Mask Ventilation during Induction of General Anesthesia

Influences of Obstructive Sleep Apnea

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ABSTRACT

Background: Depending on upper airway patency during anesthesia induction, tidal volume achieved by mask ventilation may vary. In 80 adult patients undergoing general anesthesia, the authors tested a hypothesis that tidal volume during mask ventilation is smaller in patients with sleep-disordered breathing priorly defined as apnea hypopnea index greater than 5 per hour.

Methods: One-hand mask ventilation with a constant ventilator setting (pressure-controlled ventilation) was started 20 s after injection of rocuronium and maintained for 1 min during anesthesia induction. Mask ventilation efficiency was assessed by the breath number needed to initially exceed 5 ml/kg ideal body weight of expiratory tidal volume (primary outcome) and tidal volumes (secondary outcomes) during initial 15 breaths (UMIN000012494).

Results: Tidal volume progressively increased by more than 70% in 1 min and did not differ between sleep-disordered breathing (n = 42) and non–sleep-disordered breathing (n = 38) patients. In *post hoc* subgroup analyses, the primary outcome breath number (mean [95% CI], 5.7 [4.1 to 7.3] *vs.* 1.7 [0.2 to 3.2] breath; $P = 0.001$) and mean tidal volume (6.5 [4.6 to 8.3] *vs.* 9.6 [7.7 to 11.4] ml/kg ideal body weight; $P = 0.032$) were significantly smaller in 20 sleep-disordered breathing patients with higher apnea hypopnea index (median [25th to 75th percentile]: 21.7 [17.6 to 31] per hour) than in 20 non–sleep disordered breathing subjects with lower apnea hypopnea index (1.0 [0.3 to 1.5] per hour). Obesity and occurrence of expiratory flow limitation during one-hand mask ventilation independently explained the reduction of efficiency of mask ventilation, while the use of two hands effectively normalized inefficient mask ventilation during one-hand mask ventilation.

Conclusions: One-hand mask ventilation is difficult in patients with obesity and severe sleep-disordered breathing particularly when expiratory flow limitation occurs during mask ventilation. **(ANESTHESIOLOGY 2017; 126:28-38)**

ANESTHESIOLOGISTS perform mask ventilation (MV) with proper airway maintenance maneuvers during induction of general anesthesia. Proper oxygenation is only secured by the MV when tracheal intubation is difficult or impossible. Despite the clinical significance, MV technique has changed little in contrast to significant improvement of tracheal intubation techniques and devices in the past decade. The incidence of difficult and impossible MV determined by the four-point grading scale is reported to be 1.4 to 5% and 0.15%, respectively,[1–3] and difficult MV combined with difficult tracheal intubation occurs 0.14% in adult patients undergoing general anesthesia.[4] While these recent large epidemiology studies identified various patient characteristics as independent risk factors for difficult MV, we lack knowledge on how these risk factors make MV difficult. Elucidation of the mechanisms of difficult MV might facilitate development of a new MV technique for safer airway management during anesthesia induction.

What We Already Know about This Topic

- Mask ventilation technique has changed little over the past decades, but the predictors of difficult mask ventilation requiring alterations of technique have not been well described

What This Article Tells Us That Is New

- In a study of 80 patients, tidal volume administered during one-hand mask ventilation at the time of anesthetic induction was reduced in patients with a diagnosis of sleep disordered breathing, but was restored with two-hand ventilation

None of the previous studies preoperatively assessed severity of sleep-disordered breathing (SDB) in all analyzed subjects among the risk factors, whereas prevalence of the SDB is as high as 69% of the general surgical population.[5] We previously reported that pharyngeal airways of patients with SDB under general anesthesia and paralysis are narrower and more collapsible than those of non-SDB subjects,[6] and mandibular

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advancement is less effective particularly in obese subjects.[7] Anesthesia depth, consciousness, and upper airwaydilating muscle activity, which are significant determinants of the upper airway patency, dynamically change during anesthesia induction.[8–10] Therefore, SDB patients would be more vulnerable to anesthesia induction, possibly leading to insufficient tidal volume (TV) during MV. Despite these indirect evidences, no previous studies have quantitatively characterized dynamic changes of ventilation during MV in SDB patients.

Accordingly, we continuously measured the TV changes during routine MV in order to explore mechanisms of inefficient MV in adult persons. We specifically tested a hypothesis that the presence of SDB, defined as apnea hypopnea index (AHI) greater than 5 per hour, reduces the efficiency of MV assessed by TV achieved by constant mechanical ventilation.

Materials and Methods

Subjects

The investigation was approved by the institutional Ethics Committee (Graduate School of Medicine, Chiba University, Chiba, Japan) and registered in University Hospital Medical Information Network Clinical Trial Registry (UMIN000012494, December 5, 2013: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000014629&language=E). Written informed consent was obtained from each subject after the aim and potential risks of the study were fully explained to each. Subject enrollment in this prospective hypothesis testing study was terminated on December, 2015. Inclusion criteria were adult patients (20 to 80 yr old) undergoing scheduled surgeries under general anesthesia in Chiba University Hospital, Chiba, Japan, and exclusion criteria were patients who are eligible for awake intubation, patients with full stomach, patients with severe comorbidities (American Society of Anesthesiologists physical status, more than 2), and patients with allergies to rocuronium or propofol.

Preoperative Airway Assessments and Sleep Study

For each anesthetic case, airway assessments were performed in addition to a standard history and physical examination, allowing scoring of 12 independent predictors for both difficult MV and direct tracheal intubation reported by Kheterpal *et al.*[4] We modified the score reported by Kheterpal *et al.*[4] by setting the thresholds for limited thyromental distance, thick neck, diagnosed sleep apnea, and limited or severely limited jaw protrusion as 60 mm, 40 cm, AHI greater than 5 per hour, and upper lip bite test class 3, respectively.

A preoperative sleep study was performed by a nocturnal portable monitor that measured respiratory airflow and arterial oxygen saturation (SpO_2; SAS2100; Nihon Kohden, Japan). All subjects were instructed to attach an oximetry finger probe and nasal cannula before sleep and to remove them on awakening. After checking the quality of the recordings, respiratory and oximetry variables were calculated using computer software. The severity of SDB was quantified by AHI, the frequency of desaturation more than 3% from the baseline, the percent of time spent at SpO_2 less than 90%, and lowest SpO_2. All subjects were divided into two groups based on the results of the overnight sleep study: subjects with AHI equal to or less than 5 per hour were denoted as the non-SDB group, and subjects with AHI greater than 5 per hour denoted as the SDB group.

The sleep study was performed in 88 subjects whose consents were obtained; however, eight subjects were excluded from the analyses due to failure of TV measurements during anesthesia induction.

