and resulted in a significantly higher nadir SpO_2 (CPAP vs. AP: $93 \pm 5\%$ vs. $89 \pm 6\%$; MLM with RI: LRT, $P < 0.001$; ES, 3.3; 95% CI, 1.3 to 5.2, $P = 0.002$).

CPAP had stabilizing effects on breathing during wakefulness and sleep. A representative sample of combined polysomnography and spirometry data is shown in figure 5. CPAP treatment was associated with significantly higher values of V_T (RLM: LRT, $P < 0.001$; ES, 112.3; 95% CI, 64.1 to 160.5, $P < 0.001$), PIF (MLM with random effects of lapsed PACU time: LRT, $P < 0.001$; ES, 0.055; 95% CI, 0.022 to 0.088, $P = 0.001$), and MV (RLM: LRT, $P = 0.004$; ES, 1.2; 95% CI, 0.5 to 2.0, $P = 0.001$, fig. 6) and ameliorated the respiratory-depressant effects of wake-sleep transition on breathing. We observed a positive interaction effect of arousal state (wakefulness vs. NREM2) and treatment regimen (AP vs. CPAP) on V_T (RLM: LRT, $P = 0.769$; ES, 42.3; 95% CI, 22.4 to 62.4, $P = 0.001$), PIF (MLM with random effects of lapsed PACU time: LRT, $P < 0.001$; ES, 0.115; 95% CI, 0.029 to 0.200, $P < 0.001$), MV (RLM: LRT, $P = 0.001$, ES, 3.0; 95% CI, 0.8 to 5.1, $P < 0.001$),

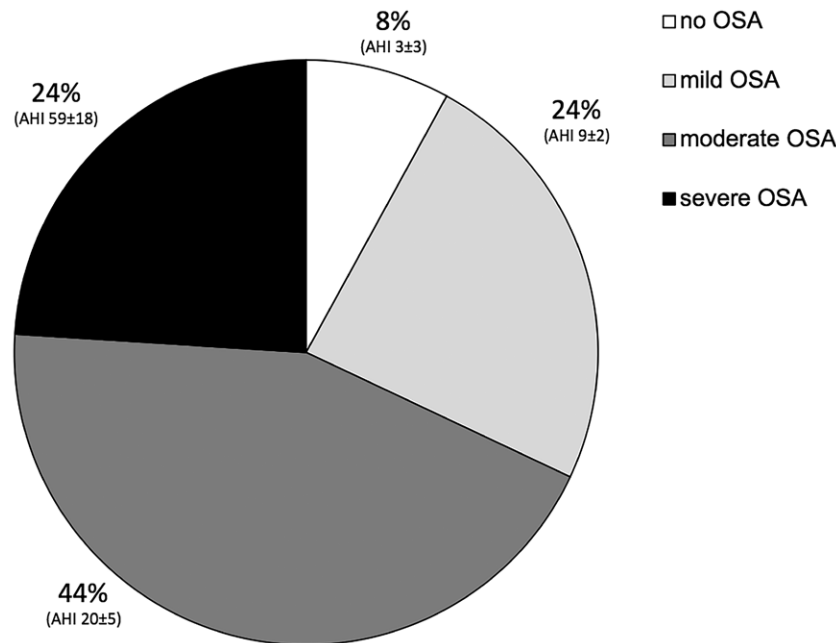


Fig. 3. Severity of obstructive sleep apnea (OSA) at baseline. The majority of the patients scheduled for weight-loss surgery had sleep apnea (92%), which was moderate or severe in 44 and 24% of patients, respectively. Data are shown as prevalence (%) and were obtained from 26 patients who had completed baseline sleep apnea testing; apnea hypopnea index (AHI), mean ± SD.

and RR (MLM with RI: LRT, $P < 0.001$; ES, 4.0; 95% CI, 2.4 to 5.4, $P < 0.001$), indicating a larger effect of CPAP treatment on improving breathing during non-REM sleep, compared to wakefulness. The number of arousals from sleep did not differ significantly between treatments (arousal index $9.6 \pm 1.7/h$ during AP compared to $9.3 \pm 1.7/h$ during CPAP, $P = 0.983$), and the positive effects of CPAP were independent of randomization group (absence of order effect).

