Original Article

End-tidal capnographic monitoring during flexible bronchoscopy under fentanyl and midazolam sedation

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Background: Bronchoscopic examination including endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is well established for lung cancer diagnosis and staging. Sedation using fentanyl and midazolam is recommended during bronchoscopic examinations. Meanwhile, inadvertent oversedation is a clinical problem. The objective of this research was to estimate the frequency of apnea episodes by end-tidal capnography under fentanyl and midazolam sedation during bronchoscopy.

Methods: Eighty-five patients were enrolled retrospectively between August 2017 and March 2018 at Okayama Medical Center. Apnea was defined as the cessation of airflow for more than 10 seconds. We reviewed medical records, including capnographic data, by cap-ONE YG-227T (NIHON KOHDEN, Tokyo, Japan) during flexible bronchoscopy under fentanyl and midazolam sedation.

Results: Patients received 49.4±20.6 μg of fentanyl [mean ± standard deviation (SD)] and 4.35±2.0 mg of midazolam (mean ± SD). The patients included 52 males and 33 females; the median age was 71 (range, 31–88) years were enrolled. Apnea episodes were recorded (median duration 18 seconds) in 85 patients (100%). Prolonged apnea episodes with more than 30 seconds occurred in 56 patients (65.8%). Furthermore, the median time was 32 (range, 5–102) seconds whose delay between the onset of an apnea episode and decline in the SpO_2 level of ≥4% from baseline.

Conclusions: End-tidal capnography, cap-ONE YG-227T was effective for detecting the occurrence of apnea in patients undergoing a bronchoscopic examination under fentanyl and midazolam sedation. Monitoring might be useful for preventing inadvertent oversedation.

Keywords: End-tidal capnography; bronchoscopic examination; fentanyl and midazolam sedation

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Introduction

Sedation is widely used in the USA and Europe by pulmonary physicians for bronchoscopic examinations (1-5). Bronchoscopic examination including endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a useful tool for lung cancer diagnosis and staging (6-8). The American College of Chest Physicians recommends the use of benzodiazepine/opiate combination

during bronchoscopy for sedation (9). British Thoracic Society guidelines in adults also recommend using these drugs for diagnostic flexible bronchoscopy (10). We showed previously, for the first time, that sedation with fentanyl and midazolam was safe and effective during bronchoscopic examinations in Japanese patients (11,12). Furthermore, we reported that sedation with fentanyl and midazolam facilitated the diagnosis of peripheral pulmonary lung cancers (13). Meanwhile, inadvertent oversedation can be a clinical problem. Forster *et al.* (14). reported that oversedation using midazolam and diazepam led to deep sedation and apnea episodes. Moderate sedation is necessary for safe bronchoscopy examination to prevent apnea and oxygen desaturation. End-tidal capnography monitored the occurrence of apnea episodes at a high frequency in patients during a bronchoscopic examination under midazolam sedation in a clinical setting (15,16). Here, we retrospectively revealed the occurrence of apnea episodes during bronchoscopic examinations under fentanyl and midazolam sedation by end-tidal capnography. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1009).

Methods

Patient population and study design

Eighty-five patients were enrolled in this retrospective study between August 2017 and March 2018 at Okayama Medical Center. They were surely consecutive all cases who undergo bronchoscopy in the hospital. We reviewed medical records, including capnographic data, by cap-ONE YG-227T (NIHON KOHDEN, Tokyo, Japan) during flexible bronchoscopy under fentanyl and midazolam sedation. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of the National Hospital Organization, Okayama Medical Center on October 25, 2017 (approval No. H29-RINKEN-ZINSOKU-65), and individual consent for this retrospective analysis was waived.

Bronchoscopy procedure

Bronchoscopic examination (one of the following: P260F, BF-260, 6C260, 1T260, P290, or UC260 Bronchovideoscope; Olympus Corp., Tokyo, Japan) was performed. All bronchoscopic procedures were performed on an inpatient basis. A total of 5 mL of 2% lidocaine was sprayed into the pharynx, and 15 mL of 2% lidocaine was administered through the channel during the procedure. Before each procedure, we sprayed 5 mL of 2% (w/v) lidocaine into the pharynx. The bronchoscope was inserted orally under conscious sedation. When fentanyl is administered with other sedatives, an initial dose of 25–50 μg is recommended with additional doses of 25 μg, as required, until the desired effect is achieved. The recommended dose of midazolam is 0.01–0.1 mg/kg (12,13). As Japanese are, on average, physically smaller than Westerners, we selected a lower dose of fentanyl.