Anesthesia Induction Technique and Respiratory Measurements

Each subject was placed in the supine position and in the neutral head position under cardiorespiratory monitoring (Life Scope J, BSM-9100; Nihon Kohden) in the operating room. In addition to pulse oximetry and an electrocardiogram, respiratory variables such as respiratory flow (accuracy: ± 0.025 l/s), TV (accuracy: ± 10 ml), airway pressure (accuracy: ± 1 cm H_2O; GF-220R Multigas/Flow unit; Nihon Kohden), and carbon dioxide concentration with a mainstream capnometer (CAP-ONE, TG-970P; Nihon Kohden; accuracy: ± 2 mmHg) were continuously monitored. Blood pressure was noninvasively measured every 5 min, and neuromuscular function with acceleromyography (TOF-Watch; Organon Ireland Ltd., Ireland) was assessed by a train of four stimulations every 15 s (no calibration). All these variables were displayed on the cardiorespiratory monitoring screen, and the moving images were captured and stored in a computer for later analyses. Analyses of the respiratory variables were performed by digitized cardiorespiratory monitoring images by an investigator who had no knowledge of the sleep study results. General anesthesia was induced by intravenous administration of 2 μg/kg fentanyl and 1 mg/kg propofol after 3-min inhalation of pure oxygen through an anesthesia circuit. Appropriate anesthesia depth was clinically assessed by the anesthetist without Bispectral Index Score monitoring, and additional propofol was injected if necessary. After confirming the loss of consciousness and starting intermittent train of four stimulations through an ulnar nerve by a 50-mA current, rocuronium 1 mg/kg real bodyweight was injected.[11] In this one-handed maneuver, the thumb and index fingers hold the anesthesia full-face mask (Air Cushion Face Mask KM202; Koo Medical Equipment Co., Ltd., China), the third and fourth fingers are placed on the left mandibular ramus, and the fifth finger is placed at the left mandibular angle. The anesthetist was instructed to perform his/her best airway opening technique during the anesthesia induction. Twenty-seven anesthesia providers with a wide range of clinical experience of anesthesia management participated in this study without any previous knowledge of the purpose of this study although the results were informed. Twenty seconds after injection of rocuronium, pressure-controlled ventilation by using an anesthesia machine ventilator through the full-face mask (peak inspiratory pressure, 15 cm H_2O; positive end-expiratory pressure, 0; I:E ratio, 0.4; and respiratory rate, 15 cycles per minute) was started and continued for 1 min.

Efficiency of MV: Assessments for Primary and Secondary Outcomes

Efficiency of MV with one hand during the initial 15 breaths was assessed by TV achieved by constant mechanical ventilation. We predetermined the breath number needed to initially exceed 5 ml/kg ideal body weight (IBW) of expiratory TV ($B\text{-}_{TV5}$) as the primary outcome to test the hypothesis and TV of the second breath (TV_{2nd}), a mean value of the expiratory TV for 1 min (TV_{mean}), and TV of the 15th breath (TV_{15th}) as the secondary outcomes in this study. TV was also measured during MV with two hands (TV_{2hands}) and after either placement of tracheal tube or supraglottic airway (TV_{tube}; 62 tracheal tubes and 12 supraglottic airways). The efficiency of MV was also assessed by the capnogram waveform. In accordance with 2014 Japanese Society of Anesthesiologists (JSA) airway guideline,[12] we determined normal capnogram (V1) when all phases of capnogram wave including phase III characterized by a plateau are identified on the waveform, subnormal capnogram (V2) when the phase II waveform characterized by a sole rapid upswing is identified (lack of the phase III), and abnormal ventilation (V3) when no capnogram waveform is identified.

Statistical Analyses

There has been no previous study, to date, that compares the primary outcome ($B\text{-}_{TV5}$) between SDB and non-SDB subjects. Based on the $B\text{-}_{TV5}$ (mean ± SD: 5.5 ± 5.3 breaths) obtained in our preliminary study of 10 anesthesia patients, we expected a 2.5 difference between the non-SDB and SDB groups and calculated the samples size as 73 subjects for this study assuming $\alpha = 0.05$ (two tailed) and $\beta = 0.8$ (SigmaPlot 12.0; Systat Software Inc., USA). Accordingly, total sample size was set to be 80. Since the prevalence of SDB patients in Japanese general anesthesia population is unknown, we intentionally recruited participants who were suspected of having SDB to ensure that we would observe similar numbers of SDB and non-SDB patients based on clinical and physical features of SDB such as higher STOP-Bang score,[13,14] obesity, and small maxilla-mandibular structure with excessive submandible soft tissue.[15,16]

For the baseline variables, summary statistics were constructed using frequencies and proportions for categorical data and means and SDs for continuous variables. Patient characteristics were compared using Fisher exact test for categorical outcomes and Student's *t* test or Wilcoxon rank sum test for continuous variables, as appropriate. For the primary analysis, we compared the efficiency of MV between groups using an analysis of covariance (ANCOVA) model, taking into account the variation caused by MV effects and using the baseline body mass index (BMI) as covariate. Multiple linear regression analyses were performed with six potential predictors including severity of expiratory flow limitation (EFL) during one-hand MV and five factors (age, BMI, Mallampati class, thyromental distance, upper lip bite test, and AHI), which were selected from 12 previously reported independent risk factors for difficult and impossible MV.[1–3] The definition of SDB is arbitrary and varies among the studies. Our previously determined SDB definition AHI more than 5 includes mild SDB patients and therefore possibly failed to discriminate the influence of SDB on efficacy of MV. As *post hoc* subgroup analyses, we compared efficacy of MV between 20 non-SDB patients with lower AHI and 20 SDB patients with higher AHI. A value of $P < 0.05$ was considered statistically significant, and all *P* values were two sided. All statistical analyses were performed using SAS version 9.4 (SAS Institute, USA).

Results

The study was successfully completed in 80 adult subjects. Neither an oral nor nasal airway was inserted during the MV. None had cardiorespiratory complications such as hypoxemia and hypotension during anesthesia induction. Table 1 represents patient characteristics and results of the sleep study. SDB patients (n = 42) were significantly more obese than non-SDB patients (n = 38) and had more hypoxemic SDB episodes by definition. No SDB patient was preoperatively treated with nasal continuous positive airway pressure.

Planned Analysis: Comparison of Efficiency of MV between Non-SDB and SDB Groups

As indicated in table 2, TV greater than 5 ml/kg IBW (primary outcome) was achieved significantly earlier by one breath with greater TV in non-SDB patients (n = 38) than in SDB patients (n = 42). Other respiratory variables representing efficiency of MV such as TV_{2nd}, TV_{15th}, and TV_{mean} (secondary outcomes) were also significantly better in non-SDB patients than in SDB patients. These statistical differences disappeared when the variables were adjusted by BMI, which significantly differed between the groups among the background patients' characteristics (table 3). No statistically significant difference of the MV efficiency was observed during two-hand MV.

