ANESTHESIOLOGY

Nasopharyngeal Tube Effects on Breathing during Sedation for Dental Procedures

A Randomized Controlled Trial

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ABSTRACT

Background: Intravenous sedation is effective in patients undergoing dental procedures, but fatal hypoxemic events have been documented. It was hypothesized that abnormal breathing events occur frequently and are underdetected by pulse oximetry during sedation for dental procedures (primary hypothesis) and that insertion of a small-diameter nasopharyngeal tube reduces the frequency of the abnormal breathing events (secondary hypothesis).

Methods: In this nonblinded randomized control study, frequency of abnormal breathing episodes per hour (abnormal breathing index) of the patients under sedation for dental procedures was determined and used as a primary outcome to test the hypotheses. Abnormal breathing indexes were measured by a portable sleep monitor. Of the 46 participants, 43 were randomly allocated to the control group (n = 23, no nasopharyngeal tube) and the nasopharyngeal tube group (n = 20).

Results: In the control group, nondesaturated abnormal breathing index was higher than the desaturated abnormal breathing index (35.2 [20.6, 48.0] *vs.* 7.2 [4.1, 18.5] h^{-1}, difference: 25.1 [95% CI, 13.8 to 36.4], $P < 0.001$). The obstructive abnormal breathing index was greater than central abnormal breathing index ($P < 0.001$), and half of abnormal breathing indexes were followed by irregular breathing. Despite the obstructive nature of abnormal breathing, the nasopharyngeal tube did not significantly reduce the abnormal breathing index (48.0 [33.8, 64.4] h^{-1} *vs.* 50.5 [36.4, 63.9] h^{-1}, difference: −2.0 [95% CI, −15.2 to 11.2], $P = 0.846$), not supporting the secondary hypothesis.

Conclusions: Patients under sedation for dental procedure frequently encounter obstructive apnea/hypopnea events. The majority of the obstructive apnea/hypopnea events were not detectable by pulse oximetry. The effectiveness of a small-diameter nasopharyngeal tube to mitigate the events is limited.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Dental procedures under sedation can cause hypoxic events and even death. However, the mechanism of such hypoxic events is not well understood.

What This Article Tells Us That Is New

- Apnea and hypopnea occur frequently during dental procedures under sedation. The majority of the events are not detectable with pulse oximetry. Insertion of a nasal tube with small diameter does not reduce the incidence of apnea/hypopnea.

Intravenous sedation in combination with regional anesthesia is an effective medical technique commonly applied for minimizing anxiety, pain, and physical stress for the patients undergoing various medical procedures such as minor surgeries, endoscopic examinations, and dental treatments.[1–3] Despite its effectiveness, sedation-associated adverse outcomes such as cardiac arrest and death have been documented.[4,5] A detailed survey from dental practitioners in Illinois, covering the period between 1996 and 2005, revealed two mortalities and two long-term morbidities for 115,940 sedations, and 30 cases requiring emergency transfer to a hospital despite the widespread use of pulse oximetry during dental sedation.[6] Jastak and Peskin[7] reported that the most common cause of adverse events resulting in death during dental procedures was hypoxemia due to abnormal breathing caused by airway obstruction and/or respiratory depression. According to Heinrich's safety triangle, it would be prudent to treat abnormal breathing with lower severity to provide increased safety during dental sedation.[8] However, no study has explored the nature of breathing, oxygenation, and consciousness level concurrently with sedation for dental procedures and clarified mechanisms for the adverse outcomes.

This article is featured in "This Month in Anesthesiology," page 1A. This article has a visual abstract available in the online version. Part of the work presented in this article has been presented as poster at the 40th annual meeting of the Japanese Society of Sleep Research in Tochigi, Japan, July 2, 2015, and at the 25th anniversary meeting of the American Academy of Dental Sleep Medicine in Denver, Colorado, June 10, 2016.

Submitted for publication December 20, 2017. Accepted for publication January 27, 2019. From the Department of Anesthesiology, Graduate School of Medicine, Chiba University, Chiba, Japan (Y.K., S.I.); the Department of Anesthesiology, Showa University Koto Toyosu Hospital, Tokyo, Japan (Y.K., T.S.); the Department of Perioperative Medicine, Division of Anesthesiology, Showa University School of Dentistry, Tokyo, Japan (Y.K., S.O., A.K., T.I.); the Department of Dental Anesthesiology and Orofacial Pain, Graduate School of Dentistry, Kyusyu Dental University, Fukuoka, Japan (K.K.); the Department of Oral Health Sciences, Faculty of Dentistry, University of British Columbia, Vancouver, Canada (F.R.A.); and the Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, Japan (Y.S.).

Although the guidelines from the American Society of Anesthesiologists and the American Dental Association recommend appropriate levels of sedation for dental procedures,[2,9–11] it is difficult to practically maintain the target depth of sedation. Therefore, oversedation and its associated consequences are frequently encountered. Furthermore, injection of water into the oral cavity during dental procedures may increase the chance of upper airway reflexes such as coughs and laryngospasm, leading to abnormal breathing.[12,13] This suggests the presence of an inherently high risk of abnormal breathing with and without desaturation in the sedation for dental procedures. Although the use of both pulse oximetry and oxygen administration during dental sedation are strongly recommended in the guidelines, detection of abnormal breathing with pulse oximetry is often delayed, and the value in reporting the abnormal breathing seems limited.[11,14] The addition of capnography to pulse oximetry improves detection of abnormal breathing and reduces the risk of developing hypoxemia.[15] However, capnography does not accurately characterize the nature of breathing in detail. In this context, a portable sleep monitor measuring nasal pressure with nasal cannula and respiratory efforts can provide detailed information on breathing and oxygenation. Accordingly, the primary purpose of this study is to describe the nature of breathing during dental sedation and test a hypothesis that during sedation for dental procedures, apneas/hypopneas frequently occur that are underdetected by pulse oximetry (primary hypothesis).

If upper airway obstruction is a major cause of apneas/hypopneas during dental sedation, a device that improves the patient's airway patency in other populations may be effective in the patients under sedation for dental procedures. A recent meta-analysis evidenced effectiveness of a nasopharyngeal tube for obstructive sleep apnea[16]; however, discomfort and pain caused by a large-bore tube into the nasal passage limits its clinical application. Even more, a small-diameter tube (3- to 4-mm inner diameter) significantly reduced the frequency of obstructive sleep apnea by more than 50%, with a 44% tolerance rate.[17] Based on the promising results in patients with obstructive sleep apnea, we hypothesized that a small-diameter nasopharyngeal tube inserted immediately after induction of sedation reduces the number of the abnormal breathing episodes during dental sedation (secondary hypothesis). Accordingly, we designed a randomized control study to test the primary and secondary hypotheses by assessing the frequency of the abnormal breathing (primary outcome variable) using a portable sleep monitor in adult patients undergoing sedation for dental procedures.

