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Efficacy of End-Tidal Capnography Monitoring during Flexible Bronchoscopy in Nonintubated Patients under Sedation: A Randomized Controlled Study

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Bronchoscopy · Apnea · Hypoxemia · Monitoring

Abstract
Background: Although appropriate sedation is recommended during flexible bronchoscopy (FB), patients are at risk for hypoventilation due to inadvertent oversedation. End-tidal capnography is expected as an additional useful monitor for these patients during FB. ***Objectives:*** The aim of this study was to evaluate the benefit of additional end-tidal capnography monitoring in reducing the incidence of hypoxemia during FB in patients under sedation. ***Methods:*** Patients undergoing FB under moderate sedation without tracheal intubation were randomly assigned to receive standard monitoring including pulse oximetry or additional capnography monitoring. Bronchoscopy examiners for the only capnography group were informed of apnea events by alarms and display of the capnography monitor. ***Results:*** A total of 185 patients were enrolled. Patient characteristics were well balanced between the two groups. Hypoxemia (at least one episode of pulse oximeter oxygen saturation [SpO_2] <90%) was observed in 27 out of 94 patients in the capnography group (29%) and in 42 out of 91 patients in the control group (46%; $p = 0.014$), resulting in an absolute risk difference of −17.4% (95% confidence interval, −31.1 to −3.7). In the capnography group, hypoxemia duration was shorter (20.4 vs. 41.7 s, $p = 0.029$), severe hypoxemic events (SpO_2 <85%) were observed less frequently (16 [17%] vs. 29 [32%], $p = 0.019$), and the mean lowest SpO_2 value was higher (90.5 vs. 87.6%, $p = 0.002$). ***Conclusion:*** End-tidal capnography monitoring can reduce the incidence and duration of hypoxemia during FB in nonintubated patients under sedation.

Introduction

Sedation is necessary and recommended for bronchoscopic procedures to alleviate patient discomfort [1]. Benzodiazepines and/or opioids are commonly used sedative regimens in bronchoscopy to improve patient tolerance [2–4]. However, inadvertent oversedation that occurs in real-world settings causes respiratory depression and oxygen desaturation [5]. One of the keys for safe procedural sedation is to detect hypoventilation as early as possible [2, 3, 6].

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End-tidal capnography is a noninvasive and continuous method to monitor ventilation. In a retrospective study, we reported that end-tidal capnography was a graphic approach that could easily detect frequent apnea episodes during flexible bronchoscopy (FB) under moderate sedation and that it could detect apnea earlier than standard pulse oximetry monitoring [7]. However, the utility of end-tidal capnography monitoring in reducing hypoxemia during FB under sedation has not been fully evaluated. Hence, the aim of this prospective, randomized controlled study was to evaluate the benefit of additional end-tidal capnography monitoring in reducing the incidence of hypoxemia during FB in patients under sedation.

Materials and Methods

Study Design

This was a prospective, randomized controlled study conducted at an academic center in Japan between September 2016 and May 2017. The study protocol was approved by the Chiba University Institutional Review Board (No. 2395). Written informed consent was obtained from all participants. This study was registered at the University Hospital Medical Information Network Clinical Trial Registration (UMIN-CTR), Japan (registration No.: UMIN000023633).

Study Population and Randomization

The inclusion criteria were as follows: (1) age above 20 years, (2) undergoing FB using sedatives for moderate sedation, in accordance with the American Society of Anesthesiologists (ASA) definition of sedation [8]. Patients who met the following criteria were excluded: (1) ASA physical status ≥IV [9], (2) severe sleep apnea syndrome (apnea-hypopnea index >40), (3) undergoing FB without the use of sedatives, (4) undergoing bronchoalveolar lavage, or (5) undergoing therapeutic bronchoscopy such as bronchial dilation, stent insertion, or laser therapy. In this study, we excluded the patients who planned to undergo bronchoalveolar lavage or therapeutic bronchoscopy because we aimed to assess oxygen desaturation induced only by apnea or hypoventilation episodes associated with oversedation, eliminating the other causes of oxygen desaturation.

Patients were randomly assigned with a 1:1 ratio using permuted block randomization with a block size of two. The bronchoscopy team members were not informed whether patients were assigned to the capnography or the control group until the day of bronchoscopy.