Post Hoc *Analysis for Testing the Hypothesis: Subgroup Comparison of Efficiency of MV*

Subgroup analyses for 20 lower AHI non-SDB patients and 20 higher AHI SDB patients clarified the impact of SDB on the efficiency of MV (tables 2 and 3). The primary outcome ($B\text{-}_{TV5}$) was significantly earlier by two breaths in non-SDB patients than in SDB patients. The secondary outcomes representing efficiency of MV such as TV_{2nd}, TV_{15th}, and TV_{mean} were also significantly better in non-SDB patients

Table 1. Patients' Characteristics and Results of Sleep Study

	All Subjects	Non-SDB	SDB	*P* Value	Non-SDB with Lower AHI	SDB with Higher AHI	*P* Value
No. of subjects (M/F)	80 (42/38)	38 (17/21)	42 (25/17)	0.262	20 (10–10)	20 (13–7)	0.523
Age (y)	66 (57.5–71)	64 (47–70)	66 (62–71)	0.14	64 (44–70)	64.5 (61–69.5)	0.343
ASA-PS (1/2)	(15/65)	(15/23)	(0/42)	< 0.001	(9/11)	(0/20)	< 0.001
Height (cm)	161 (155–167)	160 (155–166)	162 (155–168)	0.426	162 (157–166)	163 (157–168)	0.364
Weight (kg)	61.0 (54.0–70.0)	58.0 (52.0–66.5)	67.0 (56.6–72.0)	0.004	54.0 (50.0–58.0)	69.5 (62.0–74.0)	< 0.001
Body mass index (kg/m^2)	24.1 (21.2–26.1)	21.9 (20.3–25.0)	24.8 (23.3–27.1)	0.005	20.9 (20.0–23.0)	25.0 (24.0–27.9)	< 0.001
Neck circumference (cm)	36.2 (34.4–38)	35.5 (32.9–36.3)	37.5 (35.8–38.5)	< 0.001	35.6 (32.5–36.3)	37.8 (36.6–38.2)	< 0.001
Mallampati class (I/II/III/IV)	37/28/11/4	18/16/3/1	18/13/8/3	0.335	11/8/1/0	7/6/5/2	0.12
Thyromental distance (mm)	70 (65–80)	71.5 (65–80)	70 (65–80)	0.629	71.5 (66–81)	73 (64.5–83.5)	0.892
Interincisor distance (mm)	43 (40–50)	43 (40–50)	44 (40–50)	1	44 (42–49.5)	45.5 (40.5–51)	0.694
Upper lip bite test (I/II/III)	38/38/4	20/17/1	18/21/3	0.514	10/10/0	9/9/2	0.349
Modified Kheterpal score	3 (2.5–4)	2 (2–3)	4 (4–5)	< 0.001	2 (2–3)	4 (4–5)	< 0.001
AHI (h^{-1})	5.7 (2.2–13.2)	2.1 (1–3.4)	12.4 (8.3–21.5)	< 0.001	1.0 (0.3–1.5)	21.7 (17.6–31)	< 0.001
3% ODI (h^{-1})	7.6 (3.5–16.7)	3.2 (2.1–5,3)	15.9 (9.8–25.5)	< 0.001	2.4 (1.3–3.1)	25.6 (21.8–32.8)	< 0.001
CT90 (%)	0.3 (0.1–1.3)	0.1 (0–0.2)	1.2 (0.4–4.2)	< 0.001	0 (0–0.04)	3.9 (1.3–6.1)	< 0.001
Mean nadir Spo_2 (%)	92 (91–93.8)	93 (92–95)	91 (90–92.3)	< 0.001	94 (93–95)	90 (90–91.8)	< 0.001
Lowest Spo_2 (%)	87 (81–89.5)	89.5 (88–92)	82 (78–87)	< 0.001	92 (89.5–93.5)	80 (75.5–82)	< 0.001
Anesthetists' experience (yr)	3 (1–8)	3 (1–8)	3 (1–8)	0.544	3 (1–8)	1 (1–9)	0.555

All subjects were classified by our previously determined SDB definition AHI more than 5 as SDB and non-SDB groups. As *post hoc* subgroup analyses, we selected 20 non-SDB patients with lower AHI and 20 SDB patients with higher AHI. Values are median (25 to 75 percentile). Group difference was assessed by rank-sum test for continuous variables and either Fisher exact test or chi-square test for the categorized variables.

AHI = apnea hypopnea index; ASA-PS = American Society of Anesthesiologists physical status; CT_{90} = percent of time spent SpO_2 less than 90%; ODI = oxygen desaturation index; SDB = patients with sleep-disordered breathing; SpO_2 = arterial oxygen saturation.

than in SDB patients (table 2). Even after adjustment by BMI, ANCOVA revealed significant differences of variables representing efficiency of MV such as $B\text{-}_{TV5}$, TV_{2nd}, and TV_{mean} between the subgroups (table 3).

Post Hoc *Exploratory Analysis 1: Dynamic Changes of TV during MV*

Changes of TV during one-hand MV and during two-hand MV are presented for each of the subgroups in figure 1. Smaller TV despite the same ventilator setting in the severe SDB patients than in the non-SDB subjects was clearly illustrated during one-hand MV. The difference between the groups was not eliminated by the two-hand MV (table 2). It is also notable that TV was initially smaller but progressively increased by more than 70% in 1 min during the MV in both groups.

Post Hoc *Exploratory Analysis 2: EFL and Its Reversal by Two-hand MV*

We noted three different flow patterns during MV (fig. 2). After achieving maximal expiratory flow, the expiratory flow gradually decreased, and no difference between inspiratory and expiratory TV was observed in 57 patients (EFL-1: fig. 2A). Normal capnogram waveforms (V1) were observed in the no-EFL breaths. In contrast, expiratory flow abruptly decreased immediately after peak expiratory flow (EFL), and both inspiration and expiration were significantly impaired with V3 capnogram waveform for more than four breaths in nine patients (EFL-3: fig. 2C). In 14 patients, expiratory flow was abruptly decreased but maintained during expiration for more than four breaths. Inspiratory flow was not impaired as noted by the difference between the inspiratory and expiratory TV (EFL-2: fig. 2B). V2 capnogram waveforms were observed in the EFL-1 breaths.