CPAP did not have a significant effect on the average mean arterial pressure (AP *vs.* CPAP: 95 ± 12 mmHg *vs.* 97 ± 13 mmHg, $P = 0.16$) or heart rate (AP *vs.* CPAP: 74 ± 12 beats/min *vs.* 76 ± 13 beats/min, $P = 0.17$).

Effects of CPAP on Opioid-induced Respiratory Depression

Of the 38 patients who completed the study, 7 did not receive opioids by PCA in the PACU during AP or CPAP treatment. In the remaining 31 patients, opioids were administered a total of 144 times during the study period—79 applications during AP and 65 applications during CPAP. In addition, 15 patients received morphine while study equipment was applied; on average, this amounted to a total dose of 2.1 ± 4.5 mg morphine (or equivalent dose) between PACU admission and the initiation of the study recording. During the study treatment, the total morphine-equivalent dose applied *via* PCA did not differ significantly during AP and CPAP treatment and amounted to 2.9 ± 3.4 and 2.5 ± 2.7 mg, respectively ($P = 0.608$). A total of 96 applications fulfilled our strict *a priori*-defined inclusion criteria for polysomnography-based analysis of the effects of opioid and CPAP on AHI,

ODI, and mean and nadir SpO_2 . Electroencephalography activity did not differ between the pre- and postopioid episodes (fig. 7).

The degree of opioid-induced respiratory depression was reduced during CPAP treatment compared with AP treatment. When self-administered during AP, opioids increased AHI by 13%, from $28 \pm 32/h$ to $32 \pm 58/h$ (pre- *vs.* post-opioid). In contrast, during CPAP administration, self-administration of opioids minimally increased AHI from $6 \pm 11/h$ by 4% (fig. 8A). During sleep, CPAP improved V_T (fig. 8B) after opioid application and abolished the impairing effect of opioids on MV (10.5 ± 5.7 to 9.2 ± 5.3 l/min during AP *vs.* 12.3 ± 5.6 to 12.4 ± 6.6 l/min; fig. 8C). CPAP also improved PIF (fig. 8D), which was paralleled by improved oxygenation. Of note, CPAP also reduced the impairing effects of opioids on these variables (table 2). We observed a significant interaction effect between treatment type (CPAP *vs.* AP) and opioid application on AHI (RLM, $P < 0.001$; LRT, $P < 0.001$), ODI (MLM with random effect of time to first opioid administration within study, $P = 0.010$; LRT, $P < 0.001$), mean SpO_2 (MLM with RI, $P = 0.029$; LRT, $P < 0.001$), and nadir SpO_2 (MLM with RI, $P = 0.006$; LRT, $P < 0.001$), as well as V_T (MLM with random effect of lapsed PACU time and time to first opioid administration within study, $P = 0.01$; LRT, $P < 0.001$), PIF (MLM with RI, $P = 0.002$; LRT, $P < 0.001$), MV (MLM with RI, $P = 0.015$; LRT, $P < 0.001$), and RR (MLM with RI, $P < 0.001$; LRT, $P < 0.001$).

Opioids given before study start did not have any effect on any of our outcomes (variance estimate of random effect, $P > 0.05$). In accordance, in contrast to the