Materials and Methods

Participants

This prospective, nonblinded, and randomized control trial from August 2015 to March 2016 was performed at Showa University Koto Toyosu Hospital, Tokyo, Japan, and approved by its institutional ethics board (14T5026: Showa University Koto Toyosu Hospital Ethics Committee, Tokyo, Japan) and registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN000018600: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=history&action=list&type=summary&recptno=R000021525&language=E. Accessed August 8, 2015). Contact information for the full trial information is available at the University Hospital Medical Information Network website. The inclusion criteria were: both sexes, 20 yr or older, American Society of Anesthesiologists physical status I or II, and a scheduled dental operation under intravenous sedation. The exclusion criteria were: altered mental status and an allergy history for the drugs used in this study. Based on the inclusion and exclusion criteria of this study and the operation schedule for the oral and maxillofacial surgeries, one of two oral surgeons asked the eligible patients their interest in participating in this clinical study at his outpatient clinic and noted their interest in the study on the medical records. One of the authors, who was in charge of sedation, confirmed their eligibility for this study and enrolled them in the study after obtaining a written informed consent from each participant. In addition to the potential development of hypoxemia and other cardiopulmonary complications as risks for sedation procedures not relating to this study, possible discomfort of the nasopharyngeal tube and minor nasal bleeding were explained as risks of this clinical study. Before initiation of patient recruitment, the primary investigator (Y.K.) produced a random number table by using Mersenne twister (IBM SPSS Statistics, version 22, IBM Corp., USA).[18] The random number table was kept in his desk drawer to conceal it from anesthesia care providers. To reduce a potential bias, the predetermined random allocation order was strictly applied to all consecutive consenting patients during the study period. Compliance of the order was confirmed by another investigator (S.I.) at the end of the data collection. The patients were randomly allocated either to the control group in which sedation was performed as normal or to the nasopharyngeal tube group in which a small-diameter nasopharyngeal tube (a soft lubricated silicone tube with an internal diameter of 4 mm: nastent classic; Seven Dreamers Laboratories Inc., Japan) was inserted during sedation. The randomization was designed to assign patients either condition in a 1:1 ratio without blocking or stratification. The anesthesiologist revealed allocation of the participant immediately before sedation.

Preparation of the Subjects and Measurements

Upon arrival at the outpatient clinic of the oral and maxillofacial surgery, an in-room anesthesia care provider assessed the patient's general condition, fluid restriction, and fasting as instructed, as well as clinical symptoms suggesting obstructive sleep apnea, including a STOP-BANG questionnaire.[19] Before the induction of sedation, electrodes for a type 3 portable sleep apnea monitor (Smart Watch, 300EX, Pacific Medico, Japan) and a portable electroencephalogram

monitor (Sleep Profiler, Advanced Brain Monitoring Inc., USA), as well as a routine vital-sign monitor including electrocardiogram, noninvasive blood pressure, and pulse oximetry, were attached to a patient sitting on a reclining dental chair (fig. 1). The sleep apnea monitor measured nasal pressure using a nasal cannula for assessing nasal airflow, chest wall movements for assessing respiratory efforts, and arterial oxygen saturation (Spo_2) using pulse oximetry. In addition to assessment of the Ramsey sedation score, consciousness was assessed by the portable electroencephalogram monitor measuring three channels of frontal electroencephalograms and the submental electromyogram activities. A Ramsey score between 2 and 4 was considered to be an appropriate sedation level in this study.

Supplemental oxygen was administered at a flow rate of 3 l/min through another nasal cannula for both groups. Both nasal pressure cannula and nasal oxygen cannula were inserted together into the nares, and it was confirmed that there was no increase of dyspnea during nasal breathing. The dental anesthesiologist provided the conscious sedation by a bolus intravenous injection of midazolam (1 to 3 mg) and propofol (5 to 10 mg), followed by continuous infusions of propofol (1 to 3 $mg \cdot kg^{-1} \cdot h^{-1}$).[20] Sedation was performed by one of four dental anesthesiologists, with experience from more than 100 cases involving dental sedation, based solely on the routine monitoring. For patients assigned to the nasopharyngeal tube group, a small-diameter nasal airway tube was carefully inserted through a naris during sedation so that the distal end reached about 5 mm below the uvula (fig. 1). The entire nasopharyngeal tube was in the nose, and the entrance of the nasopharyngeal tube was located 3 to 5 mm below the nose entrance, creating a space between the nasal pressure cannula and the nasal tube while a curved wire was hooked on the columella preventing movements of the nasopharyngeal tube. When the target sedation level (Ramsey score between 2 and 4) was achieved, local anesthesia containing 2% lidocaine was administered by the surgeon. The measurements were terminated, and the nasopharyngeal tube was removed after completion of the surgeries and cessation of propofol infusion. The patient was sent to the recovery room and remained there until gaining a full level of consciousness and an acceptable physical performance assessment by the dental anesthesiologist. After recovery of full consciousness in the recovery room, a questionnaire was provided. The patient was asked whether they were (1) satisfied, (2) indifferent, or (3) dissatisfied with the quality of sedation.

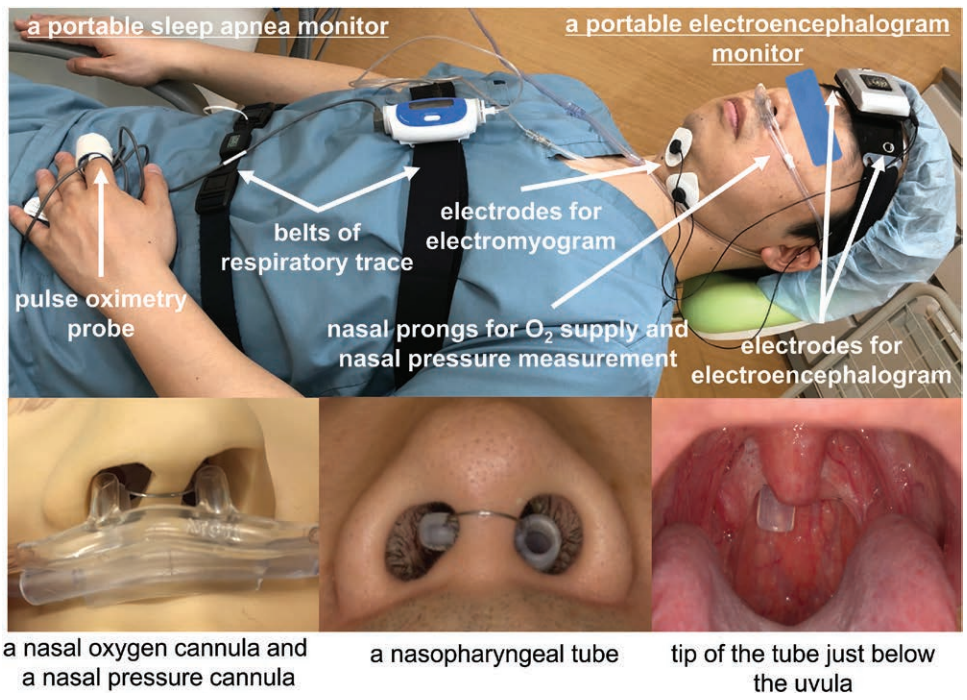

Fig. 1. Experimental set up. The measurements of respiration and oxygenation were carried out with a portable sleep apnea monitor and sedation level with a portable electroencephalogram monitor (*upper*). A nasal oxygen cannula and a nasal cannula for measurement of nasal pressure were placed through the naris (*left lower*). Patients in the nasopharyngeal tube group had a soft 4-mm internal diameter nasopharyngeal tube inserted through a naris, and the distal end nasopharyngeal tube was kept about 5 mm passing the uvula. Note that the proximal end of nasopharyngeal tube did not interfere the nasal cannulas for oxygen supply (*middle lower*) nor the nasal cannulas for measurement of nasal pressure (*right lower*).