TV_{2hands} was significantly greater than TV_{15th}, and patterns of capnogram wave form significantly improved by the two-hand MV compared with one-hand MV (table 2; fig. 1), which suggest the advantage of using two hands for improving efficiency of MV. However, the EFL pattern was not normalized even by using two hands in seven of 23 patients (fig. 2D), while the abnormal flow pattern disappeared in majority of patients (fig. 2, B and C). Interestingly, TV_{2hands} was significantly greater than the TV_{tube}, indicating that two-hand airway

Table 2. Comparisons of Efficacy of MV between Non-SDB and SDB and between Subgroup Non-SDB and SDB Patients

	All Subjects (n = 80)	Non-SDB (n = 38)	SDB (n = 42)	*P* Value	Non-SDB with Lower AHI	SDB with Higher AHI	*P* Value
One hand							
TOFR at the first breath (%)	91 (65–111)	82 (20–109)	98 (78–111)	0.109	85 (20–95.5)	91 (66–106)	0.325
TV_{2nd} (ml/kg IBW)	5.3 (2.5–9.3)*	6.6 (4.0–10.3)*	4.7 (0.8–8.0)*	0.019	8.2 (4.8–10.9)*	4.0 (0.8–6.2)*	0.009
Subjects achieving TV > 5 ml/kg, n (%)	69 (86)	33 (87)	36 (86)	1	18 (90)	16 (80)	0.661
$B\text{-}_{TV5}$	2 (2–3)	2 (2–2.3)	3 (2–5)	0.012	2 (2–2)	4 (2–6)	0.002
TV at $B\text{-}_{TV5}$ (ml/kg IBW)	7.7 (5.7–9.8)*,†	9.3 (6.1–11.0)*,†	7.1 (5.4–9.0)*,†	0.025	9.0 (6.5–10.9)*	6.3 (5.5–8.6)*,†	0.133
End-tidal carbon dioxide at $B\text{-}_{TV5}$ (%)	27 (24–33)*	28 (24–34)*	26 (24–31)*	0.176	28 (24–39)	26 (23.5–33)	0.468
Capnogram at $B\text{-}_{TV5}$ (V1/V2/V3)	(34/46/0)*	(18/20/0)*	(16/26/0)*	0.498	(12/6/0)	(5/11/0)	0.084
TV_{15th} (ml/kg IBW)	9.5 (5.9–10.8)*,†	10.3 (7.4–12.1)*,†	8.2 (5.2–10.3)*,†	0.023	10.6 (9.1–12.4)†	7.6 (5.7–10.1)*,†	0.003
TOFR at the 15th breath (%)	0 (0–4)†	0 (0–0)†	0 (0–10)†	0.043	0 (0–0)	0 (0–0)	0.653
TV_{mean} (ml/kg IBW)	8.7 (5.2–10.8)*,†	9.1 (6.7–11.6)*,†	6.6 (4.5–9.7)*,†	0.017	9.8 (8.7–12.2)*,†	5.9 (3.1–8.8)*,†	0.004
EFL patterns (1/2/3)	(57/14/9)*	(30/5/3)	(27/9/6)	0.349	(17/2/1)	(11/5/4)	0.112
Two hands							
TV_{2hands} (ml/kg IBW)	11.2 (8.2–13.3)	12.2 (9.4–13.7)	10.6 (7.6–12.1)	0.121	12.4 (10.4–14.1)†	9.2 (7.4–11.4)†	0.027
End-tidal carbon dioxide at two-hand MV (%)	35 (30.5–37.5)	35.5 (30–37)	34.5 (31–38)	0.835	35 (30–38)	36 (35–39.5)	0.098
Capnogram patterns (V1/V2/V3)	(58/9/3)	(29/7/2)	(29/12/1)	0.484	(17/3/0)	(13/7/0)	0.273
EFL patterns (1/2/3)	(70/5/5)	(35/1/2)	(35/4/3)	0.406	(19/1/0)	(16/3/1)	0.323
Tube							
TV_{tube} (ml/kg IBW)	9.0 (7.8–10.6)*,†	9.7 (7.8–11.0)*,†	8.7 (7.8–10.6)†	0.59	10.1 (8.1–12.3)*,†	8.4 (7.9–10.5)†	0.199

All subjects were classified by our previously determined SDB definition AHI more than 5 as SDB and non-SDB groups. As *post hoc* subgroup analyses, we selected 20 non-SDB patients with lower AHI and 20 SDB patients with higher AHI. Values are median (25 to 75 percentile). Group difference was assessed by rank-sum test for continuous variables and either Fisher exact test or chi-square test for the categorized variables (*P* value). Signed rank test was used to compare differences of the variables at the different timings.

**P* < 0.05 *vs.* two-hand MV.†*P* < 0.05 *vs.* second breath.

AHI = apnea hypopnea index; ANCOVA = analysis of covariance; $B\text{-}_{TV5}$ = the breath number needed to initially exceed 5 ml/kg ideal body weight of expiratory TV; EFL = expiratory flow limitation; IBW = ideal body weight; MV = mask ventilation; SDB = patients with sleep-disordered breathing; TOFR = ratio of train of four responses; TV = tidal volume during expiration; TV_{2nd} = TV of the second breath; TV_{2hands} = TV with using two hands of the anesthesia provider; TV_{15th} = TV of the 15th breath; TV_{mean} = a mean value of the TV for 1 min; TV_{tube} = TV after either placement of tracheal tube or supraglottic airway.

maneuvers can establish wider upper airway lumen compared to a tracheal tube (table 2). It should be also noted that the TV_{tube} did not differ between non-SDB and SDB patients, implying similar respiratory compliance between them.

Post Hoc *Exploratory Analysis 3: Factors Explaining Reduction of MV Efficiency*

Results of the multiple linear regression analyses with six potential predictors are presented in table 4. Occurrence of EFL was a statistically significant factor increasing $B\text{-}_{TV5}$, decreasing TV_{2nd}, TV_{15th}, and TV_{mean}, and therefore, explaining the reduction of one-hand MV efficiency. Obesity was a significant factor in the decrease of TV_{15th} and TV_{mean} in the model. Notably, both are still the significant factors for explaining reduction of MV efficiency with two hands.

Post Hoc *Exploratory Analysis 4: Capnogram Waveform Differences and TV Range during MV*

We took this opportunity to assess the relationship between TV and capnogram waveform (V1, V2, and V3) by using data at the fifth breath MV. As illustrated by the box plots in figure 3, TV ranges were overlapped among the subjects with V1 and V2 capnogram waveforms. Notably, minimum TV of patients with V2 capnogram waveform was approximately 2 ml/kg IBW, which is close to the physiologic dead space for adults, and the TV was less than the 2 ml/kg IBW in all subjects with V3 capnogram waveform pattern. Similarly, the minimum TV of subjects with V1 capnogram waveform was approximately 6 ml/kg IBW. End-tidal carbon dioxide concentration was higher in subjects with V1 than those with V2 capnogram waveform, indicating the increasing alveolar-arterial difference of carbon dioxide concentration. Two-hand MV significantly increased the number of subjects with V1 and end-tidal carbon dioxide concentration (table 2).