Monitoring

All patients received standard monitoring including physical assessment, pulse oximetry, chest wall impedance, automated blood pressure measurement, and electrocardiogram. Patients in the capnography group received additional end-tidal capnographic monitoring. Although capnographic data were obtained and recorded in the control group as well, display of the capnography monitor was hidden with a silenced alarm in the control group. Vital signs data were routinely collected and recorded into the patient database after every FB examination.

A Smart CapnoLine Guardian™ (Medtronic, Ireland) was used as a capnography mouth device [7] that was connected via a sampling tube to an automated capnographic monitoring device (Capnostream 20P™, Medtronic, Ireland). This monitoring device performs continuous measurement of carbon dioxide concentrations in the expired air of patients and shows capnographic data as a curved line on a front display. A flat line implies cessation of airflow. In this study, an apnea episode was defined as cessation of airflow for more than 10 s. One clinical observer confirmed true apneas by physical assessment and excluded false apneas caused by continuous suctioning or sample tube disconnection when the capnogram displayed a flat line.

Study Procedures and Interventions

All FB procedures were performed without tracheal intubation. After the pulmonologist administered sedatives intravenously to the patient lying supine on the table, a bronchoscope was inserted through the mouth. All patients received supplemental oxygen through a nasal cannula at a flow rate of 2 L/min at the start of the FB procedure.

Moderate sedation according to the ASA guidelines was targeted in this study [9]. To minimize variations in sedation methods, the initial sedation protocol was standardized by bolus injection of 0.35 mg/kg pethidine and 0.04 mg/kg midazolam. Adjustment of additional doses of pethidine and midazolam was left to the operator's discretion.

Interventions against apnea or hypoxemia episodes included increasing oxygen flow, chin-lift/jaw-thrust maneuver, suctioning of secretions in patients' mouth, and withholding administration of additional sedatives. These interventions were initiated in cases where the bronchoscopy team noted hypoxemia by pulse oximetry monitoring in both groups or apnea episodes based on findings from the capnogram displayed in the capnography group.

Sedation management and airway interventions were conducted by trained pulmonologists without the assistance of an anesthesiologist.

Outcomes

Primary outcome of this study was incidence of hypoxemia defined as SpO_2 <90%. Secondary outcomes were duration of hypoxemia, incidence of severe hypoxemia (SpO_2 <85%), lowest SpO_2 value, incidence of bradycardia and hypotension as complications, interventions against apnea or hypoxemia episodes, and patient tolerance to FB. Patient tolerance to FB was measured by a questionnaire including a visual analog scale using a horizontal 100-mm-long line between 0 for no discomfort and 100 for worst possible discomfort. Patients were also queried about their memory during FB and their consent for re-examination, if necessary. Additionally, frequency and causes of false apnea alarms by capnography were assessed as exploratory outcomes.

Sample Size and Statistical Analysis

Sample size calculation was based on the results of our retrospective study [7] which determined hypoxemic incidence rate as 47.6% in patients under sedation. We assumed a reduction of hypoxemia from 50 to 30% as clinically relevant. Based on the χ^2 test, a sample size of 93 patients was required for each group with a significance level of 0.05 and a power of 0.80. With an assumption