Definitions of the Abnormal Breathing Index (Primary Outcome Variable)

For testing the hypotheses, abnormal breathing was predetermined by the portable sleep apnea monitor based on five expected features of abnormal breathing: (1) obstructive or central, (2) apnea or hypopnea, (3) with or without desaturation, (4) with or without irregular breathing, and (5) bradypnea or tachypnea. Upper airway obstruction was determined by the presence of respiratory efforts for an apnea, and the presence of inspiratory flow limitation was evidenced by a flattened nasal pressure signal for a hypopnea.[21] The definitions of apnea and hypopnea used in this study differ from those recommended for scoring abnormal breathing during sleep because of oxygen administration and possible influences of water in the oral cavity on breathing.[22] Apnea was defined by complete cessation of the nasal pressure changes for more than 10 s. Hypopnea was defined by more than a 50% reduction of the nasal pressure amplitude for more than 10 s. Desaturation was defined by more than a 2% reduction of Spo_2 for more than 10 s. Irregular breathing was determined when the nasal pressure signal frequency (respiratory rate) and amplitude fluctuated more than twofold after the apnea or hypopnea. The irregular breathing was considered to be elicited by laryngeal stimulation with the water inside the oral cavity and subsequent cough reflexes. Bradypnea and tachypnea were defined by a respiratory rate of less than 10 and greater than 30 min^{-1}, respectively. The abnormal breathing index (primary outcome variable), calculated as the number of abnormal breathing instances per hour of the operation period, was used for the statistical analyses of the study hypotheses. All data analyses were blindly performed by the primary investigator without the group information.

Sample Size

There is no previous study comparing the primary outcome (abnormal breathing index) between groups. In our preliminary study of 10 sedation patients, total abnormal breathing index, desaturated abnormal breathing index, and nondesaturated abnormal breathing index were 37.1 ± 29.5, 12.0 ± 12.7, and 25.1 ± 17.3 h^{-1} (means ± SD). For testing the primary hypothesis, we expected a 13 h^{-1} difference between desaturated and nondesaturated abnormal breathing indexes, and for testing the secondary hypothesis, we expected a 25 h^{-1} difference of total abnormal breathing index between the control and nasopharyngeal tube groups.[17] Assuming $\alpha = 0.05$ (two-tailed) and $\beta = 0.8$, the appropriate sample sizes for testing the primary and secondary hypotheses were calculated as 16 control subjects and 23 subjects for each group, respectively. We then set the total sample size as 46 subjects (JMP Pro 12.0.1; SAS Institute Inc., USA).

Statistical Analyses

For baseline variables, summary statistics were constructed using the number of patients for categorical data, as well as means and SDs for continuous variables. Baseline variables were compared using the Fisher's exact test or chi-square test for categorical outcomes and Student's *t* test for continuous variables. The Mann–Whitney rank sum test was used for comparisons of the respiratory variables between the groups. The Wilcoxon signed rank test was used to assess changes of the respiratory variables within the group. The Wilcoxon signed rank test was used to evaluate the primary hypothesis by comparing both the nondesaturated abnormal breathing index and desaturated abnormal breathing index in the control group. The Mann–Whitney rank sum test was used to assess the secondary hypothesis by comparing the abnormal breathing index between control and nasopharyngeal groups. All values are expressed as either means ± SD or median [first quartile, third quartile]. All statistical analyses were performed using SAS software version 9.4 (SAS Institute) and SigmaPlot 12.0 (Systat Software Inc., USA). All *P* values were two-sided, and a value of $P < 0.05$ was considered statistically significant. As for testing the primary hypothesis, multiple comparison type I error adjustment was based on a Bonferroni-adjusted criterion with four adjustments ($P < 0.05/4=0.0125$) during the peer reviewing process.

Results

Characteristics of the Participants

A CONSORT (CONsolidated Standards of Reporting Trials) flow diagram is presented in figure 2. A total of 62 patients scheduled for dental operation under intravenous sedation were initially invited, and 46 patients gave consent to participate in this study from August 2015 to March 2016. There were 24 patients randomly assigned to the control group, whereas the remaining 22 patients were assigned to the nasopharyngeal tube group. Because of failures in the measurements, one patient from the control and one from the nasopharyngeal tube group were excluded. Another patient in the nasopharyngeal tube group was excluded because of a persistent gag reflex caused by the nasopharyngeal tube. In total, 43 patients completed the study protocol (control group: n = 23, nasopharyngeal tube group: n = 20). Anthropometric variables and predictors of obstructive sleep apnea are shown in table 1. A majority of the patients were relatively young and nonobese and had low likelihood of obstructive sleep apnea. There were no significant differences in the demographic variables between the groups.

Clinical Course of the Sedation and Dental Procedures

Table 2 presents results of the sedation and operation. All scheduled dental procedures (dental extraction: n = 40, apicoectomy: n = 2, dental implant surgery: n =1) were successfully accomplished without apparent adverse events. The in-room anesthesia care providers did not recognize any instances of abnormal breathing during the surgeries. In fact,

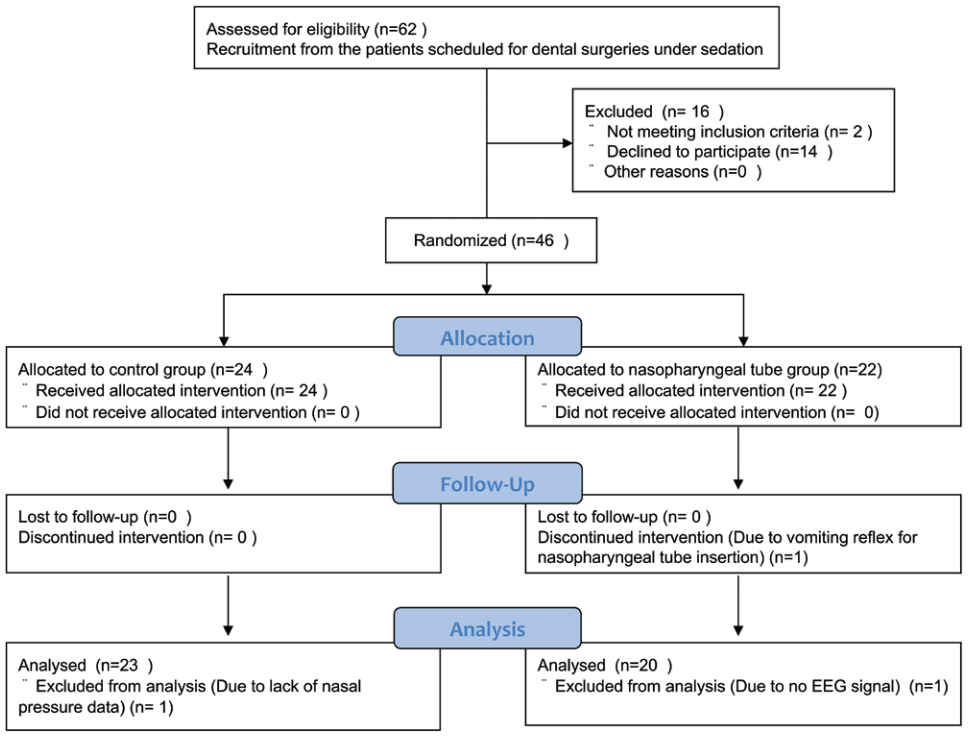

Fig. 2. A CONSORT (CONsolidated Standards of Reporting Trials) flow diagram of this study. EEG, electroencephalogram.