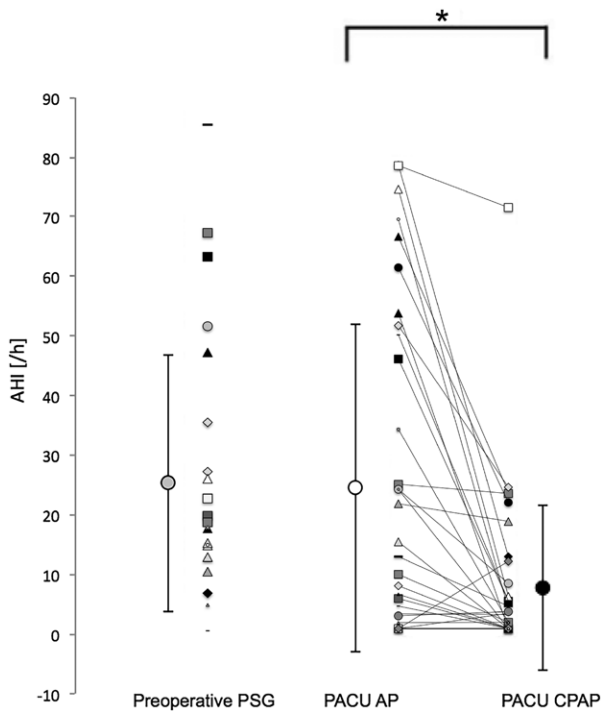


Fig. 4. Effects of continuous positive airway pressure (CPAP) on postoperative sleep apnea and breathing in the postanesthesia care unit (PACU). Apnea hypopnea index (AHI) during baseline preoperative evaluation visit ($n = 26$) and in the PACU after surgery ($n = 33$). Values for AHI during PACU stay are shown as mean \pm SD (circle with error bars on left) and individual values (right). Severity of sleep apnea was unchanged from baseline at the start of study in the PACU (baseline AHI vs. PACU atmospheric pressure [AP] AHI, $P = 0.927$). During the study, CPAP treatment improved AHI ($P < 0.05$), compared to standard of care. *Statistically significant difference. PSG = polysomnography.

respiratory-depressant effects of low-dose opioids during sleep, we did not observe any effect of 1 mg morphine equivalent on PIF and V_T during wakefulness. Mean PIF were 557.8 ± 297.1 ml/s before versus 555.6 ± 308.1 ml/s after opioid application ($P = 0.381$, before vs. after) during AP and were 616.8 ± 233.2 ml/s before versus 607.8 ± 212.3 ml/s after opioid application ($P = 0.790$) during CPAP. Mean V_T was 503 ± 181 ml before versus 504 ± 286 ml after opioid application ($P = 0.266$) during AP and 604 ± 277 ml before versus 621 ± 244 ml after opioid application ($P = 0.093$) during CPAP. MV also did not change after low-dose opioid application (9.9 ± 3.3 l/min vs. 9.5 ± 4.1 l/min [$P = 0.586$] during AP and 10.8 ± 2.9 l/min vs. 10.9 ± 3.2 l/min [$P = 1.00$] during CPAP).

Discussion

This pharmacophysiologic interaction trial demonstrates beneficial effects of early postoperative CPAP treatment across the continuum of wakefulness and non-REM sleep and on the respiratory-depressant effects of opioids used for pain management in the recovery room. CPAP mitigated opioid-induced worsening of SDB early after bariatric surgery.

Effect of Early Postoperative CPAP on Sleep-disordered Breathing and Oxygenation

CPAP administered to patients immediately after bariatric surgery improved AHI and ventilation (PIF, V_T , and MV) during sleep compared with breathing in AP, which is the standard of care for CPAP-naïve patients undergoing weight-loss surgery at our institution. As expected, V_T and PIF decreased during the wake-sleep transition, consistent with previous reports in patients without residual effects of anesthetics, analgesics, and neuromuscular blockade.¹⁷ The magnitude of the observed reductions in V_T and PIF was smaller during CPAP treatment. These effects can in part be explained by the improved airway patency associated with CPAP treatment.

The currently available data on the effect of CPAP on SDB in the early postoperative period are conflicting. Some data suggest that CPAP treatment prevents respiratory complications after abdominal^{9,10} and cardiac surgery²⁴ and improves AHI and oxygen saturation during the first night after orthopedic surgery.²⁵ In another study, CPAP was applied during the first through fifth night after abdominal surgery in patients with high risk of OSA, and CPAP was found to improve AHI from 30/h to less than 5/h.²⁵

Recent studies found that postoperative CPAP did not consistently improve postoperative SDB. Drummond *et al.*¹² did not find a beneficial effect of CPAP autotitration on SDB after major abdominal surgery. In their parallel-group designed study of 48 patients, the authors found no difference in ODI between AP and CPAP on the first postoperative night. However, the study investigated the effect of CPAP in patients undergoing general abdominal surgery, and none of these patients had signs or symptoms of sleep apnea preoperatively. In contrast, our study focused on bariatric surgery patients, a surgical population with a high prevalence of sleep apnea. Similarly, O’Gorman *et al.*¹¹ studied the effects of CPAP auto-titration versus oxygen therapy at AP in patients with OSA undergoing orthopedic surgeries. The authors surprisingly found a higher number of oxygen desaturations to an SpO_2 less than 90% in patients in the CPAP group compared with those in AP. Possible explanations of this negative finding include poor compliance with CPAP treatment and lower inspiratory oxygen concentration in the CPAP group. In fact, median usage of CPAP in that study was only 3 h 4 min, and patients may not have received any treatment during the rest of the night that was captured by polysomnography recordings. Furthermore, the authors were not able to control inspiratory oxygen concentration with the device during the time the patients used CPAP. In our study, we applied a standardized F_{IO_2} of 0.3 across treatments by using a custom-made high-flow CPAP device in a supervised setting of a postsurgery recovery room. The CPAP pressure of 8.7 ± 0.6 cm H_2O applied in our study was similar to the pressure applied in previous studies using autotitration CPAP devices.¹¹ A CPAP pressure of approximately 10 cm H_2O has been reported to provide sufficient