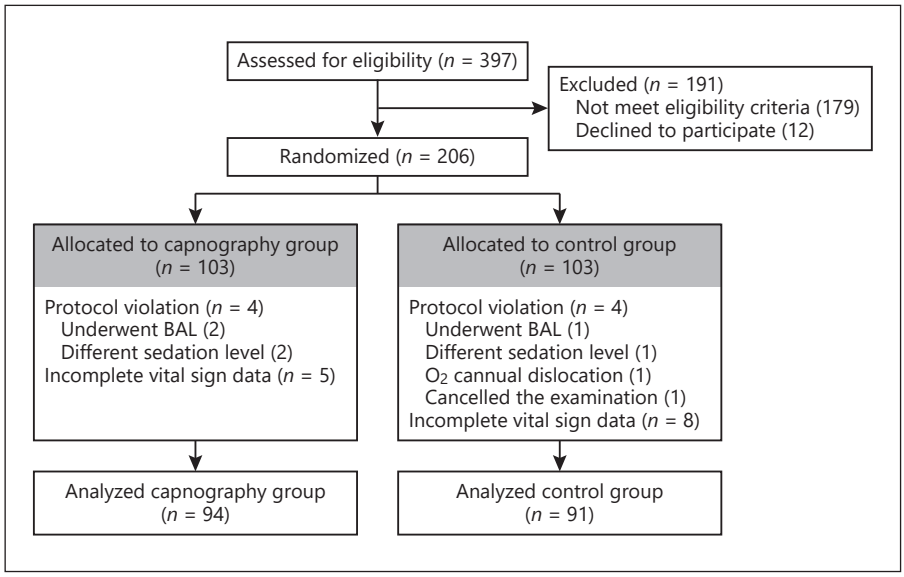

Fig. 1. Flexible bronchoscopy enrollment and randomization flowchart. BAL, bronchoalveolar lavage.

of 10% protocol violation, a total of 206 patients were planned for enrollment in this study.

Continuous data were expressed as means with standard deviation, and descriptive data were expressed as numbers (percentages). For statistical comparison, continuous data were compared using Student's *t* test, and descriptive data were compared using the χ^2 or Fisher's exact test. All *p* values were two-sided, and the statistical significance level was set at 0.05. Kaplan-Meier curves were compared using the Gehan-Breslow-Wilcoxon test. All analyses and interpretations of data were conducted using Graph Pad Prism 6 (GraphPad Software, USA).

Results

Study Population and Characteristics

A total of 397 patients scheduled for FB were screened for enrollment. One hundred and seventy-nine patients failed to meet the eligibility criteria, and 12 patients declined participation. A total of 206 patients were randomized and allocated into the two groups (Fig. 1). Nine patients in the capnography group and 12 patients in the control group were excluded from analysis because of protocol violation or incomplete data on vital signs. Thus, a total of 185 patients with 94 patients in the capnography group and 91 patients in the control group were included in the final analysis.

Patient characteristics were well balanced between the two groups (Table 1). Total midazolam and pethidine amounts and FB time were not significantly different between the two groups.

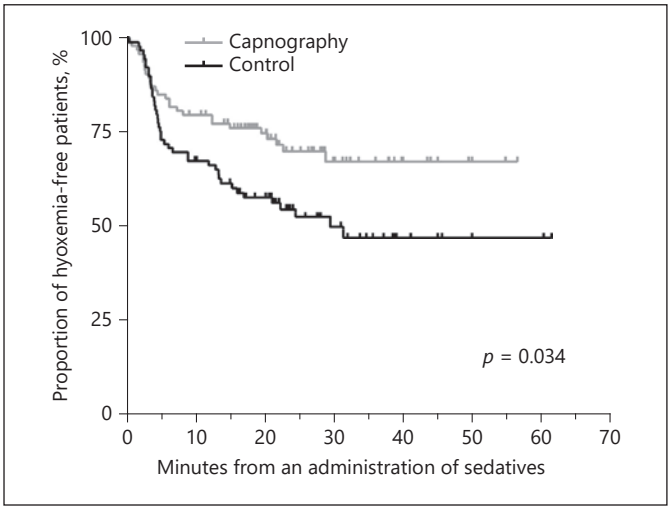

Fig. 2. Kaplan-Meier curves for hypoxemia event-free patients during flexible bronchoscopy. Horizontal axis shows time (min) from administration of sedatives. Completion of bronchoscopy examination was censored. The Gehan-Breslow-Wilcoxon test shows a *p* value of 0.034 and a hazard ratio of 0.56 (95% CI, 0.35–0.91).

Incidence of Hypoxemia

Hypoxemia, defined as at least one episode of SpO_2 < 90%, was observed in 27 (29%) and 42 (46%) patients in the capnography and control groups ($p = 0.014$), respectively, resulting in an absolute risk difference of −17.4% (95% confidence interval [CI], −31.1 to −3.7) (Table 2).