in this study, no patients had a level of Spo_2 less than 90%. However, four patients in the control group and five patients in the nasopharyngeal tube group accidentally underwent sedation level deeper than the target level. Insertion of the nasopharyngeal tube was difficult in one patient in the nasopharyngeal tube group. In the questionnaire, this patient rated

Table 1. Anthropometric Variables and Predictors of Obstructive Sleep Apnea

	Control Group (n = 23)	Nasopharyngeal Tube Group (n = 20)	*P* Value
Anthropometric variables			
Age, yr	34.6 ± 10.1	37.0 ± 13.7	0.523
Sex, male/female	6/17	7/13	0.845
Height, m	1.62 ± 0.09	1.63 ± 0.09	0.801
Weight, kg	53.3 ± 12.1	56.3 ± 9.9	0.377
Body mass index, kg/m^2	20.0 ± 2.9	21.0 ± 2.5	0.204
ASA physical status, I/II	16/7	16/4	0.501
Interincisors distance, cm	4.6 ± 0.7	4.4 ± 0.7	0.254
Thyromental distance, cm	7.4 ± 1.4	7.4 ± 1.4	0.978
Upper lip bite test, 1/2/3	23/0/0	17/3/0	0.092
Mallampati class, 1,2/3,4	15/8	13/7	0.988
Predictors of obstructive sleep apnea			
Snoring, yes/no	7/16	8/12	0.54
STOP-BANG score, 0–2/3–8	(21/2)	(16/4)	0.393
Epworth sleepiness score, 0–10/11–24	(23/0)	(18/2)	0.21
Indications for the sedation			
Anxiety, yes/no	9/14	4/16	0.203
Gag reflex, yes/no	1/22	4/16	0.167

The values are described in terms of means ± SD (continuous variables) and the number of the patients (categorical values). Group difference was assessed by Mann–Whitney rank sum test for continuous variables and either chi-square test or Fisher exact test for the categorical variables.

ASA, American Society of Anesthesiologists.

Table 2. Results of the Sedation and Operation

	Control (n = 23)	Nasopharyngeal Tube Group (n = 20)	*P* Value
Operation time, min	30.7 ± 22.2	27.1 ± 15.7	0.548
Propofol, mg/kg	1.98 ± 0.81	2.58 ± 1.47	0.111
Midazolam, mg/kg	0.05 ± 0.01	0.05 ± 0.02	0.175
2% lidocaine, ml/kg	0.09 ± 0.04	0.12 ± 0.07	0.147
Ramsey score, 2/3/4/5	(0/3/16/4)	(1/3/11/5)	0.213
Baseline Spo_2, %	99.3±0.6	99.4±0.7	0.671
Lowest Spo_2, %	94.7±3.4	95.4±3.0	0.51
Spo_2 reduction, %	4.5±3.3	4.0±2.9	0.551
The number of patients with Spo_2 less than 90%	0	0	> 0.999

The values are means ± SD. Group difference was assessed by Mann–Whitney rank sum test for continuous variables and chi-square test for the categorical variables.
Spo_2, arterial oxygen saturation measured with pulse oximetry.

the quality of their sedation "indifferent," but the remaining 42 patients rated "satisfied" with the quality of sedation.

Typical Abnormal Breathing during Sedation for Dental Procedures

Instances of typical abnormal breathing are shown in figures 3 and 4. Obstructive apnea was evidenced by the presence of breathing efforts during apneas and flat line of nasal pressure trace (fig. 3). Hypopnea was evidenced by the presence but limited of nasal pressure alteration. Notably, Spo_2 is maintained above 98% despite the long apneas and hypopneas. It is evident that a series of coughs at the restoration of breathing immediately after an apnea induced the irregular breathing and tachycardia. Repetitive periodic obstructive hypopneas similar to those seen in patients with sleep-disordered breathing during sleep were another common pattern of abnormal breathing during the sedation (fig. 4).

Results of the Primary Hypothesis: Desaturated *versus* Nondesaturated Abnormal Breathing Index in the Control Group

Among the five predetermined features of the abnormal breathing patterns, no bradypnea and tachypnea was observed in this study, and therefore four features of the abnormal breathing patterns were used to classify and analyze them (table 3). Figures 5 and 6 present frequencies and durations for each of the four features of the abnormal breathing in the control group. A median abnormal breathing index, including all patterns of abnormal breathing, was 48.0 [33.8, 64.4] (h^{-1}) in the control group, and 20 of 23 patients (87%) had an abnormal breathing index of more than $30\,h^{-1}$, which corresponded to the frequency of severe obstructive sleep apnea. Duration of abnormal breathing varied even within a subject ranging from 10 s to more than 2 min (median duration: 24.3 [17.6, 34.3] s). Although the

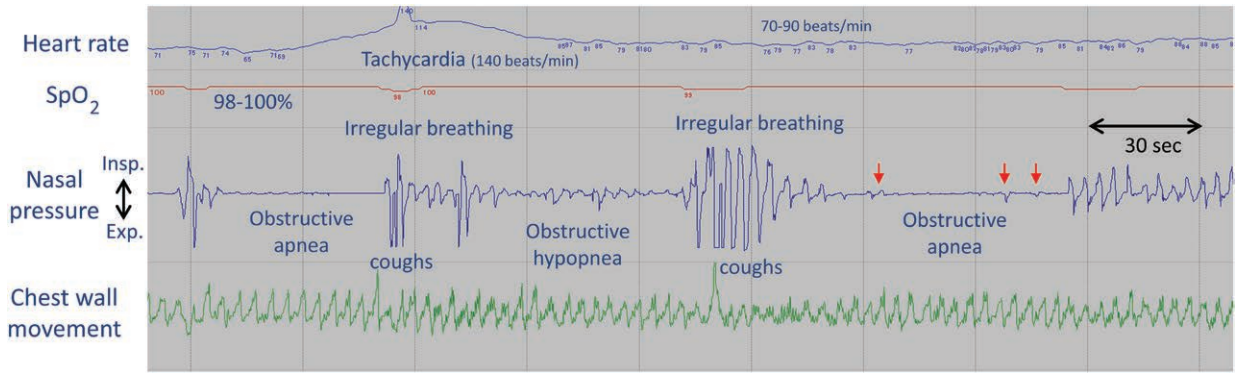

Fig. 3. An example of typical adverse respiratory events observed during dental sedation in a 57-yr-old patient with body mass index of 24.3 kg/m^2. Note obstructive apneas evidenced by the presence of breathing efforts and hypopneas evidenced by the presence of inspiratory (Insp.) airflow limitations. A series of coughs at the restoration of breathing immediately after an apnea appear to induce the irregular breathing and tachycardia. Oxygen saturation measured by pulse oximetry (Spo_2) is maintained above 98% despite the long apneas and hypopneas. Although speculative, this is possibly due to apneic oxygenation in association with an occasional small amount of ventilation evidenced by the small respiratory fluctuations of the nasal pressure tracing (*red arrows*) during the apnea. Exp., expiratory.