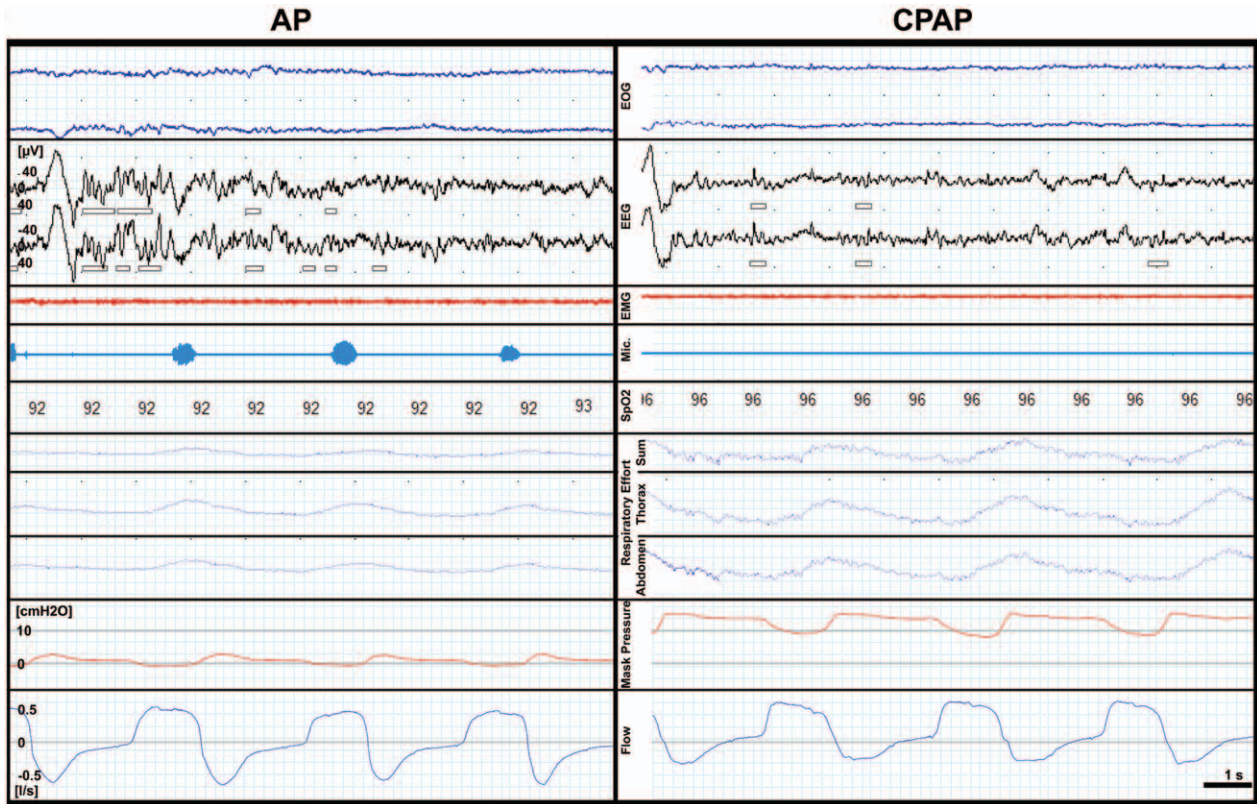


Fig. 5. Polysomnography recorded in the postanesthesia care unit during breathing at atmospheric pressure (AP) and continuous positive airway pressure (CPAP). During non-rapid eye movement sleep stage 2, hypopneas with flow limitation occurred, as indicated by the flattening of the flow curve (blue curve), during AP, but not during CPAP treatment. Flow limitation was characterized by decreased tidal volume, peak inspiratory flow, and minute ventilation due to impaired upper airway patency and was accompanied by snoring in the microphone channel (Mic.; light blue). This resulted ultimately in upper airway collapse and apneas during sleep in some cases. EEG = electroencephalography; EMG = electromyography of the chin; EOG = electro-oculography; Flow = respiratory flow signal derived from spirometry; Respiratory Effort = respiratory effort signal derived from impedance plethysmography belts (abdomen and thorax belts, as well as combined signal—sum); SpO₂ = oxygen saturation.