Discussion

This is the first study that quantitatively assessed the efficiency of MV during anesthesia induction and explored whether the presence of SDB worsens the efficiency of

Table 3. Results of ANCOVA for Comparisons of Efficacy of Mask Ventilation between Non-SDB and SDB and between Subgroup Non-SDB and SDB Patients

		All Subjects (n = 80)			Subgroup (n = 40)		
Variables	Group	LS mean	95% CI	*P* Value	LS Mean	95% CI	*P* Value
TV_{2nd} (ml/kg IBW)	Non-SDB	6.6	5.3–7.8	0.074	7.4	5.5–9.3	0.034
	SDB	5.0	3.8–6.2		4.2	2.3–6.1	
$B\text{-}_{TV5}$	Non-SDB	2.9	1.8–3.9	0.106	1.7	0.2–3.2	0.001
	SDB	4.1	3.1–5.1		5.7	4.1–7.3	
TV_{15th} (ml/kg IBW)	Non-SDB	9.0	7.7–10.3	0.219	10.0	8.2–11.9	0.086
	SDB	7.9	6.7–9.1		7.5	5.7–9.4	
TV_{mean} (ml/kg IBW)	Non-SDB	8.6	7.4–9.8	0.138	9.6	7.7–11.4	0.032
	SDB	7.4	6.3–8.5		6.5	4.6–8.3	
TV_{2hands} (ml/kg IBW)	Non-SDB	10.6	9.3–11.9	0.913	12	10.3–13.7	0.133
	SDB	10.5	9.2–11.7		10.0	8.3–11.8	
TV_{tube} (ml/kg IBW)	Non-SDB	9.0	8.2–9.7	0.341	9.6	8.5–10.7	0.781
	SDB	9.5	8.7–10.2		9.9	8.8–10.9	

All subjects were classified by our previously determined SDB definition AHI more than 5 as SDB and non-SDB groups. As *post hoc* subgroup analyses, we selected 20 non-SDB patients with lower AHI and 20 SDB patients with higher AHI. Group comparison was adjusted by BMI as a significant confounding factor for the dependent variables.

AHI = apnea hypopnea index; ANCOVA = analysis of covariance; $B\text{-}_{TV5}$ = the breath number needed to initially exceed 5 ml/kg ideal body weight of expiratory TV; BMI = body mass index; IBW = ideal body weight; SDB = patients with sleep-disordered breathing; TV = tidal volume during expiration; TV_{2nd} = TV of the second breath; TV_{2hands} = TV with using two hands of the anesthesia provider; TV_{15th} = TV of the 15th breath; TV_{mean} = a mean value of the TV for 1 min; TV_{tube} = TV after either placement of tracheal tube or supraglottic airway.

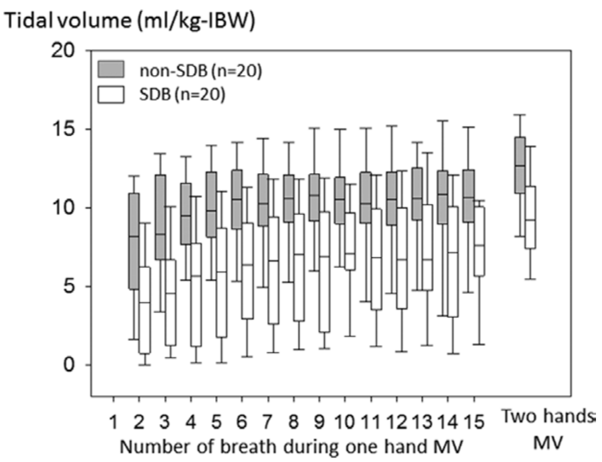

Fig. 1. Box plots showing changes of tidal volume during one-hand mask ventilation (MV) and tidal volume during two-hand MV in 20 non–sleep-disordered breathing (SDB) patients with lower apnea hypopnea index (*gray boxes*) and 20 SDB patients with higher apnea hypopnea index (*white boxes*). Median values are indicated by *horizontal bar* within each box; *bars* above and below each box represent 25th and 75th percentiles, and the end of *vertical lines* denote minimum and maximum. Note the progressive increase of the tidal volume in both groups, clear differences between the groups, and greater tidal volume by two-hand MV. IBW = ideal body weight.

MV. We found that (1) TV during one-hand MV progressively increased by more than 70% in 1 min, (2) one-hand MV was more difficult in patients with severe SDB than in non-SDB patients, (3) higher BMI and occurrence of EFL independently decreased the efficiency of one-hand MV, (4) two-hand MV maximized the efficiency of MV although limited by obesity and occurrence of EFL, and (5) capnogram waveform patterns well reflected the efficiency of MV.

Time Dependency of MV

We first demonstrated that one-hand MV is more difficult at the beginning of the procedure than during the latter period. This well-recognized phenomenon for clinical anesthesiologists is commonly attributed to increasing depth of either anesthesia or muscle relaxant,[17] while no previous study systematically explored its mechanisms. Joffe *et al.*[18] assessed TV changes during one-hand and two-hand MV during anesthesia induction in their randomized cross-over study. Unlike the results of our study, they found no TV change during one-hand MV but progressive increase of the TV during two-hand MV in anesthetized nonparalyzed patients with oral airway in place. Differences of the results and study designs between the study by Joffe *et al.*[18] and our studies suggest involvement of mechanisms other than depth of anesthesia and muscle relaxant. In fact, the ratio of train of four responses at the 15th breath was significantly greater in the SDB group than in the non-SDB group (table 2), but the MV efficiency did not differ between the groups when ANCOVA was performed (table 3). Furthermore, in the subgroup analyses, the depth of neuromuscular block did not differ between the subgroups, but efficiency was higher in the non-SDB subgroup. However, the results of this study should be carefully interpreted when rocuronium is given based on ideal body weight. Learning effects,[19] pharyngeal airway hysteresis due to surface adhesive force on the pharyngeal mucosa,[20] change of lung volume influence on pharyngeal airway collapsibility,[21] and opioid-induced rigidity of chest wall and vocal cords[22] would be additional