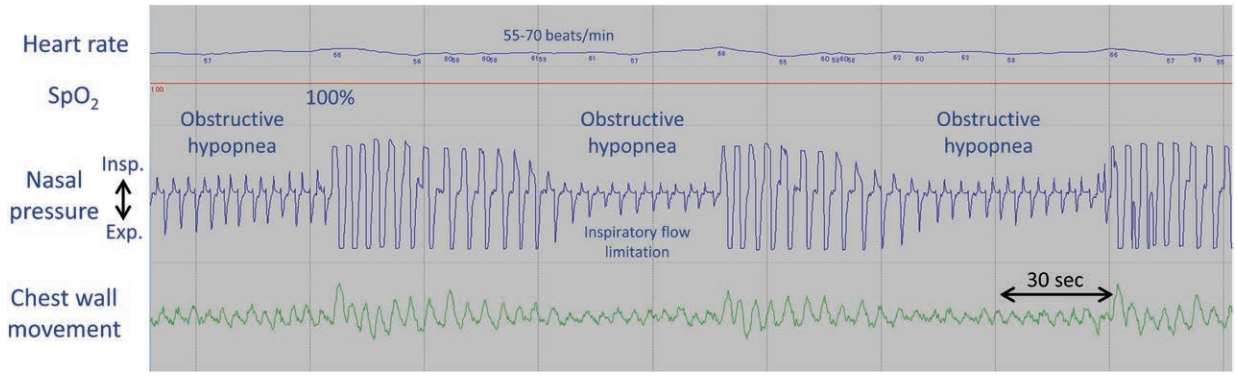

Fig. 4. In the same patient presented in figure 3, repetitive periodic obstructive hypopneas similar to those seen in patients with sleep disordered breathing during sleep were also observed. Exp., expiratory; Insp., inspiratory; Spo_2, oxygen saturation measured by pulse oximetry.

majority of apneas and hypopneas lasted less than 1 min (abnormal breathing index: 43.2 [31.3, 60.9] h^{-1}, median duration: 19.9 [16.4, 22.1] s), apneas and hypopneas lasting more than 1 min were less frequently observed (abnormal breathing index: 2.4 [0, 6.0] h^{-1}, median duration: 80 [70.3, 106.9] s).

Nondesaturated abnormal breathing index was more frequent (35.2 [20.6, 48.0] *vs.* 7.2 [4.1, 18.5] h^{-1}, difference: 25.1 [95% CI, 13.8 to 36.4], $P < 0.001$), supporting the difficulty of detecting the abnormal breathing episodes by pulse oximetry alone. Nondesaturated abnormal breathing tended shorter in duration (18.4 [16.3, 24.1] *vs.* 30.0 [23.0, 45.0] s, difference: 10.4 [95%CI, 2.7 to 18.1], $P = 0.014$) than the desaturated abnormal breathing. Obstructive abnormal breathing episodes were more frequent ($P < 0.001$) and longer in duration ($P = 0.005$) than central abnormal breathing episodes. The frequency ($P = 0.649$) and duration ($P = 0.065$) of apneic abnormal breathing episodes did not differ from those of hypopneic abnormal breathing episodes. Approximately half of the abnormal breathing episodes were followed by irregular breathing. Solo irregular abnormal breathing without preceding apnea

Table 3. A Summary of the Frequency and Duration for Each of 16 Categories of the Abnormal Breathing during Dental Sedation in the Control Group

	Four Features of Abnormal Breathing				
Oxygenation	**Type**	**Severity**	**Irregularity**	**Frequency, h^{-1}**	**Duration, s**
Desaturation	Obstructive	Apnea	Yes	2.0 [0, 6.9]	26.7 [16.1, 55.5]
			No	0 [0, 0.6]	25.4 [10.0, 31.3]
		Hypopnea	Yes	1.9 [0, 6.0]	25.0 [16.7, 45.0]
			No	0 [0, 1.9]	28.3 [11.3, 42.3]
	Central	Apnea	Yes	0 [0, 0]	12.5 [10.0, 15.0]
			No	0 [0, 0]	17.5 [10.0, 25.0]
		Hypopnea	Yes	0 [0, 0]	NA
			No	0 [0, 0]	NA
	Desaturated abnormal breathing			7.2 [4.1, 18.5]	30.0 [23.0, 45.0]
No desaturation	Obstructive	Apnea	Yes	4.8 [0, 12.0]	15.6 [12.3, 20.9]
			No	2.6 [0, 8.6]	14.7 [10.0, 24.2]
		Hypopnea	Yes	5.0 [1.7, 13.8]	20.0 [13.3, 26.3]
			No	9.7 [4.4, 15.8]	19.6 [15.0, 28.0]
	Central	Apnea	Yes	0 [0, 3.8]	15.0 [13.0, 20.3]
			No	0 [0, 1.8]	15.0 [10.0, 17.5]
		Hypopnea	Yes	0 [0, 0]	NA
			No	0 [0, 0]	NA
	Nondesaturated abnormal breathing			35.2 [20.6, 48.0]	18.4 [16.3, 24.1]
	All abnormal breathing			48.0 [33.8, 64.4]	24.3 [17.6, 34.3]

Wilcoxon signed rank test was used to assess changes of the respiratory variables within the group. All values are expressed as medians (the first quartile, the third quartile).

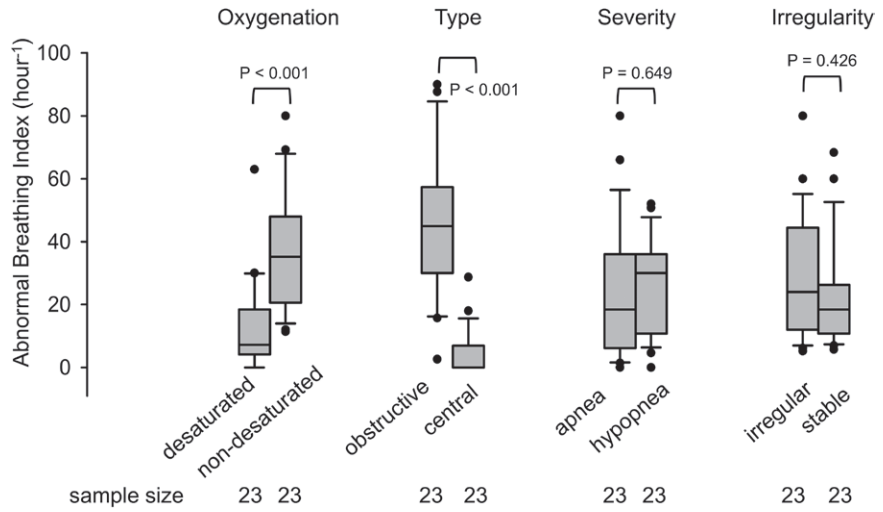

Fig. 5. Box plots presenting comparisons of abnormal breathing index for each of four features of the abnormal breathing in control group. Median values are indicated by a *horizontal bar* within each *box*; *bars* above and below each *box* represent 25 and 75 percentiles, ends of *vertical lines* denote 5 and 95 percentiles, and *black circles* are outliers. Comparisons within the feature were performed by Wilcoxon signed rank test. Note that a predominant abnormal breathing pattern was nonhypoxemic obstructive apneas or hypopneas and half of the instances of abnormal breathing were followed by irregular breathing. $P < 0.0125$ was considered statistically significant for adjusting the multiplicity of the comparison.

