ANESTHESIOLOGY

Combination Therapy of High-flow Nasal Cannula and Upper-body Elevation for Postoperative Sleep-disordered Breathing: Randomized Crossover Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Patients with moderate to severe obstructive sleep apnea (OSA) are considered to have increased risk for postoperative respiratory and cardiovascular complications
- Proper use of continuous positive airway pressure *via* a face or nasal mask can be effective in reducing risk
- As some patients may not tolerate conventional therapy and/or some institutions may not be able to provide it preoperatively, alternate methods may be of value

What This Article Tells Us That Is New

- The authors evaluated the role of high-flow nasal cannula (20 l/min with 40% oxygen concentration) with or without 30-degree head-of-bed elevation in patients with moderate to severe obstructive sleep apnea (OSA), all of whom had perioperative sleep studies evaluated by the modified apnea hypopnea index, based exclusively on the airflow signal without arterial oxygen saturation criteria
- Both high-flow nasal cannula and head-of-bed elevation, independently, improved OSA significantly with an additive effect when combined
- The combination of high-flow nasal cannula and upper-body elevation may be considered as an alternative postoperative airway management strategy where continuous positive airway pressure, a standard of care, is refused or is unsuitable

ABSTRACT

Background: The low acceptance rate of continuous positive airway pressure therapy in postoperative patients with untreated obstructive sleep apnea (OSA) indicates the necessity for development of an alternative postoperative airway management strategy. The authors considered whether the combination of high-flow nasal cannula and upper-body elevation could improve postoperative OSA.

Methods: This nonblinded randomized crossover study performed at a single university hospital investigated the effect on a modified apnea hypopnea index, based exclusively on the airflow signal without arterial oxygen saturation criteria (flow-based apnea hypopnea index, primary outcome), of high-flow nasal cannula (20 l · min^{-1} with 40% oxygen concentration) with and without upper-body elevation in patients with moderate to severe OSA. Preoperative sleep studies were performed at home (control, no head-of-bed elevation) and in hospital (30-degree head-of-bed elevation). On the first and second postoperative nights, high-flow nasal cannula was applied with or without 30-degree head-of-bed elevation, assigned in random order to 23 eligible participants.

Results: Twenty-two of the 23 (96%) accepted high-flow nasal cannula. Four participants resigned from the study. Control flow-based apnea hypopnea index (mean ± SD, 60 ± 12 events · h^{-1}; n = 19) was reduced by 15 (95% CI, 6 to 30) events · h^{-1} with head-of-bed elevation alone ($P = 0.002$), 10.9 (95% CI, 1 to 21) events · h^{-1} with high-flow nasal cannula alone ($P = 0.028$), and 23 (95% CI, 13 to 32) events · h^{-1} with combined head-of-bed elevation and high-flow nasal cannula ($P < 0.001$). Compared to sole high-flow nasal cannula, additional intervention with head-of-bed elevation significantly decreased flow-based apnea hypopnea index by 12 events · h^{-1} (95% CI, 2 to 21; $P = 0.022$). High-flow nasal cannula, alone or in combination with head-of-bed elevation, also improved overnight oxygenation. No harmful events were observed.

Conclusions: The combination of high-flow nasal cannula and upper-body elevation reduced OSA severity and nocturnal hypoxemia, suggesting a role for it as an alternate postoperative airway management strategy.

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Obstructive sleep apnea (OSA) is an independent risk factor for postoperative respiratory and cardiovascular complications, as systematic reviews demonstrate.[1,2] Although continuous positive airway pressure therapy was reported to decrease the OSA frequency, its effects on postoperative complications and length of hospital stay are controversial currently.[3–5] It should be noted that postoperative continuous positive airway pressure adherence defined as continuous positive airway pressure use more than 4 h per night was only 33% in newly diagnosed untreated OSA patients.[6] Liao *et al.* reported a postoperative progressive decrease of continuous positive airway pressure adherence rate down to 26% by the fifth postoperative night, and median continuous positive airway pressure usage period was less than 2 h.[3] These data suggest the necessity of developing perioperative OSA therapeutic strategies alternative to continuous positive airway pressure use.

Recently, high-flow nasal cannula therapy is actively used for improvement of oxygenation in hypoxemic patients with various pathologies.[7] Increase of pharyngeal airway pressure produced by high-flow oxygen gas delivery through an open nasal cannula may be capable of improving the pharyngeal airway patency in patients with OSA.[8] Better acceptance by the first-time users, adjustable oxygen concentration, and improvement of cilia function due to high performance of entire-airway humidification are considered to be advantageous features of high-flow nasal cannula over continuous positive airway pressure as respiratory therapy for postoperative patients. In fact, three clinical trials demonstrated statistically significant improvement of OSA severity by use of high-flow nasal cannula at 20 $l \cdot min^{-1}$ flow rate to patients with mild to moderate OSA visiting sleep clinics, while no previous studies tested its effectiveness in postoperative OSA patients.[9–11] Reduction of apnea hypopnea index by high-flow nasal cannula is, however, variable and inferior to that of continuous positive airway pressure in the recent two studies questioning its clinical application.[10,11]

Fowler or upper-body elevation posture changes direction of gravity on the tongue and soft palate and has been demonstrated to dilate the pharyngeal airway in anesthetized paralyzed OSA patients.[12] Compared to sleep in the supine position, sleep in the upper-body elevation position was reported to decrease apnea index by more than 50% in patients with moderate to severe OSA without changing sleep efficiency.[13] Both studies performed the tests in the 60-degree upper-body elevation position, which appears to be too steep in postoperative patients attached to numerous drainage tubes and intravenous lines, for maintaining a stable and safe body position on the bed. Accordingly, a less than 60-degree upper-body elevation steepness was considered to reduce OSA severity and enhance the effect of high-flow nasal cannula therapy, due to differing effects on the pharyngeal airway.[14]

Accordingly, we aimed to evaluate potential clinical values of high-flow nasal cannula therapy and head-of-bed elevation for postoperative nocturnal respiratory managements in patients with untreated moderate to severe OSA. This randomized crossover study was designed to test a hypothesis that 30-degree head-of-bed elevation effectively improves the modified apnea hypopnea index based exclusively on the air flow signal without oxygen saturation measured by pulse oximetry Spo_2 criteria (primary outcome) in OSA patients receiving high-flow nasal cannula therapy during the first and second postoperative nights.