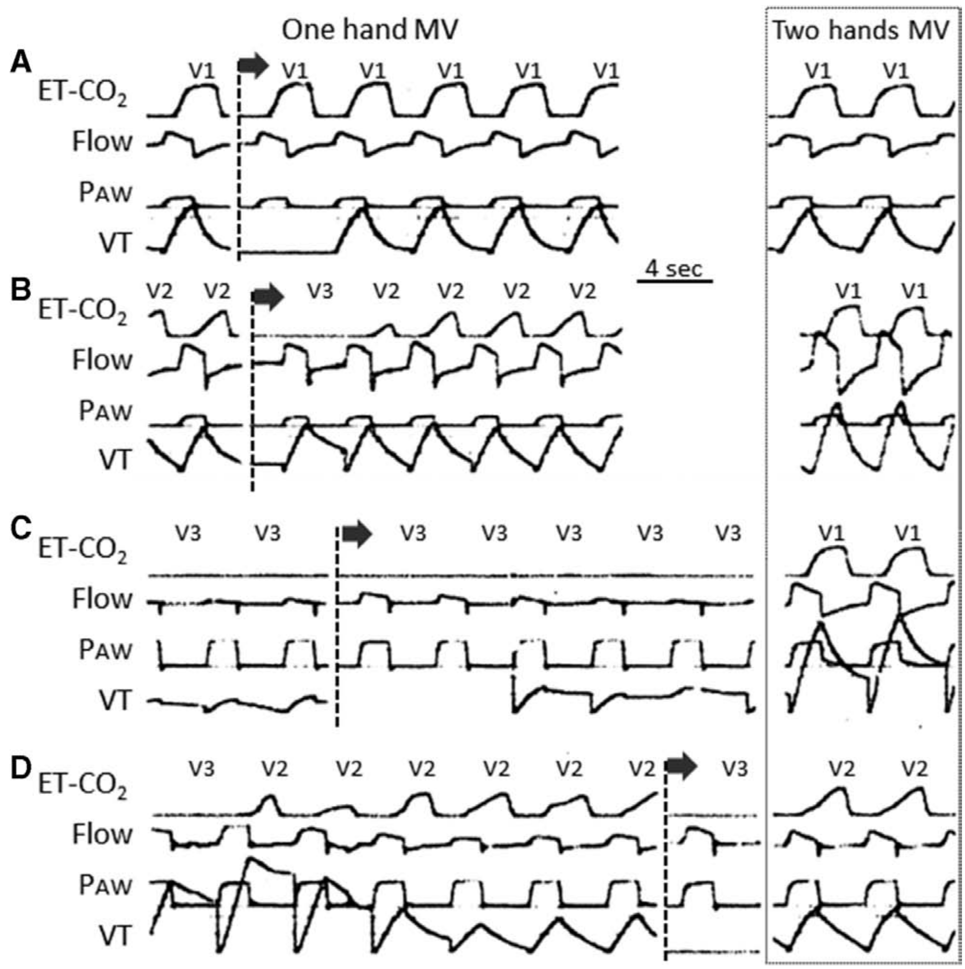

Fig. 2. Tracings of respiratory variables (capnogram: carbon dioxide concentration; flow: respiratory flow; airway pressure [P_{AW}]; tidal volume [TV]) during one-hand mask ventilation (MV) showing three different expiratory flow patterns and influences of two-hand MV on the respiration. The images were taken from the cardiorespiratory monitor, and the *vertical dotted lines* denote beginnings of tracings. Note the three different flow patterns. (*A*) Normal flow pattern without difference between inspiratory and expiratory TV (expiratory flow limitation [EFL]-1) in a non–sleep-disordered breathing (SDB) subject. (*B*, *D*) EFL-2, characterized by abrupt expiratory flow reduction immediately after peak expiratory flow, with smaller expiratory TV than inspiratory TV in SDB patients. (*C*) More severe EFL-3 with smaller TV during both inspiration and expiration in a SDB patient. Note the reversal of expiratory flow limitation and significant TV increase during two-hand MV in the cases (*B*) and (*C*) but not in the case (*D*). Capnogram waveforms were classified in accordance with the 2014 JSA airway guideline ventilation (reference 12). ET CO_2 = end-tidal carbon dioxide concentration; flow = flow rate measured by pneumotachograph; V1 = normal capnogram with the presence of phase III; V2 = subnormal capnogram with the presence of phase II but lack of phase III; V3 = abnormal capnogram without capnogram waveform.

candidates for the mechanisms. Recognition of this time-dependent nature of MV should help anesthesiologists diagnose truly difficult MV during anesthesia induction.

Is SDB an Independent Risk Factor for Difficulty of One-hand MV?

Our SDB patients comprise a wide spectrum of sleep-related breathing abnormalities: mild asymptomatic SDB to severe symptomatic untreated SDB patients. We found that MV during anesthesia induction is more difficult in the subgroup patients with severe SDB than in non-SDB patients although the 5 per hour AHI cutoff for the SDB group used in this study is not yet clear cut. Although the AHI is a marker for SDB severity, AHI thresholds vary and differ depending on the SDB-related symptoms and comorbidities.[23] To our knowledge, no study has determined such an AHI threshold for difficult MV.

Anesthetized paralyzed patients with severe SDB are reported to have higher pharyngeal closing pressures than non-SDB and mild SDB patients.[6] Furthermore, improvement of pharyngeal collapsibility by various airway interventions is limited by the severity of the preexisting collapsibility of the pharynx.[24] In the previous epidemiologic studies that identified SDB as an independent risk factor, SDB was preoperatively documented and treated by nasal continuous positive airway pressure that is usually prescribed for symptomatic moderate to severe SDB

Table 4. Multiple Linear Regression Models for Explaining Efficacy of Mask Ventilation

	Constant	Age	BMI	Mallampati Class	TMD	ULBT	AHI	EFL with One Hand
Ventilation efficacy with one hand								
$B\text{-}_{TV5}$								
Coefficient	−3.274	0.00132	−0.0447	0.105	0.0405	0.0954	0.0586	3.019
SE	3.377	0.0232	0.0836	0.34	0.0263	0.489	0.0305	0.519
P value	0.336	0.955	0.595	0.759	0.129	0.846	0.059	< 0.001
TV_{2nd}								
Coefficient	14.6	−0.0514	−0.161	0.216	0.0159	0.292	−0.047	−2.337
SE	4.634	0.0321	0.104	0.46	0.037	0.693	0.0404	0.621
P value	0.002	0.115	0.124	0.641	0.668	0.674	0.247	< 0.001
TV_{15th}								
Coefficient	11.047	−0.0032	−0.332	0.189	0.125	0.394	−0.007	−3.057
SE	4.334	0.0301	0.097	0.431	0.0346	0.648	0.0378	0.581
P value	0.013	0.915	0.001	0.661	< 0.001	0.545	0.85	< 0.001
TV_{mean}								
Coefficient	15.32	−0.0285	−0.23	0.0671	0.0518	0.494	−0.034	−3.093
SE	3.796	0.0263	0.085	0.377	0.0303	0.568	0.0331	0.509
P value	< 0.001	0.283	0.009	0.859	0.091	0.387	0.305	< 0.001
Ventilation efficacy with two hands								
TV_{2hands}								
Coefficient	12.596	−0.0004	−0.277	−0.0983	0.0829	0.783	−0.029	−1.384
SE	5.018	0.0346	0.113	0.492	0.0407	0.752	0.0449	0.685
P value	0.014	0.99	0.017	0.842	0.045	0.302	0.524	0.047

AHI = apnea hypopnea index; BMI = body mass index; $B\text{-}_{TV5}$ = the breath number needed to initially exceed 5 ml/kg ideal body weight of expiratory tidal volume; EFL = expiratory flow limitation; SDB = patients with sleep-disordered breathing; TMD = thyromental distance; TV = tidal volume during expiration; TV_{2nd} = TV of the second breath; TV_{2hands} = TV with using two hands of the anesthesia provider; TV_{15th} = TV of the 15th breath; TV_{mean} = a mean value of the TV for 1 min; ULBT = upper lip bite test.