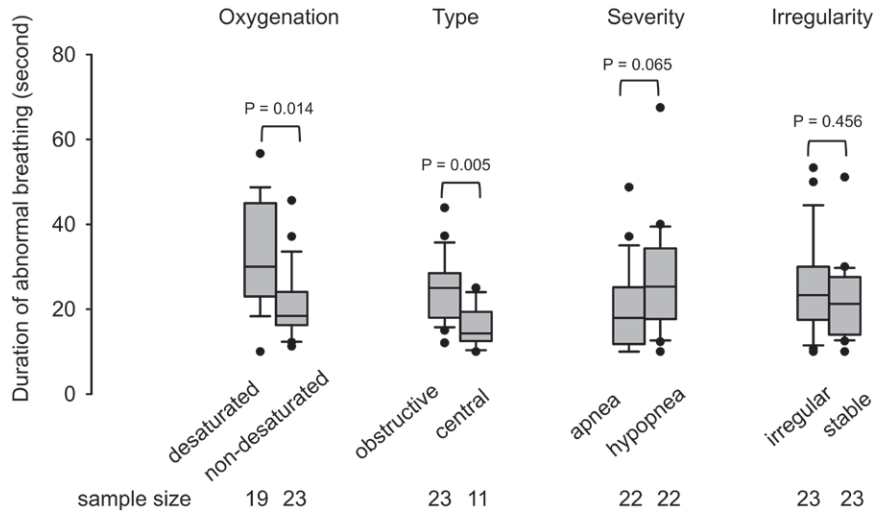

Fig. 6. Box plots presenting comparisons of abnormal breathing duration for each of four features of the abnormal breathing in control group. Median values are indicated by a *horizontal bar* within each *box*; *bars* above and below each *box* represent 25 and 75 percentiles, end of *vertical lines* denote 5 and 95 percentiles, and *black circles* are outliers. Comparisons within the feature were performed by Wilcoxon signed rank test. $P < 0.0125$ was considered statistically significant for adjusting the multiplicity of the comparison.

or hypopnea was much less frequent (2.3 [0, 4.0] *vs.* 24.0 [12.0, 44.4] h^{-1}: $P < 0.001$). Interestingly, the occurrence of irregular breathing was significantly more common in patients with obstructive apneas with desaturation (2.0 [0, 6.9] *vs.* 0 [0, 0.6], $P = 0.003$).

Results of the Secondary Hypothesis: Effects of Nasopharyngeal Tube on Abnormal Breathing during Dental Sedation

Figure 7 presents the comparison between the control and the nasopharyngeal tube groups with respect to abnormal breathing

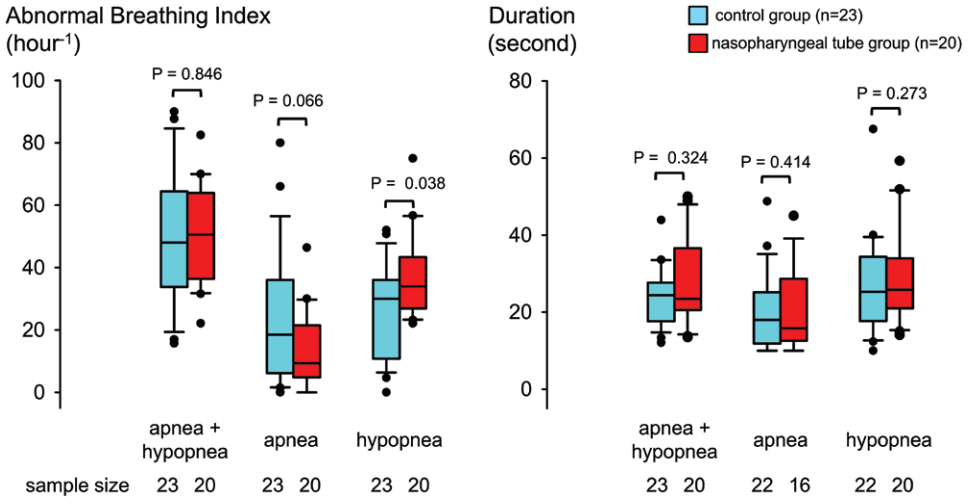

Fig. 7. Box plots presenting effects of nasopharyngeal tube insertion on abdominal breathing index and duration of abnormal breathing during dental sedation. Median values are indicated by a *horizontal bar* within each *box*; *bars* above and below each *box* represent 25 and 75 percentiles, ends of *vertical lines* denote 5 and 95 percentiles, and *black circles* are outliers. Comparisons within the feature were performed by Mann–Whitney rank sum test. Note the significant increase of hypopneic abnormal breathing index in the nasopharyngeal tube group despite no difference of total abdominal breathing index. There was a significant interaction between changes of apneic and hypopneic abnormal breathing indexes for presence or absence of the nasopharyngeal tube ($P = 0.001$).

during dental sedation. The frequencies (48.0 [33.8, 64.4] *vs.* 50.5 [36.4, 63.9] h^{-1}, difference: −2.0 [95% CI, −15.2 to 11.2], $P = 0.846$) and duration ($P = 0.324$) of all abnormal breathing episodes, including both apneas and hypopneas, did not differ between the two groups. However, the hypopneic abnormal breathing index in the nasopharyngeal tube group was significantly higher than that in the control group (33.9 [26.9, 43.4] *vs.* 30.0 [10.8, 36.0] h^{-1}, difference: 13.1 [95% CI, 5.3 to 21.8], $P = 0.038$). The apneic abnormal breathing index did not statistically differ between the groups, whereas the apneic abnormal breathing index tended to be lower in the nasopharyngeal tube group. There was a statistically significant interaction between changes of the apneic and hypopneic frequencies in the presence or absence of the nasopharyngeal tube ($P = 0.001$).

Discussion

We successfully characterized features of abnormal breathing during sedation for dental procedures and found that (1) there were as many as 50 h^{-1} abnormal breathing episodes occurring in patients under sedation for dental procedures; (2) the majority of the abnormal breathing episodes were nonhypoxemic obstructive apneas or hypopneas; and (3) insertion of a nasopharyngeal tube with small diameter has limited effect on abnormal breathing.

The Nature and Possible Mechanisms of Breathing Abnormality during Sedation for Dental Procedures

It was of great surprise to see frequent obstructive apneas and hypopneas in nonobese middle-aged adults without clinical symptoms, suggesting obstructive sleep apnea. This indicates a possible inherent risk for the induction of abnormal breathing patterns from sedation for dental procedures. The sedatives used in this study are reported to selectively decrease the activity of upper airway dilating muscles, and therefore, sedation *per se* should make the patients susceptible to pharyngeal obstruction.[23,24] However, previous studies using drug-induced sleep endoscopy have never reported such a high susceptibility to pharyngeal obstruction in the patient population as those obtained in this study.[25] Furthermore, deeper sedation only occurred in 20% of the participants, and the targeted conscious sedation level (Ramsey score between 2 and 4) was successfully maintained in most of the participants. Therefore, an overdose of the sedatives would not explain the results of this study.