Materials and Methods

Participants

Registration and Recruitment. This nonblinded prospective randomized crossover controlled study from July 2019 to March 2021 was performed at Chiba University Hospital (Chiba, Japan). Ethical approval for this study (Ethical Committee number: 3326, principal investigator: Shiroh Isono, M.D.) was provided by the Ethical Committee of Chiba University Graduate School of Medicine (Chiba, Japan; Chairperson, M. Iyo, M.D., Ph.D.) on February 19, 2019. The study protocol was registered in University Hospital Medical Information Network Clinical Trial Registry, where contact information for request of the full trial information is available (UMIN000037265; July 4, 2019; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000042488).

Written informed consent was obtained from each subject after the aim and potential risks of the study were fully explained to each. In addition to the purpose of the study, criteria for participants, the randomization method, the research funding source, the stopping criteria, and the potential merits and risks were fully explained to the candidates. Inclusion criteria were adult OSA patients with apnea hypopnea index greater than 20 events $\cdot h^{-1}$ undergoing scheduled surgeries under elective general anesthesia at Chiba University Hospital. Apnea hypopnea index used for the inclusion criteria was determined by preoperative sleep study as described in the Preoperative OSA Screening and Perioperative Sleep Studies section. Exclusion criteria were patients with history of head or neck surgery, patients with nasogastric tube, OSA patients already using nasal continuous positive airway pressure, patients with limited neck mobility, and patients with high risk of aspiration. The primary investigator (Y. Sakaguchi) selected eligible patients from the surgical list based on their medical record information, after which candidate patients fulfilling the inclusion criteria were recruited. Eligibility of 27 candidate patients were confirmed, of whom 23 agreed to participate in this study (fig. 1: Consolidated Standard of Reporting Trials diagram).

Randomization and Allocation. In this crossover trial, participants were randomly allocated to either the head-of-bed elevation 0/30 group in which participants sleep on a bed with no head-of-bed elevation on the first postoperative night and sleep on the bed with 30-degree head-of-bed elevation on the second postoperative night, or the head-of-bed elevation 30/0 group in which participants sleep on

a bed with 30-degree head-of-bed elevation on the first postoperative night and sleep on the bed with no head-of-bed elevation on the second postoperative night (fig. 1). Third-person allocation mechanisms were used to conceal future randomization schedule. Assignment tables for stratified and block randomization were priorly created by an independent investigator (M.H.) with computer software (Stata/SE 15.1, Stata Corp. LP, USA) and stored in a locked drawer. For each sex, group randomization was performed for each of four consecutive patients. We expected a two-to-one ratio of men to women among the candidates in this study because of the male-predominant prevalence of OSA in general population.[15] The primary investigator (Y. Sakaguchi) was blinded to the allocation tables and the block size to minimize the selection bias. On the operation day, the independent investigator (M.H.) checked the allocation tables and announced the randomization schedule result in the order indicated in the tables to all medical staff in the operating room and ward, as well as the participant.

Preoperative OSA Screening and Perioperative Sleep Studies

Based on our routine preoperative assessments of the STOP questionnaire[16] and other OSA clinical features, such as obesity and small mandible, the selected patients undergoing scheduled surgeries under general anesthesia were screened for possible OSA through preoperative sleep study at home with a type 4 nocturnal portable monitor that measured respiratory airflow with nasal pressure, snoring, Spo_2, and pulse rate (SAS2100; Nihon Kohden; Japan). The apnea hypopnea index for study inclusion criteria was calculated using apneas and hypopneas determined by both respiratory signal criteria and Spo_2 criteria (equal to or greater than 3% Spo_2 reduction from the baseline), whereas subsequent analyses concentrated on apneas and hypopneas judged from airflow criteria alone.

For participants of this study, three additional sleep studies were performed by use of the same sleep study device after admission. All subjects were instructed to attach an oximetry