pressure transmission to the trachea²⁶ and was found to be an effective treatment pressure for OSA when allied with supplemental oxygen.²⁷

The available evidence on perioperative CPAP treatment in bariatric surgery patients is inconclusive. Although several

studies have found beneficial effects of postoperative treatment of OSA on weight loss after bariatric surgery compared to bariatric surgery alone,^{28–30} long-term improvement of metabolic and cardiovascular comorbidities after bariatric surgery might be linked more closely to weight loss than

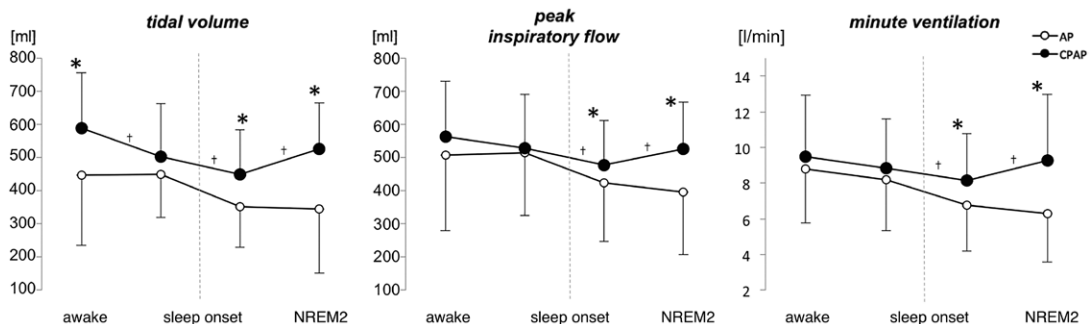


Fig. 6. Effects of continuous positive airway pressure (CPAP) on breathing during wake–sleep transition. During wake and sleep transitions, tidal volume, minute ventilation, and peak inspiratory flow decreased and the magnitude of respiratory depression was smaller during CPAP compared to atmospheric pressure (AP). *Statistically significant main effect of treatment on breathing ($P < 0.05$). †Statistically significant interaction effect between treatment and sleep stage on breathing ($P < 0.05$). Data obtained from 31 patients with complete breathing data. NREM2 = non-rapid eye movement sleep stage 2.

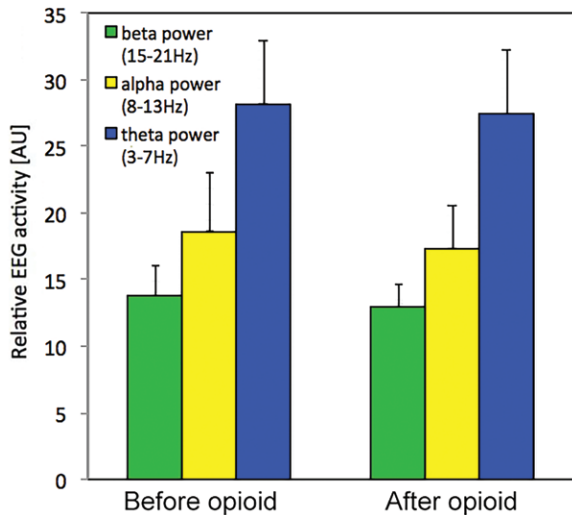


Fig. 7. Electroencephalography (EEG) activity during measurements before and after opioid application. EEG activity was quantified by EEG spectroscopy as indicators of cortical arousal. Beta-, alpha, and theta-frequency bands were calculated using fast Fourier transformation (nonoverlapping Hann 256 bit windows) on 5-s epochs of the filtered EEG signal 0.8 to 55 Hz. The spectral distribution was categorized into beta (15 to 21 Hz), alpha (8 to 13 Hz), and theta (3 to 7 Hz) frequency bands and was expressed as a percentage of total EEG power across the entire frequency band in each 20-s epoch of sleep. Alpha, beta, and theta EEG activity did not differ during measurements before and after opioid application. AU = arbitrary units.