We suspect an increase of pharyngeal collapsibility in the dental procedures as a possible mechanism for the abnormal breathing observed. First, wider mouth opening is required to increase the space for the intraoral procedures. Mouth opening increases the collapsibility of the retropalatal airway, which is part of the nasal breathing route, and in fact limits maximum inspiratory flow through the nose.[26,27] Neck flexion and a head-down position, often preferred by the surgeon, should further increase the pharyngeal collapsibility.[26,28] Second, because of depression of the swallowing reflex during sedation,[29] water injected for cooling the rotating drill and the tooth is often accumulated in the oral cavity and may block the oral breathing route. Therefore, the patient is forced to breathe exclusively through the nasal passage already narrowed by mouth opening, further increasing the chance of apnea and hypopnea caused by the

pharyngeal obstruction. At the end of obstructive apnea and hypopnea during sleep, both the oral and nasal breathing routes are reported to open to restore breathing.[30] The oronasal breathing, if it occurs during sedation, may increase the chance of laryngeal stimulation and pulmonary aspiration. In fact, Kohjitani *et al.*[13] reported that accumulation of water in the oropharynx increased vulnerability to the cough reflex in dental treatments under intravenous sedation. Accordingly, the unique abnormal breathing patterns characterized by apnea and hypopnea followed by irregular breathing would be a result of interaction between the airway maintenance and airway protective mechanisms.

Usefulness of a Nasopharyngeal Tube for Improving Breathing during Dental Sedation

We found that the nasopharyngeal tube used in this study decreased the severity of abnormal breathing but did not change the total abnormal breathing frequency, indicating possible airway obstruction at the pharyngeal airway, not the larynx during dental sedation and limited clinical usefulness of the nasopharyngeal tube to maintain the airway patency during the sedation for the dental procedures. A recent meta-analysis evidenced effectiveness of a nasopharyngeal tube for obstructive sleep apnea.[16] Care must be taken to interpret the result because the inner diameter of the nasopharyngeal tube used in this study was 4 mm, which is much narrower than the one usually used for the unconscious subjects. We consider that the small diameter is not responsible for the limited effectiveness of the nasal airway because Nahmias and Karetzky[17] demonstrated more than 50% reduction of sleep disordered breathing by a nasopharyngeal tube with a 3 to 4 mm inner diameter, and Kochi and Nishino[31] reported stable breathing without an increase of carbon dioxide, even through a 4-mm diameter tube in anesthetized, spontaneously breathing adult subjects. These studies demonstrated the effectiveness of nasal tube with a small diameter. Therefore, we believe that failure of the nasal tube to improve breathing efficiency observed in this study was unlikely to be due to the small diameter of the nasal tube. We are uncertain whether the position of the distal end of the tube was appropriate and whether patency of the tube lumen was maintained throughout the sedation.

Clinical Implications of the Study

Because we successfully clarified the nature of abnormal breathing during sedation for the dental procedures, the results of this study have various clinical implications. First, it should be noted that the nasal pressure monitoring was able to detect abnormal breathing during dental sedation in patients with the mouth widely open. Accurate assessment of breathing in a patient covered by surgical drapes and at a remote location from the anesthesiologist is difficult and delayed if pulse oximetry is only used, as evidenced by the results of this study. In this context, capnography is usually recommended as an effective respiratory monitor during sedation and the postoperative period,[32] and the results of this study raised the possible clinical usefulness of the nasal pressure monitoring in agreement with the strong recommendation by the American Academy of Sleep Medicine.[22] Future studies should address clinical usefulness of the nasal pressure measurements in perioperative medicine.

Second, we doubt that clarification of the mechanisms of abnormal breathing and development of monitoring device for abnormal breathing alone would lead to the reduction of mortality and morbidity incidences during dental sedation because of the inherent risks in the procedures discussed above. Whereas the upper airway is a vital organ for breathing and airway protection, the space has to be shared with the surgeon during dental sedation. No fundamental solution would be achieved without separating the space and functions in the oral and pharyngeal cavity.

Third, the subjects studied in this study are healthy and relatively young. Although the incidence rate of mortality and morbidity from dental sedation is low, Jastak and Peskin[7] found more patients with comorbidities such as obesity and cardiovascular diseases in the victims during the dental sedation. The apneas and hypopneas identified in this study would result in more severe hypoxemia, leading to cardiovascular complications in patients with comorbidities. Silent pulmonary aspiration would be symptomatic in elderly patients with a depressed laryngeal reflex and immunosuppression.

Limitations of this Study

Clearly, this study has several major limitations. First, the result of allocation was not blinded to both anesthesiologist and patient. Because of the nature of the intervention, we considered it difficult to perform a nasopharyngeal tube without being recognized by the patient. However, we believe the primary outcome variable predefined in this study, *i.e.*, abnormal breathing index, is a safe parameter with minimum influence of the open bias. Furthermore, blind analyses of the data should further minimize the bias.

Second, we did not assess any baseline breathing abnormality during sleep before the study. The predictors for obstructive sleep apnea used in this study may not accurately assess the severity of nocturnal breathing abnormalities, whereas the severity of abnormal breathing may be associated with that during sleep.

Third, the number of abnormal breathing episodes detected by the nasal pressure signal alone may have been overestimated because of the presence of oral breathing. The effects of breathing routes on the nature of breathing were previously documented in sleeping humans but not in patients during dental sedation. Although mouth opening was common particularly in patients with obstructive sleep apnea (70% of total sleep time),[33] exclusively oral breathing was extremely rare in sleep apnea patients (2% of total sleep time) and exclusively nasal and oronasal breathing was very common.[34] Notably, both mouth opening and the exclusively oral and oronasal breathing patterns were independent risk factors for increasing frequency of apneas and

hypopneas.[35–37] High incidence of apneas and hypopneas despite mouth opening agrees with the results of this study and rather supports validity of monitoring nasal breathing with either nasal pressure or capnography in patients under dental sedation. Teichtahl *et al.*[38] evidenced that nasal pressure signal alone correctly scored 97% of matched respiratory events scored by oronasal thermistor flow signal in sleep apnea patients. Clearly, routes of breathing during dental sedation and appropriate respiratory monitoring are to be studied in the near future.

Despite electroencephalogram recorded to assess the sedation level, the quality of the data was suboptimal, and we were unable to analyze the data. The poor quality of electroencephalogram seemed to be from interference of the dental drilling and surgeon's hand movements. Therefore, we are unable to relate the occurrence of hypopnea and apnea events to the deep sedation. Last, the study was only performed in a single large private university hospital, and a uniform sedation technique was used by the dental anesthesiologists. Accordingly, multicenter studies with various sedation techniques performed by various personnel, including nonanesthesiologists, should be conducted in the future to generalize the findings of this study.

In conclusion, patients undergoing dental procedures with sedation frequently developed nonhypoxemic obstructive apneas/hypopneas that are not effectively treated with a small-diameter nasopharyngeal airway. Further studies are needed to explore the mechanism of abnormal breathing during sedation and to develop an effective therapy for this unique clinical scenario.