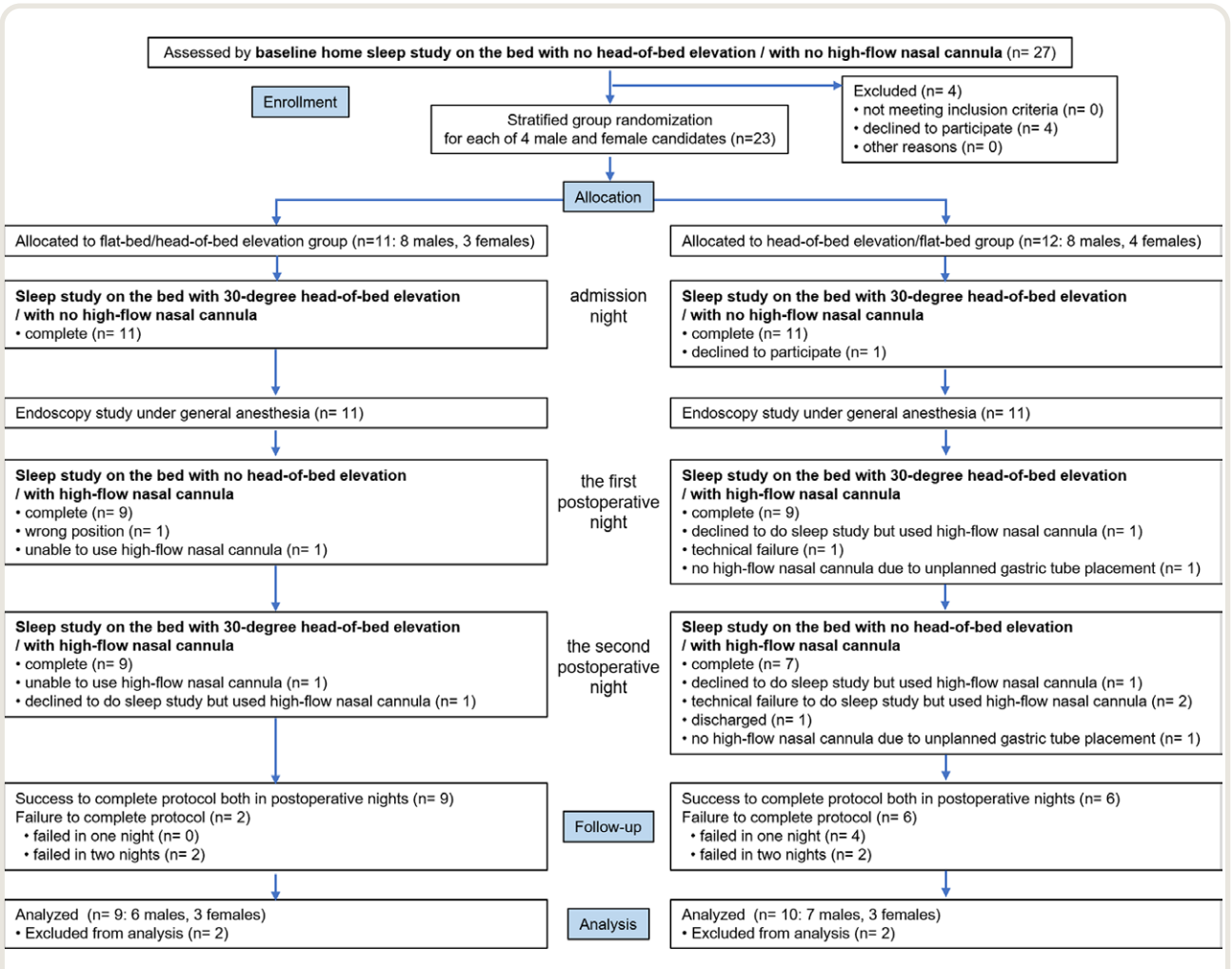

Fig. 1. Consolidated Standard of Reporting Trials diagram of this randomized crossover trial. High-flow nasal cannula: 20 l · min^{-1} flow rate with 40% oxygen concentration.

finger probe and nasal cannula before sleep and to remove them on awakening. After checking quality of the recordings by Y. Sakaguchi, respiratory and oximetry variables were calculated by computer software (QP-021W; Nihon Kohden; Japan). No manual correction of the analyses results was executed. Since oxygen was administered after surgery, apneas and hypopneas were determined by only respiratory signals without Spo_2 criteria in all four sleep studies including the preoperative sleep study. Apnea was defined as reduction of respiratory signals greater than 90% for 10 s or more. Hypopnea was defined as reduction of respiratory signals greater than 50% and less than 90% for 10 s or more.[17] Consequently, for the analysis of this study, the apnea hypopnea index determined by only flow signals (flow-based apnea hypopnea index, primary outcome) was calculated as the frequencies of apneas and hypopneas per hour of the monitoring time. Similarly, apnea index (flow-based apnea index) and hypopnea index (flow-based hypopnea index) were also determined by only flow signals. The 3% oxygen desaturation index, defined as frequency of desaturation episodes exceeding 3% below baseline per hour, mean nadir Spo_2, defined as mean value of the lowest Spo_2 during desaturation, the lowest Spo_2 value, and the percentage of time spent at Spo_2 less than 90% were also analyzed by using Spo_2 data.

All participants underwent two preoperative sleep studies: first, at home on the bed with no head-of-bed elevation, and second, in the hospital on the bed with 30-degree head-of-bed elevation. Furthermore, two postoperative sleep studies were planned on the first and second postoperative nights on the bed with different head-of-bed positions in accordance with the sleep study protocol for each assigned group (fig. 1).

Anesthesia Technique and Postoperative Managements

The anesthesia technique and surgical procedure were not affected by patients' participation in this study. The epidural catheter was placed before anesthesia induction for open abdominal surgery. General anesthesia was induced with fentanyl, remifentanil, and propofol, and complete paralysis was achieved by injection of rocuronium. As the secondary purpose of this study, endoscopic assessments of pharyngeal airway patency during application of high-flow nasal cannula were performed before tracheal intubation (results of this endoscopic study were not presented here). A polyvinyl chloride cuffed tracheal tube (6.5 to 7.5 mm internal diameter) was inserted into the trachea after complete neuromuscular blockade with rocuronium. Anesthesia was maintained with a continuous infusion of propofol or desflurane inhalation in combination with remifentanil infusion and/or administration of levobupivacaine through the epidural catheter at the discretion of the attending anesthesiologist. Depth of neuromuscular block was monitored by an acceleromyograph neuromuscular monitoring and maintained by additional 10- to 20-mg rocuronium injection(s). All patients' lungs were ventilated using pressure control ventilation in accordance with our local practice: tidal volume 6 to 8 ml · kg ideal body weight, and positive end-expiratory pressure level 5 cm H_2O. Bladder temperature was maintained above 36°C using a forced-air warming system (Bair-Hugger; Arizant Healthcare Inc.; USA). Hemodynamics was normalized by fluid infusion, blood transfusion, and vasopressor targeting mean blood pressure above 65 mmHg. Acetaminophen (1,000 mg) was intravenously administered at 30 to 60 min before predicted end of surgery in all participants. After the termination of surgery, neuromuscular blockade was reversed by injection of sugammadex based on the degree of muscle paralysis assessment by the neuromuscular monitor, after which anesthetics and remifentanil infusion were terminated to arouse the subject. After confirming wakefulness and responsiveness to verbal command, the trachea was extubated. For postoperative pain management, either continuous intravenous infusion of 20 to 40 $\mu g \cdot kg^{-1}$ fentanyl or epidural continuous infusion of the drug mixture of 0.125% 200 ml levobupivacaine, 800 μg fentanyl, and 2.5 mg droperidol at a rate of 4 ml · h^{-1} *via* a patient-controlled analgesia device was started intraoperatively and maintained for 48 h after surgery. Immediately after arrival to the ward, high-flow nasal cannula therapy (Optiflow; Fisher and Paykel Healthcare Limited; New Zealand) was started at 20 l · min^{-1} flow rate with 40% oxygen concentration. A delivery heating tube and humidifier included in the high-flow nasal cannula device maintained a temperature of 37°C and absolute humidity of 44 mg · l^{-1}. Even after cessation of oxygen therapy during the daytime, the high-flow nasal cannula therapy was performed during the first and second postoperative nights according to the patient's consent to the therapy (fig. 1). All participants slept on electrically adjustable beds allowing change of head-of-bed from 0 to 70 degree(s) (KA-96121A and KA9801A; Paramount Bed Inc., Japan). In accordance with the study protocol, the head-of-bed angle during each study night was fixed by the attending nurse and maintained throughout the night.