Table 1. Demographic, clinical, and procedural characteristics of patients

Variables	Capnography group (n = 94)	Control group n = 91)	p value
Age (mean ± SD), years	67.1±11.0	66.2±13.4	0.590
Male sex, n (%)	57 (61)	57 (63)	0.780
Body mass index (mean ± SD)	22.3±3.7	22.1±3.8	0.744
Smoking (current and ex), n (%)	56 (60)	58 (64)	0.561
Regular narcotics, n (%)	15 (16)	18 (20)	0.497
Alcohol abuse, n (%)	10 (11)	6 (7)	0.328
Liver disease, n (%)	8 (9)	8 (9)	0.946
Renal disease, n (%)	25 (27)	19 (21)	0.361
COPD, n (%)	16 (17)	15 (16)	0.922
ILD, n (%)	9 (10)	8 (9)	0.854
SAS, n (%)	0 (0)	1 (1)	0.492
ASA physical status classification, n (%)			0.873
1	7 (7)	8 (9)	
2	84 (89)	81 (89)	
3	3 (3)	2 (2)	
Indications for FB, n (%)			
Lung mass	55 (59)	52 (57)	0.851
Pulmonary infiltrates	9 (10)	9 (10)	0.942
Suspected ILD	7 (7)	5 (5)	0.590
Endobronchial evaluation	4 (4)	5 (5)	0.744
Lymph nodes evaluation	19 (20)	20 (22)	0.770
Type of procedure, n (%)			
TBB and brushing with GS	65 (69)	59 (65)	0.533
Brushing	1 (1)	3 (3)	0.363
TBB	8 (9)	9 (10)	0.745
EBB	1 (1)	4 (4)	0.206
EBUS-TBNA	19 (20)	19 (21)	0.911
Baseline vital signs			
Heart rate (mean ± SD), beats/min	75.8±12.6	77.0±14.2	0.557
Systolic blood pressure (mean ± SD), mm Hg	127.1±18.9	126.0±18.8	0.684
Oxygen saturation (mean ± SD), %	96.9±1.5	96.8±1.5	0.767
Initial amount of midazolam (mean ± SD), mg	2.1±0.8	2.2±0.9	0.685
Total amount of midazolam (mean ± SD), mg	2.9±1.5	3.0±1.4	0.842
Initial amount of pethidine (mean ± SD), mg	20.8±4.5	21.2±5.3	0.576
Total amount of pethidine (mean ± SD), mg	30.9±6.7	31.3±7.2	0.734
Procedure time (mean ± SD), min	28.3±11.3	27.4±11.6	0.587

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; EBB, endobronchial biopsy; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration FB, flexible bronchoscopy; GS, guide sheath; ILD, interstitial lung disease; SAS, sleep apnea syndrome; SD, standard deviation; TBB, transbronchial biopsy.

Assessment of hypoxemia events, including severe episodes, was performed by Kaplan-Meier curves plotted from the time of sedative administration to hypoxemic events (Fig. 2). After exclusion of 3 patients with missing time course data during FB, the Gehan-Breslow-Wilcoxon test showed a hazard ratio of 0.56 (95% CI, 0.35–0.91; p = 0.034).

Vital Parameters

A summary of vital parameters are presented in Table 2. Duration of hypoxemia (SpO_2 <90%) was significantly shorter in the capnography group than the control group (20.4 vs. 41.7 s, p = 0.029; mean difference, −21.2 s; 95% CI, −40.3 to −2.2). Severe hypoxemic events (SpO_2 < 85%) were less frequently observed in the capnography group (16 [17%] vs. 29 [32%]; p = 0.019; absolute risk dif-

Table 2. Events with abnormal vital signs during diagnostic flexible bronchoscopy under sedation

Variables	Capnography group (n = 94)	Control group (n = 91)	Absolute differences	95% CI	p value
Primary outcome					
Hypoxemia (SpO_2 <90%), n (%)	27 (29)	42 (46)	−17.4%	−31.1 to −3.7	0.014
Secondary outcomes					
Duration of hypoxemia (mean ± SD), s	20.4±39.4	41.7±84.2	−21.2 s	−40.3 to −2.2	0.029
Severe hypoxemia (SpO_2 <85%), n (%)	16 (17)	29 (32)	−14.8%	−27.1 to −2.6	0.019
Lowest SpO_2 value (mean ± SD), %	90.5±5.1	87.6±7.3	2.9%	1.0 to 4.7	0.002
Hypotension (sBP <90 mm Hg), n (%)	2 (2)	1 (1)			1.000
Bradycardia (HR <50 beats/min), n (%)	2 (2)	1 (1)			1.000

CI, confidence interval; HR, heart rate; SpO_2, pulse oximeter oxygen saturation; sBP, systolic blood pressure; SD, standard deviation.