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Competing Interests

The 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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References

1. Eichhorn V, Henzler D, Murphy MF: Standardizing care and monitoring for anesthesia or procedural sedation delivered outside the operating room. Curr Opin Anaesthesiol 2010; 23:494–9
2. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists: Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002; 96:1004–17
3. Southerland JH, Brown LR: Conscious intravenous sedation in dentistry: A review of current therapy. Dent Clin North Am 2016; 60:309–46
4. Deegan AE: Anesthesia morbidity and mortality, 1988–1999: Claims statistics from AAOMS National Insurance Company. Anesth Prog 2001; 48:89–92
5. Goudra B, Nuzat A, Singh PM, Gouda GB, Carlin A, Manjunath AK: Cardiac arrests in patients undergoing gastrointestinal endoscopy: A retrospective analysis of 73,029 procedures. Saudi J Gastroenterol 2015; 21:400–11
6. Flick WG, Katsnelson A, Alstrom H: Illinois dental anesthesia and sedation survey for 2006. Anesth Prog 2007; 54:52–8
7. Jastak JT, Peskin RM: Major morbidity or mortality from office anesthetic procedures: A closed-claim analysis of 13 cases. Anesth Prog 1991; 38:39–44
8. Yorio PL, Moore SM: Examining factors that influence the existence of Heinrich's safety triangle using site-specific H&S data from more than 25,000 establishments. Risk Anal 2018; 38:839–52
9. O'Halloran M. The use of anaesthetic agents to provide anxiolysis and sedation in dentistry and oral surgery. Australas Med J 2013; 6:713–8
10. American Dental Association. Guideline for the Use of Sedation and General Anesthesia by Dentists. 2016. Available at: http://www.ada.org/~/media/ADA/Member%20Center/FIles/anesthesia_guidelines.pdf?la=en. Accessed March 5, 2019
11. Apfelbaum JL, Connis RT, Agarkar M, Arnold DE, Cote CJ, Dutton R, Madias C, Nickinovich DG, Schwartz PJ, Tom JW, Towbin R, Tung A: Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. Anesthesiology 2018; 128:437–79

12. Nishino T, Tagaito Y, Isono S: Cough and other reflexes on irritation of airway mucosa in man. Pulm Pharmacol 1996; 9:285–92
13. Kohjitani A, Egusa M, Shimada M, Miyawaki T: Accumulated oropharyngeal water increases coughing during dental treatment with intravenous sedation. J Oral Rehabil 2008; 35:203–8
14. Fu ES, Downs JB, Schweiger JW, Miguel RV, Smith RA: Supplemental oxygen impairs detection of hypoventilation by pulse oximetry. Chest 2004; 126:1552–8
15. Parker W, Estrich CG, Abt E, Carrasco-Labra A, Waugh JB, Conway A, Lipman RD, Araujo MWB: Benefits and harms of capnography during procedures involving moderate sedation: A rapid review and meta-analysis. J Am Dent Assoc 2018; 149:38–50.e2
16. Kumar AR, Guilleminault C, Certal V, Li D, Capasso R, Camacho M: Nasopharyngeal airway stenting devices for obstructive sleep apnoea: A systematic review and meta-analysis. J Laryngol Otol 2015; 129:2–10
17. Nahmias JS, Karetzky MS: Treatment of the obstructive sleep apnea syndrome using a nasopharyngeal tube. Chest 1988; 94:1142–7
18. Matsumoto M, Nishimura T: Mersenne Twister: A 623-dimensionally equidistributed uniform pseudorandom number generator. ACM Trans Modeling Computer Simulation 1998; 8:3–30
19. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM: STOP questionnaire: A tool to screen patients for obstructive sleep apnea. Anesthesiology 2008; 108:812–21
20. Masuda R, Nonaka M, Nishimura A, Gotoh K, Oka S, Iijima T: Optimal and safe standard doses of midazolam and propofol to achieve patient and doctor satisfaction with dental treatment: A prospective cohort study. PLoS One 2017; 12:e0171627
21. Hosselet JJ, Norman RG, Ayappa I, Rapoport DM: Detection of flow limitation with a nasal cannula/pressure transducer system. Am J Respir Crit Care Med 1998; 157:1461–7
22. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM; American Academy of Sleep Medicine: Rules for scoring respiratory events in sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012; 8:597–619
23. Nishino T, Shirahata M, Yonezawa T, Honda Y: Comparison of changes in the hypoglossal and the phrenic nerve activity in response to increasing depth of anesthesia in cats. Anesthesiology 1984; 60:19–24
24. Nozaki-Taguchi N, Isono S, Nishino T, Numai T, Taguchi N: Upper airway obstruction during midazolam sedation: Modification by nasal CPAP. Can J Anaesth 1995; 42:685–90
25. Karan SB, Rackovsky ED, Voter WA, Shah AN, Ward DS: Validation of a measurement to predict upper airway collapsibility during sedation for colonoscopy. J Clin Monit Comput 2012; 26:451–7
26. Isono S, Tanaka A, Tagaito Y, Ishikawa T, Nishino T: Influences of head positions and bite opening on collapsibility of the passive pharynx. J Appl Physiol (1985) 2004; 97:339–46
27. Ayuse T, Inazawa T, Kurata S, Okayasu I, Sakamoto E, Oi K, Schneider H, Schwartz AR: Mouth-opening increases upper-airway collapsibility without changing resistance during midazolam sedation. J Dent Res 2004; 83:718–22
28. Tagaito Y, Isono S, Tanaka A, Ishikawa T, Nishino T: Sitting posture decreases collapsibility of the passive pharynx in anesthetized paralyzed patients with obstructive sleep apnea. Anesthesiology 2010; 113:812–8
29. Nishino T, Takizawa K, Yokokawa N, Hiraga K: Depression of the swallowing reflex during sedation and/or relative analgesia produced by inhalation of 50% nitrous oxide in oxygen. Anesthesiology 1987; 67:995–8
30. Kuna ST, Smickley J: Response of genioglossus muscle activity to nasal airway occlusion in normal sleeping adults. J Appl Physiol (1985) 1988; 64:347–53
31. Kochi T, Nishino T: Ventilatory responses to inspiratory resistive loading before and after gastrectomy during isoflurane anesthesia. Anesth Analg 1995; 80:1199–205
32. Overdyk FJ, Carter R, Maddox RR, Callura J, Herrin AE, Henriquez C: Continuous oximetry/capnometry monitoring reveals frequent desaturation and bradypnea during patient-controlled analgesia. Anesth Analg 2007; 105:412–8
33. Miyamoto K, Ozbek MM, Lowe AA, Sjöholm TT, Love LL, Fleetham JA, Ryan CF: Mandibular posture during sleep in patients with obstructive sleep apnoea. Arch Oral Biol 1999; 44:657–64
34. Koutsourelakis I, Vagiakis E, Roussos C, Zakynthinos S: Obstructive sleep apnoea and oral breathing in patients free of nasal obstruction. Eur Respir J 2006; 28:1222–8
35. Gleeson K, Zwillich CW, Braier K, White DP: Breathing route during sleep. Am Rev Respir Dis 1986; 134:115–20
36. Hollowell DE, Suratt PM: Mandible position and activation of submental and masseter muscles during sleep. J Appl Physiol (1985) 1991; 71:2267–73
37. Fitzpatrick MF, McLean H, Urton AM, Tan A, O'Donnell D, Driver HS: Effect of nasal or oral breathing route on upper airway resistance during sleep. Eur Respir J 2003; 22:827–32
38. Teichtahl H, Cunnington D, Cherry G, Wang D: Scoring polysomnography respiratory events: The utility of nasal pressure and oro-nasal thermal sensor recordings. Sleep Med 2003; 4:419–25