Primary and Secondary Outcomes and Sample Size Estimation

The primary outcome of this study was the modified apnea hypopnea index measured by the sleep study based exclusively on the air flow signal without Spo_2 criteria (flow-based apnea hypopnea index). Based on the results of a previous study which examined the effects of 20 l min^{-1} high-flow nasal cannula on the apnea hypopnea index in OSA patients,[8] it was our expectation that upper-body elevation would further decrease the apnea hypopnea index under high-flow nasal cannula (14 ± 9 events · h^{-1}) by 50% (7 events · h^{-1}). Assuming $\alpha = 0.05$ (two-tailed) and $\beta = 0.8$, the suitable sample size was calculated to be at least 15 subjects in this crossover randomized controlled trial (SigmaPlot 12.0; Systat Software Inc.; USA). As we also expected cases unable to complete the protocol, recruitment of the participants was continued until 15 complete sets of the

sleep study data were collected. The final study data excluded the four participants who failed to complete both of the two postoperative sleep studies, but included four participants with incomplete sets of study data for the final analysis (full analysis set; fig. 1). The secondary outcomes included all sleep study variables described in the Preoperative OSA Screening and Perioperative Sleep Studies section characterizing the severity and nature of OSA.

Statistics

Statistical analyses and reports of this trial were conducted in accordance with the Consolidated Standard of Reporting Trials statement guidelines, with primary analyses performed under the full analysis set, which was as close as possible to the intention-to-treat ideal of including all sleep study data obtained from the participants. Anthropometric variables were expressed as mean ± SD for continuous variables, and frequencies for categorical data. Superiority of sleeping on the bed with 30-degree head-of-bed elevation under high-flow nasal cannula to sleeping on the bed with no head-of-bed elevation under high-flow nasal cannula (primary hypothesis) was planned to be tested by a paired *t* test. However, due to incomplete sets of sleep study data, we decided to test the primary hypothesis with a linear mixed-effect model for flow-based apnea hypopnea index accounting for interventions (high-flow nasal cannula, 30-degree head-of-bed elevation, and their combination), and their interactions as fixed effects and subjects as a random effect while adjusting time and order. Possible carryover effects between the first postoperative night and the second postoperative night were evaluated during the analysis, and the model included adjustment for these effects. The secondary comparisons of the flow-based apnea hypopnea index, however, were not adjusted for multiplicity. All other sleep study variables (secondary outcomes) were also analyzed with the linear mixed effect model. *P* values were two-sided, and a value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute; USA) and SigmaPlot 12.0 (Systat Software Inc.; USA).

Results

Enrollment of patients started on July 8, 2019, and terminated on March 31, 2021. A Consolidated Standard of Reporting Trials flow diagram is presented in figure 1. Enrollment ceased as planned when the target sample size (15 complete sets of the sleep study data) was obtained. Interim analysis was not performed. No harmful event occurred during the study. A total of 27 eligible patients with moderate to severe OSA were approached, of whom four declined to participate in this study before random group allocations. Eleven participants were allocated to the head-of-bed elevation 0/30 group and 12 participants to head-of-bed elevation 30/0 group. Due to the various reasons presented in figure 1, four participants' data (two head-of-bed-elevation 0/30 group participants and two head-of-bed elevation 30/0 group participants) were not obtained. No additional missing data existed in this study. Therefore, 9 head-of-bed elevation 0/30 group and 10 head-of-bed elevation 30/0 group participants' data were used for the final full analysis. One of 23 participants (4%) expressed discomfort for the high-flow nasal cannula therapy and sleep study equipment. The remaining 22 participants (96%), including those with failure to complete the study protocol, received the high-flow nasal cannula therapy without expressing discomfort and any incident. Missing data were handled as assuming missing at random. The number of obtained data for each variable was presented when there were missing data. Preoperative airway assessments were waived during the COVID-19 pandemic in six participants. Background anthropometric and surgical characteristics did not differ between the groups. Fentanyl dosage used during anesthesia and after surgery did not differ between the groups. Preoperative apnea hypopnea index determined by both flow signal and Spo_2 criteria was significantly greater in the head-of-bed elevation 0/30 group compared to the head-of-bed elevation 30/0 group (table 1).

Differences of Features and Frequencies of Repetitive Sleep-disordered Breathing

Figure 2 presents representative differences of respiratory pressure signals through the nose in four different conditions of sleeping positions and use of high-flow nasal cannula in a 54-yr-old nonobese female with severe OSA (flow-based apnea hypopnea index, 60 events · h^{-1}). Despite use of high-flow nasal cannula, the respiratory signals well reflected changes of respiratory patterns. Compared to repetitive occurrence of apneas during sleep on the bed with no head-of-bed elevation or with no high-flow nasal cannula, repetitive hypopneas instead of apneas were the predominant respiration pattern feature during sleep on 30-degee head-of-bed elevation with or without high-flow nasal cannula. Table 2 summarizes the differences of observed sleep study variables including flow-based apnea hypopnea index, flow-based apnea index, and flow-based hypopnea index determined by only flow signals in four differing combinations of head-of-bed elevation and use of high-flow nasal cannula. These data were used to test the primary hypothesis.