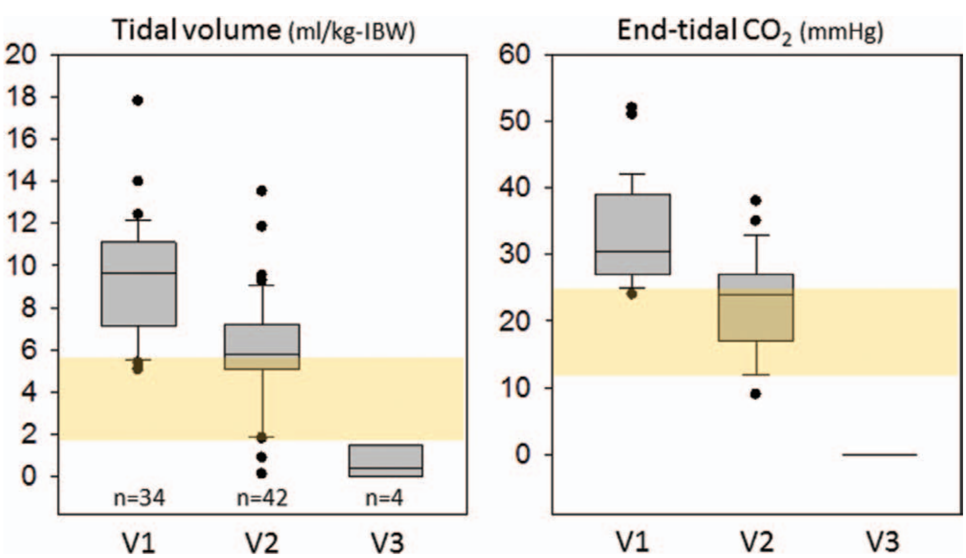

Fig. 3. Differences of tidal volume and end-tidal carbon dioxide concentration during the fifth breath mask ventilation (MV) among three distinctive capnogram waveforms (V1: normal capnogram with the presence of phase III, V2: subnormal capnogram with the presence of phase II but lack of phase III, and V3: abnormal capnogram without capnogram waveform). Median values are indicated by *horizontal bar* within each box; *bars* above and below each box represent 25th and 75th percentiles, and the end of *vertical lines* denote minimum and maximum. Outliers are presented by *closed circles*. Note that the capnogram waveform patterns appear to distinguish the ranges of tidal volume during MV.

patients.[1–4] These physiologic and epidemiologic studies suggest a higher threshold AHI for difficult or impossible MV in agreement with our findings. However, our primary hypothesis was to test the mild SDB criteria (AHI, more than 5), and this study did not test the priorly defined severe SDB criteria. A critical AHI threshold needs to be determined using an appropriate study design for the purpose.

Mechanisms of Difficult One-hand MV

We found that the presence of EFL and obesity independently accounts for reduction of MV efficiency. Safar *et al.*[25,26] first described the occurrence of expiratory obstruction during mouth-to-nose, not mouth-to-mouth, ventilation particularly in obese anesthetized patients. They speculated the cause to be a valve-like behavior of the soft palate without direct observance of the pharyngeal airway. Despite the absence of air leak from the facemask as confirmed by a stable flow trace, we noticed that the expiratory TV was smaller than the inspiratory TV, in agreement with the observation by Goodwin *et al.*[27] who, however, attributed this to high fresh gas flow used in their study. Our pneumotachograph was placed between the facemask and anesthetic circuit, which prevented the influence of fresh gas flow on the airflow measurement. We consider that greater inspiratory TV over expiratory TV reflects actual gas movement and indicates the increase of lung volume when this phenomenon occurs as Safar[26] documented in lung volume increase during the expiratory obstruction.[26] In fact, Buffington *et al.*[28] used chest rise but not fall and lack of a carbon dioxide waveform on the capnograph as a definition of expiratory obstruction during anesthesia induction. They identified age and enlarged pharyngeal soft tissue as independent factors for occurrence of the expiratory obstruction. It should be noted that patient characteristics reported by both Safar *et al.*[26] and Buffington *et al.*[28] are common features of SDB patients. Although the expiratory obstruction is believed to be caused by valve-like obstruction at the soft palate, no study has directly proved this and extensively explored how the EFL is caused in association with SDB and/or obesity. Clearly, future studies should focus on this interesting and clinically important phenomenon.

Although obesity has been repeatedly reported to be an independent risk factor for difficult and impossible MV,[1–4] no study in this field has systematically elucidated why obesity leads to difficult MV. We previously demonstrated that mandible advancement is unable to restore the airway patency behind the soft palate in obese subjects[7] and suggested the importance of MV through the mouth in accordance with the recommendation by Safar *et al.*[26] However, by using only one hand, it is practically difficult to appropriately perform airway maneuvers including mouth opening in obese patients with relatively large facial structures. Furthermore, obesity worsens SDB by increasing pharyngeal airway collapsibility through structural mechanisms such as excessive soft tissue for the craniofacial size and reduced lung volume.[29,30] Our results indicate that the use of two hands can effectively, though not perfectly, compensate for the structural abnormalities resulting in acceptable MV even in severe SDB patients. The use of oral or nasal airways would prevent the EFL at the soft plate and further improve the MV as documented by Safar *et al.*[25]

Clinical Implications and Limitations of This Study

Since this study mimicked routine anesthesia induction, we believe that its results provide clinically useful information for predicting, diagnosing, and managing difficult MV. The efficiency of MV decreased only in severe SDB patients indicating the importance of preoperative SDB screening by questionnaires and portable sleep monitor for diagnosis of the SDB severity.[31] Clinical values of the preoperative SDB diagnosis for decreasing incidence of difficult MV are worth assessing in future studies.