ference, −14.8%; 95% CI, −27.1 to −2.6). Mean lowest SpO_2 value was significantly higher in the capnography group (90.5 vs. 87.6%; p = 0.002; mean difference, 2.9%; 95% CI, 1.0–4.7). Minimum and interquartile ranges of lowest SpO_2 were 76% (88–94%) and 62% (83–93%) in the capnography and control groups, respectively. Apnea events occurred in 44 (47%) and 40 (44%) patients in the capnography and control groups, respectively (p = 0.479). Hypotension and bradycardia occurred in 2 patients in the capnography group and 1 patient in the control group. Bradycardia occurred in 2 patients in the capnography group and 1 patient in the control group as well. None of the patients developed massive bleeding or pneumothorax in this study population.

Interventions against Apnea or Hypoxemia

The most frequent intervention against apnea or hypoxemia episodes was increased O_2 flow (45 [48%] and 42 [46%] patients in the capnography and control groups, respectively), followed by the chin-lift/jaw-thrust maneuver (14 [15%] and 8 [9%] patients in the capnography and control groups, respectively) (Table 3). There were no patients requiring intubation, anesthesiology assistance, or termination of FB in the study population.

Patient Tolerance of FB

A total of 78 patients answered the questionnaire after FB (Table 4). There were no significant differences between the two groups regarding FB-associated discomfort (21 vs. 30 mm by a visual analog scale, p = 0.087), memory during FB (p = 0.302), or consent for re-examination by FB (p = 0.952).

Table 3. Interventions for apnea or hypoxemia episodes in the capnography and control groups

Intervention	Capnography group, n	Control group, n
Increased O_2 supply	45	42
Chin-lift/jaw-thrust	14	8
Stimulation	4	7
Nasal airway	1	0
Oral suction	0	2
Bag-mask ventilation	0	1
Intubation	0	0
Procedure discontinuation	0	0

False Apnea Alarms by Capnography

The independent observer detected a total of 83 false apnea alarms in 185 patients by capnography (Table 5), which ranged between 0 and 3 per FB procedure. The main reason for false apnea alarms by capnography was continuous suction in mouth or trachea with a bronchoscope.

Discussion

The current prospective, randomized controlled study revealed that end-tidal capnography reduced the risk of hypoxemia during FB in sedated, nonintubated patients. Although hypoxemic events during FB were observed in 46% of the patients in the standard monitoring group, only 29% of patients in the capnographic monitoring group experienced these events.

Table 4. Patient tolerance and perception of flexible bronchoscopy

	Capnography group (n = 40)	Control group (n = 38)	p value
Discomfort score (VAS [mean ± SD]), mm	21±22	30±24	0.087
Memory during FB[a], n (%)			0.345
Remember	3 (8)	6 (16)	
Partially remember	9 (23)	5 (13)	
Not remember	28 (70)	24 (63)	
Consent to re-examination by FB if needed, n (%)	33 (83)	28 (74)	0.346

VAS, visual analog scale using a horizontal 100-mm-long line between 0 for no discomfort and 100 for worst possible discomfort; FB, flexible bronchoscopy.

[a] Three patients in the control group did not respond to the question on memory during the procedure.

Table 5. False apnea alarms by capnography monitoring

	False apnea alarms (n = 83)
Mean false alarms per FB (range), n	0.45 (0–3)
Cause of false alarms, n (%)	
Continuous suction with bronchoscope	72 (87)
Oral suction with suction catheter	5 (6)
Disconnection or obstruction of sample line	6 (7)

FB, flexible bronchoscopy.

The current study clearly demonstrated that capnography provided a clinical benefit for safe respiratory monitoring reflected by not only a reduction in the frequency of hypoxemic events but also shorter hypoxemia duration. Furthermore, the SpO_2 decline was milder in the capnographic monitoring group. These results might be due to earlier detection of apnea episodes by capnography. Certainly, pulse oximetry demonstrates high correlation with arterial gas analysis and is widely used in various clinical settings as an indispensable device for monitoring oxygenation. However, pulse oximetry might be a late indicator of hypoventilation [10]. The decline in SpO_2 might be delayed especially in sedated patients receiving supplemental oxygen [11, 12]. In a previous study, we found that the median delay between the onset of an apnea episode and a significant SpO_2 decline was 31 s [7]. End-tidal capnography alerts of apnea episodes in real time in the form of a visual line and by setting off an alarm, which allows for the recognition of the apnea episodes earlier than pulse oximetry and prompts performance of appropriate corrective measures such as increasing supplemental oxygen flow or chin-lift/jaw-thrust maneuver. Additionally, the questionnaire in the current study revealed that patient tolerance to FB was good and that there were not significant differences in tolerance or memory during FB between the two groups. These findings suggest that interventions such as chin-lift/jaw-thrust maneuver or stimulation by waking up patients did not worsen patient tolerance.