Result of the Primary Hypothesis: Effects of Head-of-bed Angles during High-flow Nasal Cannula Therapy on OSA

Figure 3 summarizes the means and 95% CI of frequencies of repetitive OSA features estimated by linear mixed-effect model analyses in four different conditions. Except for the flow-based hypopnea index, improvements of all other OSA features either by head-of-bed elevation and/or high-flow nasal cannula application are evident. Table 3 presents results of the linear mixed-effect model analyses

Table 1. Background Variables for Each Allocation Group

Group Allocation	Head-of-bed Elevation 0/30	Head-of-bed Elevation 30/0
Number of analyzed patients (male, female)	9 (6, 3)	10 (7, 3)
Age, yr	62.1 ± 9.1	67.7 ± 13.8
Height, cm	164 ± 6	164 ± 12
Body weight, kg	72.0 ± 16.0	70.1 ± 14.4
Body mass index, kg · m^{-2}	26.6 ± 5.8	26.0 ± 3.5
Body mass index > 30 kg · m^{-2}	2 (22)	1 (10)
ASA Physical Status (I, II, III, IV)	(0, 9, 0, 0)	(0, 8, 2, 0)
Cardiovascular diseases	6 (67)	6 (60)
Metabolic diseases	6 (67)	4 (40)
Respiratory diseases	1 (11)	3 (30)
Other diseases	5 (56)	5 (50)
Mallampati class (1, 2, 3, 4) (n = 13)	(0, 6, 0, 1)	(1, 4, 1, 0)
Thyro-mental distance, mm (n = 13)	74 ± 11	77 ± 8
Inter-incisor distance, mm (n = 13)	44 ± 10	42 ± 10
Upper lip bite test (1, 2, 3) (n = 12)	(6, 1, 0)	(3, 1, 1)
STOP score (0, 1, 2, 3,4)	(0, 4, 3, 2, 0)	(1, 1, 1, 7, 0)
Habitual snoring	6 (67)	8 (80)
Daytime tiredness	2 (22)	4 (40)
Observed apnea	2 (22)	6 (60)
Hypertension	6 (67)	6 (60)
Preoperative sleep study analyzed by using both flow signal and Spo_2 value criteria		
Apnea hypopnea index, events · h^{-1}	49 ± 10	34 ± 15
Apnea index, events · h^{-1}	30 ± 11	19 ± 10
Hypopnea index, events · h^{-1}	19 ± 12	14 ± 9
3% oxygen desaturation index, events · h^{-1}	42 ± 13	29 ± 10
Mean nadir Spo_2, %	92 ± 2	93 ± 2
Lowest Spo_2, %	75 ± 14	81 ± 8
Percent time Spo_2 < 90%, %	4.4 ± 3.1	3.1 ± 3.6
Surgery type		
Nonabdominal surgery	3	5
Lower abdominal surgery: laparotomy	1	0
Lower abdominal surgery: laparoscopy	5	5
Duration of surgery, min	165 ± 53	147 ± 61
Duration of anesthesia, min	238 ± 53	234 ± 67
Opioid dose during anesthesia, μg	233 ± 94	220 ± 103
Opioid-PCA after surgery	6 (67)	4 (40)
Postoperative total opioid dose, μg	850 ± 235	1,375 ± 350

Values are mean ± SD or number of subjects (% of the group or distribution of subjects).
ASA, American Society of Anesthesiologists; PCA, patient-controlled analgesia; Spo_2, oxygen saturation measured by pulse oximetry.

for assessing effects of head-of-bed elevation and high-flow nasal cannula on sleep study variables. Both head-of-bed elevation and high-flow nasal cannula had significant effects on reducing flow-based apnea hypopnea index (primary outcome) without interaction between the interventions. Compared to high-flow nasal cannula therapy alone, additional head-of-bed elevation intervention was estimated to significantly decrease flow-based apnea hypopnea index (difference: mean, 12 events · h^{-1}; 95% CI, 2 to 21 events · h^{-1}; $P = 0.022$), supporting the primary hypothesis.

Effects of Upper-body Elevation and High-flow Nasal Cannula on OSA Frequency and Nocturnal Hypoxemia

Control (preoperative untreated) flow-based apnea hypopnea index was 60 ± 12 events · h^{-1} (mean ± SD; n = 19). This was reduced by 15 (95% CI, 6 to 30) events · h^{-1} with head-of-bed elevation alone ($P = 0.002$); 11 (95% CI, 1 to 21) events · h^{-1} with high-flow nasal cannula alone ($P = 0.028$); and 23 (95% CI, 13 to 32) events · h^{-1} (38%) with combined head-of-bed elevation and high-flow nasal cannula ($P < 0.001$; linear mixed-effects modeling; table 3). Although high-flow nasal cannula therapy alone and head-of-bed elevation alone both reduce flow-based apnea hypopnea index by a similarly small amount, combining these interventions appears to have an additive effect. Since significant effects of both head-of-bed elevation and high-flow nasal cannula on flow-based apnea index, but not on flow-based hypopnea index, were indicated, the reduction of flow-based apnea hypopnea index is considered due to transformations of breathing pattern from apnea to hypopnea and from hypopnea to normal breathing as demonstrated in figure 2. Although effects of head-of-bed elevation alone were limited to improvement of frequency of repetitive OSA features, high-flow nasal cannula either