CPAP treatment.^{31,32} During the early perioperative period, retrospective studies in patients undergoing bariatric surgery reported no differences in overall postoperative morbidity,³³

as well as no cases of death, reintubation, or cardiopulmonary complications,^{34,35} regardless of CPAP or AP treatment. CPAP was found to improve blood oxygenation in patients after open Roux-en-Y gastric bypass in some studies,³⁶ while other authors found severe and prolonged episodes of hypoxemia during the early postoperative period despite preoperative diagnosis and treatment of OSA, including the use of CPAP after bariatric surgery.³⁷ Furthermore, preoperative CPAP treatment of OSA was found to have no effect on length of stay, pulmonary complications, or mortality after bariatric surgery when CPAP was omitted during the postoperative period.³⁸

In our study, we were able to show CPAP to provide superior respiratory stability compared with AP in the PACU immediately after bariatric surgery. We found that the mean AHI during CPAP treatment applied *via* full facemask in the PACU after surgery was significantly decreased compared with the mean AHI during AP treatment (8/h *vs.* 25/h). This effect of CPAP might even be larger when applied *via* nasal mask as recently reported by Oto *et al.*³⁹ Our findings indicate that the beneficial effects of CPAP, previously observed during the first nights after surgery,²⁵ also extend to the period immediately after surgery despite lingering effects of anesthesia and surgery. However, whether or not these positive effects are associated with improved postoperative outcome is beyond the scope of this study.

In healthy controls, acutely administered CPAP can reduce cardiac index and cardiac stroke volume index due to PEEP. Decreased venous return on CPAP reduces cardiac preload and afterload by reducing left ventricular transmural pressure.⁴⁰ Thus, hypotensive periods are a potential risk with CPAP therapy. In our study, no significant hemodynamic effects were

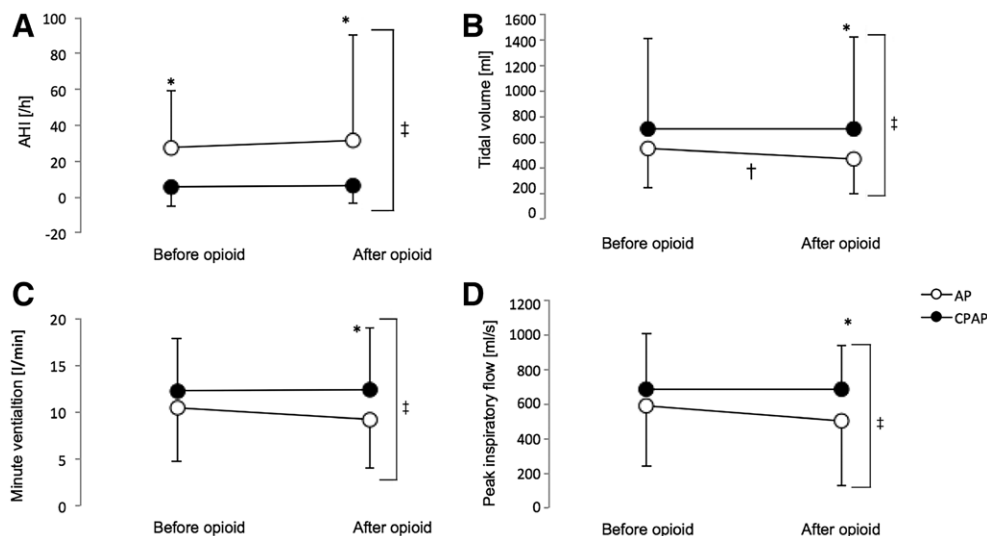


Fig. 8. Opioid-induced effects on (A) apnea hypopnea index (AHI), (B) tidal volume (V_T), (C) minute ventilation (MV), and (D) peak inspiratory flow (PIF) during continuous positive airway pressure (CPAP) and atmospheric pressure (AP). Application of opioid resulted in increases in AHI and reductions in PIF, MV, and V_T during AP treatment (white circles). Administration of CPAP (black circles) decreased these opioid-induced effects. *Statistically significant effect of CPAP treatment. †Statistically significant effect of opioid administration (within treatment group). ‡Statistically significant interaction effect between CPAP treatment and opioid application. Data from 31 patients who received opioids for postoperative pain therapy in the postanesthesia care unit.