The results of this study suggest end-tidal capnography as a potential appropriate practical option for safe monitoring during FB. Chest wall impedance, albeit commonly used to monitor chest movement in clinical practice, might fail to detect apnea episodes secondary to airway obstruction [8] because respiratory effort remains during obstructive apnea, which can lead to a false negative in apnea detection [13]. In contrast, end-tidal capnography can even detect apneas secondary to airway obstruction [14–16] by direct assessment of the existence of air flow. Furthermore, transcutaneous capnography is currently in use for long-term respiratory monitoring during procedures such as sleep studies [17]. However, response time in transcutaneous capnography is too long for early detection of apnea episodes [18, 19]. A benefit of end-tidal capnography in detecting hypoventilation in nonintubated patients under sedation was reported during monitored anesthesia care [20], emergency settings [21], and percutaneous transhepatic cholangiodrainage [22], with comparison to oxygen saturation or chest physical assessment. Conversely, the benefit of capnographic monitoring during gastrointestinal endoscopy remains controversial. Although the utility of capnography in detecting apnea was shown in colonoscopy by comparison with clinical assessment and pulse oximetry [23], the clinical benefit of preventing hypoxemic events during en-

doscopy [24, 25] and endoscopic retrograde cholangiopancreatography [26] was not shown. One reason for contradictory results between studies at gastrointestinal endoscopy and FB settings in reducing hypoxic events might be the patient position. In the present study, all patients underwent FB in the supine position, whereas a usual patient position for gastrointestinal endoscopy is the lateral decubitus position. Obstructive apnea tends to occur in the supine position because muscle relaxation by sedation causes tongue and other structures in the throat to block the airway [27]. As shown in Table 3, about 12% of patients (n = 23) recovered from hypoxemic events by the chin-lift/jaw-thrust maneuver or placement of nasal airway, implicating that obstruction of the upper airway occurs frequently in sedated patients in the supine position during FB. The benefit of capnography for the patients undergoing FB in the sitting or lateral position should be evaluated in further investigations.

In addition to the benefits of capnography, the present study revealed that the capnography device led to frequent false alarms for apnea. The most common cause of false alarms was continuous suctioning. Although sputum should be suctioned for adequate observation of endobronchial findings and successful completion of bronchoscopy, continuous suctioning of endobronchial sputum or secretion in oral cavity prevents the capnography device from sampling the expired air. Therefore, apnea alarms from capnography should be interpreted with caution in clinical use.

The current study has several limitations. First, no validated scale was used for objective measurement of sedation depth. Although the bronchoscopy team aimed at titrating the level of sedation to a moderate level using verbal assessment according to the ASA criteria, it remains possible that the sedation level might be slightly different between the two groups. In addition, the sedation level in this study might be deeper than moderate level because the incidence rate of hypoxemia in the control group was higher than that reported in previous studies [28, 29]. Second, it remains possible that not all hypoxemia events were sedation-related. Hypoxemia can result from a number of conditions including airway mucus obstruction, bleeding or pneumothorax related to procedures, and obstruction of air flow by the bronchoscope. However, there were no cases of massive bleeding or pneumothorax in the study group, and patients who were planned to undergo bronchoalveolar lavage, which can cause frequent hypoxemia events, were excluded before entering into the study. Third, one of the investigators as an independent observer and the bronchoscopy team members were not blinded to the patient assignment. Thus, there might be a bias in the assessment of apnea episodes.

Conclusions

Our data suggested that, together with standard monitoring, end-tidal capnographic monitoring could reduce the incidence and duration of hypoxemia during FB in sedated nonintubated patients. However, caution is warranted regarding capnography-related false apnea alarms in clinical use.

Disclosure Statement

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