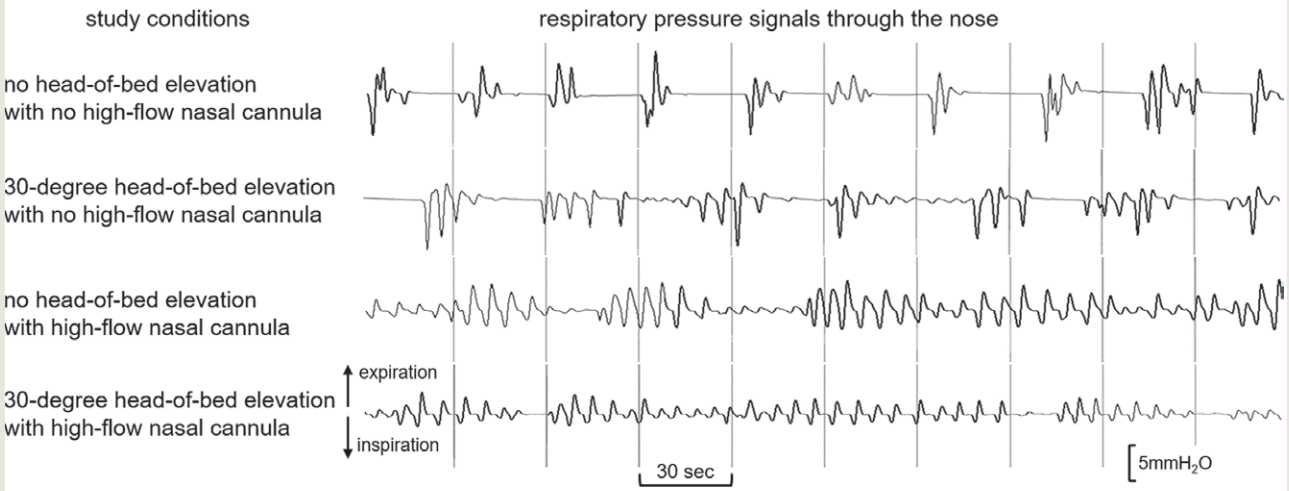

Fig. 2. Representative differences of respiratory pressure signals through the nose in four different conditions of the upper-body elevation angle, and use of high-flow nasal cannula (20 l · min^{-1} flow rate with 40% oxygen concentration) in 54-yr-old nonobese female with moderate to severe obstructive sleep apnea (modified apnea hypopnea index, 60 events · h^{-1}). Note repetitive apneas during sleep on the bed with no head-of-bed elevation or with no high-flow nasal cannula changed to repetitive hypopneas during sleep in 30-degree head-of-bed elevation angle with or without high-flow nasal cannula.

Table 2. Observed Severity of Obstructive Sleep Apnea in Four Differing Combinations of Head-of-bed Angles and Use of High-flow Nasal Cannula in 19 Analyzed Participants

Head-of-bed Elevation	**No**	**Yes**	**No**	**Yes**
High-flow Nasal Cannula	**No**	**No**	**Yes**	**Yes**
No. of subjects	19	19	16	18
Flow-based apnea hypopnea index, events · h^{-1}	60 ± 12	45 ± 10	49 ± 17	37 ± 21
Flow-based apnea index, events · h^{-1}	26 ± 11	10 ± 10	12 ± 7	7 ± 8
Flow-based hypopnea index, events · h^{-1}	34 ± 12	35 ± 7	36 ± 13	30 ± 16
3% oxygen desaturation index, events · h^{-1}	35 ± 13	20 ± 10	5 ± 6	4 ± 5
Mean nadir Spo_2, %	93 ± 2	93 ± 3	98 ± 1	97 ± 1
Lowest Spo_2, %	78 ± 12	79 ± 13	92 ± 6	92 ± 6
Percent time Spo_2 < 90%, %	3.7 ± 3.4	5.0 ± 13.3	0.1 ± 0.2	0.1 ± 0.2

Values are means ± SD. Flow-based apnea hypopnea index, flow-based apnea index and flow-based hypopnea index are modified apnea hypopnea index, apnea index, and hypopnea index, respectively, determined by only flow signals without desaturation criteria. Head-of-bed elevation = 30-degree head-of-bed elevation angle, high-flow nasal cannula = 20 l · min^{-1} flow rate with 40% oxygen concentration.

Spo_2, oxygen saturation measured by pulse oximetry.

alone or in combination with head-of-bed elevation had significant effects on improving nocturnal oxygenation variables as well as OSA frequency. High-flow nasal cannula significantly increased mean nadir Spo_2 value by 5% from preoperative untreated control condition (93 ± 2%; P < 0.001).

Discussion

In this randomized crossover trial, we found that (1) compared to high-flow nasal cannula therapy alone, simultaneous intervention of upper-body elevation by 30 degrees was estimated to significantly decrease flow-based apnea hypopnea index in postoperative patients with untreated moderate to severe OSA; (2) effects of upper-body elevation were limited to improvement of OSA frequency, whereas high-flow nasal cannula had significant effects on improvement of nocturnal hypoxemia and OSA frequency; and (3) a combination of high-flow nasal cannula and upper-body elevation decreased flow-based apnea hypopnea index by 38%.