Table 2. Effect of CPAP on Breathing and Oxygenation during Sleep before and after Application of Opioids

	Before Opioid Application			After Opioid Application		
	AP	CPAP	P Value	AP	CPAP	P Value
ODI (/h)	12 ± 23	2 ± 5	0.002	12 ± 21	3 ± 11	0.005
Mean SpO ₂ (%)	96 ± 3	97 ± 2	0.004	96 ± 2	97 ± 2	0.012
Nadir SpO ₂ (%)	94 ± 5	95 ± 4	0.022	93 ± 5	95 ± 4	0.007
V _T (ml)	546 ± 306	700 ± 332	0.004	466 ± 271	707 ± 332	0.000
PIF (ml/s)	583.6 ± 323.5	680.0 ± 343.9	0.089	498.7 ± 253.7	683.8 ± 370.7	0.007
RR (breaths/min)	20 ± 6	18 ± 4	0.002	20 ± 6	17 ± 4	0.000

Data were obtained from 31 patients who had received opioids for postoperative pain therapy in the postanesthesia care unit. All values are presented as mean ± SD.

AP = atmospheric pressure; CPAP = continuous positive airway pressure; ODI = oxygen desaturation index; PIF = peak inspiratory flow; RR = respiratory rate; SpO₂ = oxygen saturation; V_T = tidal volume.

observed when using CPAP treatment with an average pressure of 8.7 ± 0.6 cm H₂O. In fact, CPAP was well tolerated, and 86% of the study patients completed the CPAP treatment phase.

Recently, CPAP therapy has been described to be of limited benefit in patients with mild OSA.⁴¹ However, in our patient population, CPAP was effective, independent of OSA severity.

Opioids' Effects on Breathing, Airway Patency, and Interaction with CPAP

Opioids reduce airway patency and impair hypoxic and hypercarbic respiratory drive.⁴² Underlying mechanisms may include direct inhibitory effects on the pre-Bötzinger complex,⁴ as well as the retrotrapezoid nucleus and parafacial respiratory group complex, which are responsible for generating the respiratory pattern^{43,44} and decreasing effects on chest wall compliance *via* actions at various motoneurons (see Ref. 45 for review).

Although traditional clinical concepts interpret opioid-induced respiratory depression in the context of “overdosing,” our data show that low doses of opioids (1 mg morphine or equivalent dose of hydromorphone) given *via* PCA for postoperative pain treatment after bariatric surgery decrease tidal volumes and cause a trend toward lower PIF and MV, as well as higher frequency of oxygen desaturations and apneas during sleep. However, we did not observe similar impairing effects of opioids on breathing during wakefulness early after surgery, when cortical arousal and excitatory inputs to the upper airway motor neurons and respiratory drive are higher.^{8,13} Our findings indicate that the low dose of opioids applied here might be without negative effects on breathing as long as the patients stayed awake. However, we observed impairment of breathing and worsening of sleep apnea as soon as patients fell asleep and exhibited depression of cortical activity,⁴⁶ which was seen in all study patients during their PACU stay. The 1 mg morphine-equivalent dose of opioid investigated in our study was much lower than those in previous studies, and thus, effects of greater statistical significance may be observed when higher doses of opioids are given. All patients in our study slept during a significant

part of PACU treatment after weight-loss surgery. Given that bariatric patients are a population at high risk of OSA, it might be reasonable to provide sleep apnea–directed management during the early postoperative period, especially while patients remain largely immobile in bed.

Of note, the respiratory-depressant effects of low-dose opioid therapy given to treat postoperative pain occurred in an environment where stimulation by pain, PACU nursing interventions, and monitor alarms should offset some of the depressant effects of opioids. It is likely that the magnitude of opioid-induced respiratory depression increases as patients are discharged to a quiet room on the surgical ward.

The prevalence of OSA was high among our surgical cohort, and the higher sensitivity of OSA patients to opioid-induced respiratory depression is well known.⁴⁷ Furthermore, the upper airway of OSA patients is more prone to collapse when under the influence of neuromuscular blockade^{48,49} and anesthetics.⁵⁰ Therefore, clinical guidelines have suggested minimizing the use of opioids in this population. However, these patients also have a lower pain threshold compared to controls^{5,51} and require higher doses of opioids to accomplish adequate analgesia.^{6,52}

In this pharmacophysiologic interaction trial, we demonstrate that CPAP treatment can mitigate opioid-induced negative effects on AHI, V_T, and MV, potential markers of respiratory depression, and ameliorate SDB in the PACU. In contrast, among patients using daily opioid medication, CPAP does not appear to improve oxygen desaturations during sleep.⁵³ This limited effectiveness of CPAP in patients with chronic opioid use may be explained by poor compliance to CPAP treatment or tolerance to the respiratory-depressant effects of opioid with chronic use. In addition, an increased number of central apneas have been reported in patients on CPAP in some studies^{53,54} but not in others, in patients on chronic opioids.⁵⁵ In our study, we did not see a negative effect of low doses of opioids given *via* PCA on the number of central apneas in opioid-naïve patients in the PACU ($P = 0.875$).