Although prompt diagnosis of difficult MV could maximize risk management strategy, most anesthesia providers rely on their subjective assessments such as thoracic movement and resistance of the anesthetic bag, and Han scale for grading difficulty of MV also includes subjective items.[32] Our results are in agreement with the JSA airway management guideline that suggests the use of three distinct capnogram waveforms to continuously and instantaneously grade ventilation status before development of severe hypoxemia.[12] Furthermore, airflow tracing, not a TV value, if available, would help to know a possible precursor of difficult MV, *i.e.*, EFL, and indicate time to start two-hand MV or insert an oral airway. It should be also noted that two-hand MV did not normalize the EFL in 30% patients with EFL. Clearly, more effective airway intervention for improving MV needs to be tested or developed in the near future.

Despite these possible clinical implications, this study has several methodological limitations. First, we did not standardize the MV technique, and the anesthesia providers performed their best to achieve adequate MV. Although 27 anesthesia providers participating in this study have a wide range of clinical experience and their own MV techniques, this single-institute study could not cover and test the variety of MV techniques used in other institutes and countries. Second, only eight patients had BMI greater than 30 kg/m^2 while our results clearly indicated the contribution of obesity to difficult MV and that definition of obesity in Japan is 25 kg/m^2. Clearly, future studies should address how MV becomes difficult in morbidly obese SDB patients in whom SDB pathogenesis may not be completely identical to that of nonobese SDB patients. Third, we did not objectively assess the depth of anesthesia, which is a significant determinant of the upper airway patency, while the amount of propofol and fentanyl used for induction of anesthesia did not differ between the non-SDB and SDB groups (propofol: 1.0 [1.0 to 1.2] *vs.* 1.0 [0.98 to 1.05] mg/kg, respectively, $P = 0.317$; fentanyl: 2.0 [2.0 to 2.1] *vs.* 2.1 [1.9 to 2.0] μg/kg, respectively, $P = 0.106$). Lastly, our study design does not allow exploring how muscle paralysis influences efficacy of MV during routine anesthesia induction, while recent clinical studies did not indicate unfavorable effects.[27,33,34]

In conclusion, we first characterized breath-by-breath dynamic changes of ventilation during routine MV in 80 adult patients undergoing general anesthesia and found that (1) one-hand MV is more difficult in patients with severe SDB than non-SDB subjects and (2) obesity and occurrence of EFL are involved in mechanisms of inefficient one-hand

MV. The use of two hands is strongly recommended to restore efficient MV.

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Competing Interests

The authors declare no competing interests.

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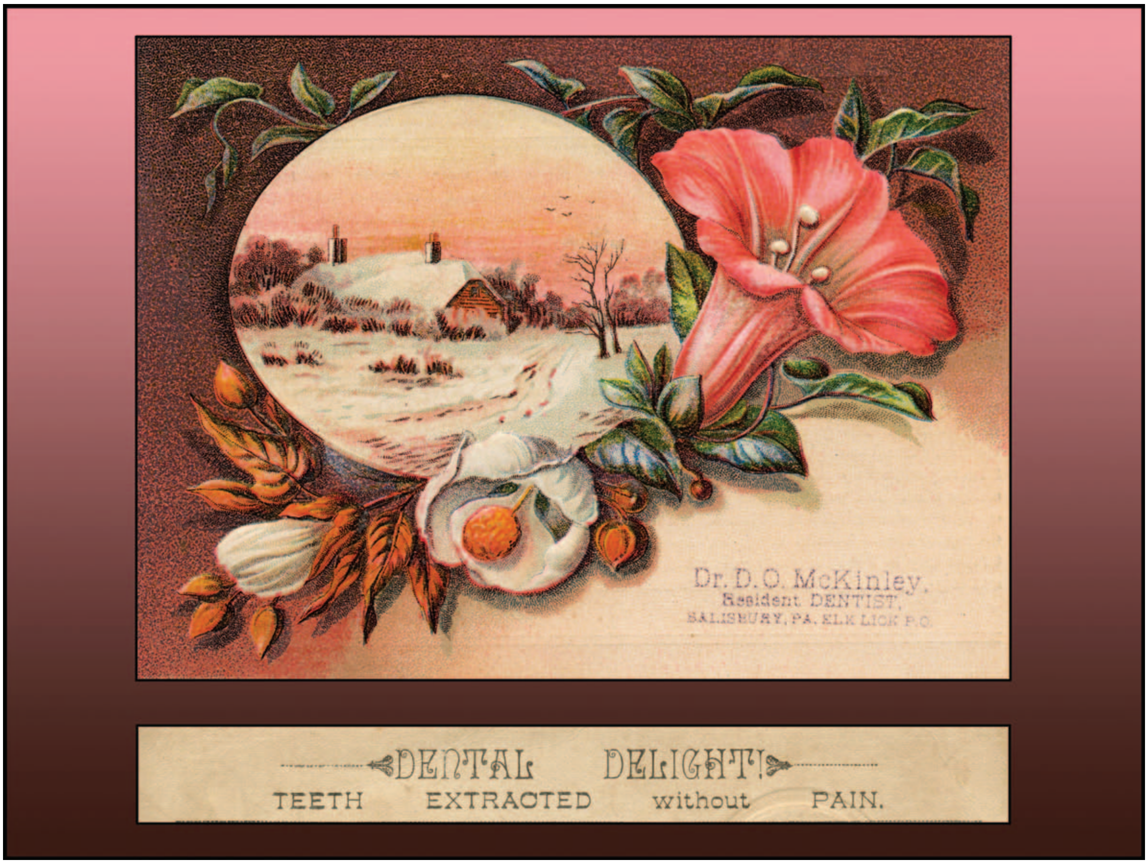
Cocaine in the "Dental Delight" of the Doctors McKinley



Gracing the obverse of this dental trade card (*high*) from the Wood Library-Museum's Ben Z. Swanson Collection, the flowers and greenery exclude the main numbing medicine used by the advertisers, a father-son team of dentists in Salisbury, Pennsylvania. Indeed, on the card's reverse, the father, Daniel O'Connell McKinley, D.D.S. (1836 to 1904), proudly touted that his son, Arthur Oberlin McKinley, M.D. (1867 to 1959), was an alumnus of Baltimore's College of Physician and Surgeons who had made a "specialty of the finer parts of Dentistry." Also on the back of the card, the Doctors McKinley promised (*low*) to use "DENTAL DELIGHT" to guarantee "TEETH EXTRACTED without PAIN." Besides providing local anesthesia, part of the delight may have been the cocaine with which the dental duo heavily laced their proprietary topical anesthetic mixture. Because the McKinleys worked in such a tiny Pennsylvania town (so small that it used the Elm Lick Post Office), they needed more than their dental practice to earn a living. The father also worked making saddles; the son, in the general practice of medicine—and all from the "Dr. McKinley House" on Salisbury's Union Street. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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