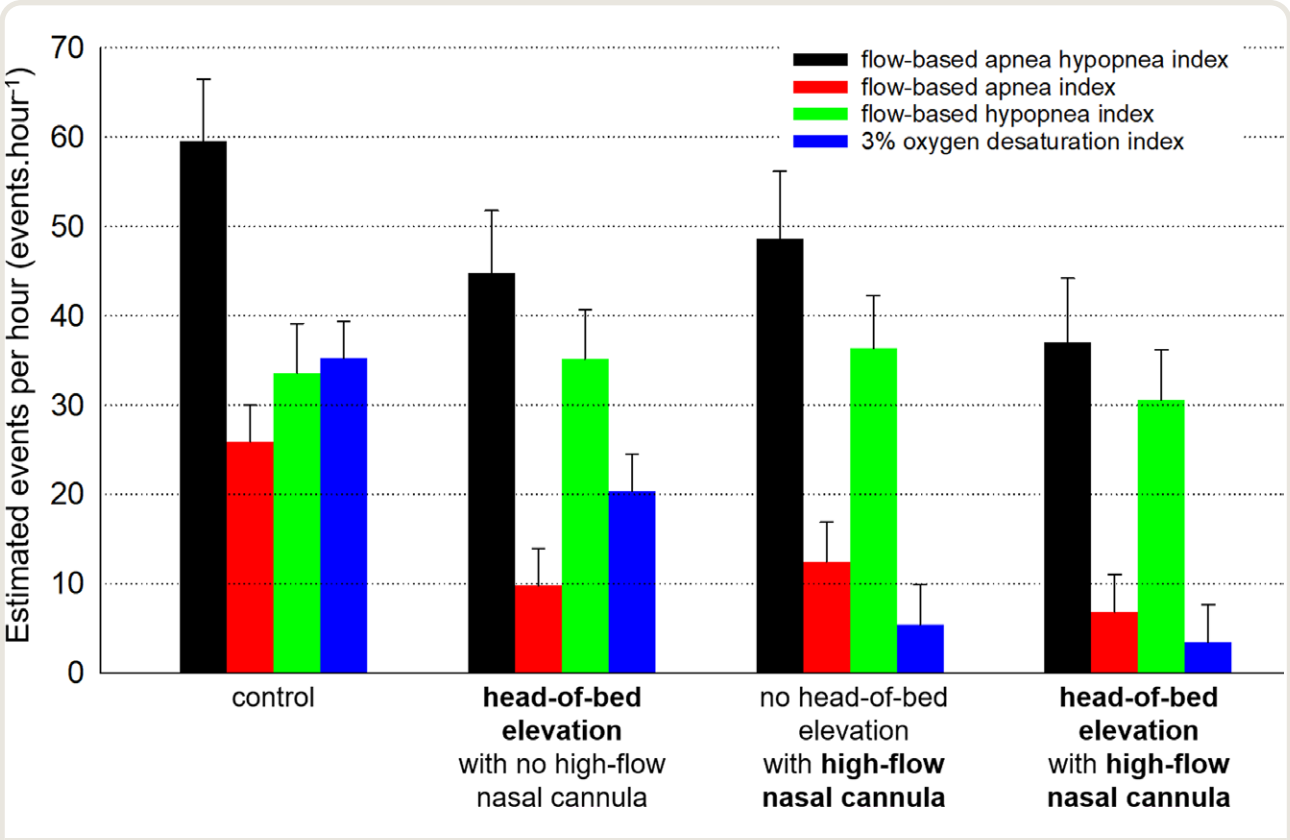

Fig. 3. Summary of frequencies of repetitive obstructive sleep apnea features estimated by linear mixed effect model analyses in four different combinations of head-of-bed angles and use of high-flow nasal cannula in 19 analyzed participants. Bars are means and 95% CI estimated by linear mixed effect model analyses in four different conditions. Flow-based apnea hypopnea index, flow-based apnea index, and flow-based hypopnea index are modified apnea hypopnea index, apnea index, and hypopnea index, respectively, determined by only flow signals without desaturation criteria. Control = no head-of-bed elevation with no high-flow nasal cannula, head-of-bed elevation = 30-degree head-of-bed elevation angle, high-flow nasal cannula = 20 l · min^{-1} flow rate with 40% oxygen concentration.

Clinical Implications of the Findings

High-flow nasal cannula therapy has become a frequently used noninvasive form of respiratory support in acute respiratory failure[18]; however, clinical usefulness of high-flow nasal cannula in the perioperative period remains uncertain and appears to be limited to the specific patient populations such as high-risk and/or obese patients after cardiac or thoracic surgery.[19,20] Upper-body elevation is the recommended position for intensive care unit and postoperative patients in prevention of silent pulmonary aspiration as well as improving lung function.[21,22] Improvement of pregnancy-related OSA without impairing sleep quality or sleep architecture early after delivery was also reported.[23–25] We confirmed the effect of 20 l · min^{-1} high-flow nasal cannula and additive effect of 30-degree upper-body elevation on treatment of postoperative OSA. Improvement of flow-based apnea hypopnea index by either high-flow nasal cannula or head-of-bed elevation was statistically significant, but clinically inadequate. However, a combination of high-flow nasal cannula and head-of-bed elevation achieved reduction of flow-based apnea hypopnea index by 38%. Furthermore, we found significant improvement of postoperative nocturnal oxygenation during high-flow nasal cannula application. Although the effect of the combination therapy on OSA is clearly smaller than nasal continuous positive airway pressure application, 96% of the participants had difficulties in accepting it throughout the study nights. The combination of high-flow nasal cannula and 30-degree upper-body elevation is a promising clinically meaningful postoperative airway management strategy in patients with moderate to severe OSA, while future studies need to carefully test its possible beneficial effects on postoperative cardiorespiratory complications, particularly in obese OSA patients who may possibly have obesity hypoventilation syndrome.[26]

Mechanisms of Improvement of OSA by Upper-body Elevation and High-flow Nasal Cannula

Both high-flow nasal cannula therapy and head-of-bed elevation significantly decreased flow-based apnea hypopnea index; however, we consider that each has differing

Table 3. Results of the Linear Mixed-effect Model Analyses for Assessing Effects of 30-degree Head-of-bed Elevation and High-flow Nasal Cannula on Sleep Study Variables

	Type 3 Analysis of Effects			Comparison between Conditions							
				No Head-of-bed Elevation with High-flow Nasal Cannula		Control		Control		Control	
				Head-of-bed Elevation with High-flow Nasal Cannula		Head-of-bed Elevation with No High-flow Nasal Cannula		No Head-of-bed Elevation with High-flow Nasal Cannula		Head-of-bed Elevation with High-flow Nasal Cannula	
	Head-of-bed Elevation	High-flow Nasal Cannula	Interaction	Difference (95% CI)	*P*	Difference (95% CI)	*P*	Difference (95% CI)	*P*	Difference (95% CI)	*P*
Flow-based apnea hypopnea index, events · h^{-1}	< 0.001	0.007	0.639	12 (2 to 21)	0.022	15 (6 to 30)	0.002	11 (1 to 21)	0.028	23 (13 to 32)	< 0.001
Flow-based apnea index, events · h^{-1}	< 0.001	< 0.001	0.019	6 (–1 to 12)	0.08	16 (10 to 22)	< 0.001	14 (7 to 20)	< 0.001	19 (13 to 25)	< 0.001
Flow-based hypopnea index, events · h^{-1}	0.405	0.702	0.148	–6 (–2 to 13)	0.120	–2 (8 to 5)	0.647	–3 (–10 to 5)	0.455	–3 (–4 to 10)	0.381
3% oxygen desaturation index, events · h^{-1}	< 0.001	< 0.001	0.001	2 (–3 to 7)	0.458	15 (10 to 20)	< 0.001	30 (25 to 35)	< 0.001	32 (27 to 37)	< 0.001
Mean nadir Spo_2, %	0.822	< 0.001	0.419	0 (–1 to 1)	0.689	0 (–2 to 1)	0.449	–5 (–6 to –4)	< 0.001	–5 (–6 to –4)	< 0.001
Lowest Spo_2, %	0.715	< 0.001	0.921	–1 (–5 to 5)	0.855	–1 (–5 to 4)	0.733	–14 (–19, –9)	< 0.001	–14 (–19 to –10)	< 0.001
Percent time Spo_2 < 90%, %	0.704	0.012	0.690	0 (–4.7 to 4.8)	0.990	–1.3 (–5.7 to 3.2)	0.569	3.6 (–1.1 to 8.3)	0.130	3.6 (–0.9 to 8.2)	0.114

Values are estimated mean difference and 95% CI. Flow-based apnea hypopnea index, flow-based apnea index, and flow-based hypopnea index are modified apnea hypopnea index, apnea index, and hypopnea index, respectively, determined by only flow signals without desaturation criteria. Control = no head-of-bed elevation with no high-flow nasal cannula, head-of-bed elevation = 30-degree head-of-bed elevation angle, high-flow nasal cannula = 20 l · min^{-1} flow rate with 40% oxygen concentration. Spo_2, oxygen saturation measured by pulse oximetry.

mechanisms for its improvement. High-flow nasal cannula increases airway pressure by approximately 1 cm H_2O with each 10 l · min^{-1} flow rate increase.[8] The flow rate of 20 l · min^{-1} applied in this study is expected to increase the airway pressure only by 2 cm H_2O, which is much smaller than the treatment level of nasal continuous positive airway pressure for moderate to severe OSA patients (8 cm H_2O or more), indicating involvement of other mechanisms. High-flow nasal cannula with higher flow rates would have led to greater reduction of flow-based apnea hypopnea index, although simultaneous increase of discomfort during treatment would have resulted.