Limitations

There are several limitations to our study and analysis. One major limitation is our use of unattended polysomnography

performed at the patient's home to diagnose baseline SDB in our population. Reassuringly, the positive predictive value of unattended polysomnography has been found to be similar to attended polysomnography,⁵⁶ and a recent multicenter trial comparing in-center to out-of-center polysomnography found the latter noninferior with regard to acceptance, adherence, time to treatment, and functional improvement due to CPAP when prescribed based on an out-of-center polysomnography.⁵⁷ A second limitation arises from our study's sample size and crossover design, which does not permit us to attribute optimal postoperative outcomes to improved AHI and oxygen saturation during CPAP treatment. A large-scale, randomized controlled parallel-group design trial is needed to detect meaningful differences between both treatments. We speculate that postoperative CPAP in patients vulnerable to postoperative airway obstruction may translate to decreased intensive care unit admission rate. Recent studies indicate sleep apnea to be associated with increased risk of reintubation.^{58,59} Of note, the incidence of OSA in our study population was high, and it is unclear if CPAP improves opioid-induced respiratory depression in patient populations without sleep apnea.

A third limitation relates to the potential disruptive and arousing stimulus effect of CPAP, especially to novel users. It is possible that patients on CPAP were slightly more alert, which in turn contributed to our finding of improved AHI. The RR observed during CPAP and AP was high compared to postoperative patients on the wards, as been reported previously^{60,61}—presumably representing the consequence of pain, anxiety, and inflammation early after surgery in the PACU setting. However, sleep architecture as well as arousal index measured by polysomnography did not differ between CPAP and AP treatment conditions.

Finally, our measurement of NREM2 sleep is subject to potential bias as application of low doses of opioids has been shown to affect sleep behavior and decreases non-REM sleep and REM sleep as measured by electroencephalography and sleep efficiency in rodents^{62,63} and humans.⁶⁴ In contrast, high doses of morphine induce sedation and are associated with slowing of the electroencephalography,^{65–68} in part mediated by central opioid inputs to sleep regulating brain areas (*e.g.*, ventrolateral preoptic nucleus).^{63,69} In our study, we ensured the presence of at least one electroencephalography sign other than specific theta frequency to define an episode as stable NREM2 sleep for our study (*e.g.*, k-complex or spindle activity) such that drug effects should not bias sleep scoring under these conditions.

Conclusion

In summary, more than 90% of patients in our cohort demonstrated SDB preoperatively during nighttime at home. Two thirds of them also show sleep apnea early after bariatric surgery in the recovery room during daytime while receiving 30% supplemental oxygen (breathing in AP). CPAP significantly improved AHI, oxygen saturation, tidal volume, PIF, and MV, and mitigated the respiratory-depressant effects observed

during sleep and during alpha–theta transition. Supervised CPAP treatment in the PACU in patients vulnerable to sleep apnea may improve postoperative respiratory safety.

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Competing Interests

Dr. Ramachandran received industry funding from Merck (Kenilworth, New Jersey) in 2014 for research on sleep apnea and early postoperative desaturation. Dr. Hess discloses relationships with Philips Respironics (Murrysville, Pennsylvania), Bayer (Robinson Township, Pennsylvania), McGraw-Hill (New York, New York), Jones and Bartlett (Burlington, Massachusetts), UpToDate (Alphen aan den Rijn, The Netherlands), and ABIM (Philadelphia, Pennsylvania). Dr. Malhotra relinquished all outside personal income since May 2012. Dr. Eikermann discloses a relationship with Calabash Bioscience Inc. (College Park, Maryland); he also received funding from Merck, Baxter Ventures (Deerfield, Illinois), and the Judy and Jeff Buzen fund (Boston, Massachusetts). The remaining authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Eikermann: meikermann@partners.org. Raw data available from Dr. Eikermann: meikermann@partners.org.

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