Participants in this study inhaled warm and humidified 40% oxygen during the high-flow nasal cannula therapy. Oxygen administration alone is reported to decrease the apnea hypopnea index by decreasing loop gain of the respiratory control system in OSA patients with higher loop gain.[27,28] The beneficial effect of oxygen administration was also confirmed in postoperative patients with OSA.[29] Loop gain may also be significantly influenced by the use of opioid and reduction of functional residual lung capacity during the postoperative period as well as inherent individual sensitivity of respiratory control.[30] Upper airway respiratory control can be also modified by the high-speed gas flow traveling through the upper airway, possibly stimulating cold, pressure, and flow receptors on the airway mucosa, while this mechanism is unlikely because of the warm temperature gas and positive airway pressure in high-flow nasal cannula therapy.[31,32]

Upper-body elevation changes direction of gravity on the upper airway soft tissues such as the tongue and increases longitudinal tension of the pharyngeal airway through lung volume increase.[31,33,34] Tagaito *et al.* demonstrated that a 60-degree sitting posture decreased pharyngeal airway closing pressure by 6 cm H_2O, corresponding to the treatment level effect of nasal continuous positive airway pressure.[12] Effectiveness of 30-degree upper-body elevation on pharyngeal airway collapsibility was tested and proved in normal subjects under sedation[35] and in severe OSA patients during natural sleep.[36] However, it remains untested whether clinically meaningful pharyngeal airway dilation is achievable by a 30-degree upper-body elevation alone and/or in combination with high-flow nasal cannula in moderate to severe OSA patients. These possibilities were tested by endoscopic assessments of pharyngeal airway patency under general anesthesia and paralysis in this study, and results of the analyses will be reported separately in the near future.

Limitations of the Study

Interpretation of the results of this clinical study is somewhat difficult due to methodologic limitations in testing this hypothesis. First, we did not perform a standard polysomnography, including measurements of sleep and wake status, and therefore, flow-based apnea hypopnea index obtained in this study may possibly be underestimated due to differences of sleep efficiency during the perioperative study period.[37] However, definitions of apneas and hypopneas were independent from Spo_2 reduction, which may have included more events of short-period apneas and hypopneas usually excluded from the analysis, consequently revealing more precise effects of upper-body elevation and high-flow nasal cannula on nocturnal breathing due to deeper inclusive definitions of the sleep study parameters. In this context, the crossover study design adopted in this study could minimize the limitation. Although crossover measurements during the two consecutive postoperative nights would not be ideal to completely wash out the carrying effect, acceptably minimum carrying effects may be considered as a potential confounding factor. Furthermore, the combination apparently altered the severity of OSA, significantly decreasing flow-based apnea index without altering flow-based hypopnea index, indicating reliance of the results. Although a negative impact on sleep quality and arousal by upper-body elevation was documented in normal subjects,[38,39] no change or improvement of sleep quality and respiratory-related arousal resulted from upper-body elevation in OSA patients monitored by polysomnography,[13,23,40] which supported our findings. Second, preoperative apnea hypopnea index at home was greater in the head-of-bed elevation 0/30 group compared to the head-of-bed elevation 30/0 group, and more participants in the head-of-bed elevation 30/0 group were unable to complete the consecutive first and second postoperative nights' sleep studies despite the appropriate process of participants' random allocation. The primary hypothesis was basically tested by changes between differing conditions within a subject by the crossover study design. The differences of preoperative OSA severity between the groups were considered to only minimally affect the results of this study. Third, head (flexion, extension, rotation) and body (lateral, supine) positions were not controlled in this study, while these factors tend to significantly influence pharyngeal airway collapsibility and apnea hypopnea index.[41–44] Fourth, opioid usage and opioid dosage, which tend to influence frequency of apneas and hypopneas, were not controlled in this study; however, total opioid dosages used postoperatively did not differ between the groups (table 1). Fifth, we did not perform preoperative airway assessments in six participants due to the COVID-19 pandemic. Inclusion of a full set of airway assessment data would not have changed the results due to only minor variations among participants. Last, we did not monitor actual participant usage of the high-flow nasal cannula throughout the study period. Unlike recent sophisticated continuous positive airway pressure machines, no high-flow nasal cannula machine commercially available included an adherence monitoring system. Accidental misalignment of the nasal prong during measurement may have affected the performance of high-flow nasal cannula therapy and consequently the results of this study. However, this episode

was considered to be rare, since the appropriateness of nasal prong installation was strictly checked before starting the sleep study, and such episodes could lead to baseline Spo_2 reduction that was not observed during manual analyses of the sleep study data.

In conclusion, the combination of high-flow nasal cannula therapy and 30-degree upper-body elevation effectively improves OSA severity and nocturnal oxygenation. Its performance for OSA treatment is inferior to continuous positive airway pressure therapy, but may be considered as an alternative postoperative airway management strategy where continuous positive airway pressure is refused or is unsuitable for other reasons.

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Competing Interests

Dr. Isono received payments for his academic advice from Nihon Kohden Japan, Tokyo, Japan, which manufactures and sells the portable sleep study device used in this study. This work is attributed to the Department of Anesthesiology, Graduate School of Medicine, Chiba University, Chiba, Japan. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: shirohisono@yahoo.co.jp. Raw data available at: shirohisono@yahoo.co.jp.

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