Patient monitoring

Patients were monitored without the presence of an anesthesiologist by electrocardiography, pulse oximetry, and blood pressure monitoring every 5 min. The oxygen flow rate was increased when the SpO_2 was less than 90% though a nasal cannula. It was defined as clinically significant that the SpO_2 level of ≥4% from baseline decreased. The cap-ONE YG-227T monitoring device (NIHON KOHDEN) measures the concentrations of carbon dioxide in expired air continuously (*Figure 1A*). When the capnogram showed a flat line (*Figure 1B*), the clinician made sure that the sample port was not disconnected. This device was used for end-tidal capnographic monitoring (*Figure 1C*). The cap-ONE bite block (YG-227T; NIHON KOHDEN, Tokyo, Japan) can deliver oxygen while measuring mainstream $EtCO_2$ during bronchoscopic procedures. In this study, apnea episodes were defined as the cessation of airflow for more than 10 seconds. We monitored the duration of the apnea episodes and the time delay between the onset of an apnea episode and a ≥4% SpO_2 decline.

Statistical analyses

We performed statistical analyses by Microsoft Office Excel 2010 (Microsoft Japan Corp., Tokyo, Japan). Between-group comparisons were made using unpaired Student's *t*-tests. P values <0.05 were considered statistically significant.

Results

The enrolled patients included 52 males and 33 females. Their median age was 71 (range, 31–88) years. The comorbidities and diagnosis with bronchoscopy were as follows: lung cancer (n=39), infectious disease (n=19),

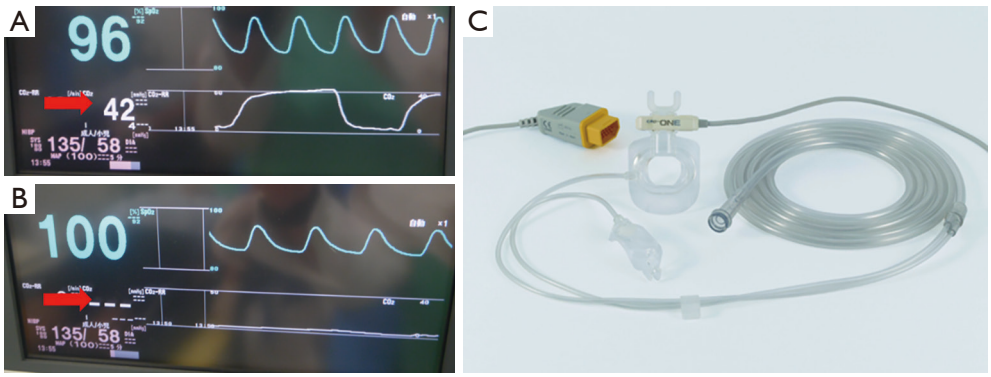

Figure 1 The monitoring device. (A) The monitoring device (cap-ONE YG-227T; NIHON KOHDEN, Tokyo, Japan) was used to measure the concentrations of carbon dioxide in expired air continuously. (B) The capnogram showed a flat line. (C) The monitoring device used was a cap-ONE YG-227T (NIHON KOHDEN). The red arrows indicate the concentrations of carbon dioxide.

Table 1 Patient characteristics

Characteristic	Value
Number of patients	85
Male/female, n	52/33
Median age [range], years	71 [31–88]
BMI, mean ± SD, kg/m^2	21.06±5.41
Comorbidities and diagnosis, n (%)	–
Lung cancer	39 (45.8)
Infectious disease	19 (22.3)
ILD	5 (5.88)
Other	22 (25.8)
Procedures, %	–
TBB	63.5
Brushing	44.7
Washing	21.1
EBUS-TBNA	8.2
Baseline SpO_2, mean ± SD, %	96.6±1.49
Minimum SpO_2, median [range], %	88 [62–94]
Maximum O_2 flow, median [range], L/min	4 [0–10]
Total dose of fentanyl, mean ± SD, μg	49.41±20.6
Total dose of midazolam, mean ± SD, mg	4.35±2.0

BMI, body mass index; SD, standard deviation; ILD, interstitial lung disease; TBB, transbronchial biopsy; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Table 2 Apnea profiles (n=85)

	Value [range]
Apnea episodes per patient, median [range], n	13 [1–48]
Duration of the apnea episodes, median [range], seconds	18 [11–161]
Maximum SpO_2 decline, %	36
Time delay between the onset of an apnea episode and SpO_2 decline of ≥4%, median [range], seconds	32 [5–102]

interstitial lung disease (n=5), and other (n=22). The bronchoscopic examination used (transbronchial biopsy, bronchial brushing, bronchial washing, or EBUS-TBNA) is shown in *Table 1*. The baseline SpO_2 level was 96.6%±1.49% (mean ± SD). The patients received 49.4±20.6 μg of fentanyl (mean ± SD) and 4.35±2.0 mg of midazolam (mean ± SD). The patients' apnea profiles are listed in *Table 2*. Apnea episodes were recorded in 85 patients (100%). The number of apnea episodes per patient was 13 (range, 1–48). The duration of the apnea episodes was 18 (range, 11–161) seconds. Furthermore, the median time was 32 (range, 5–102) seconds, delayed between the onset of an apnea episode by the cap-ONE YG-227T monitoring device (NIHON KOHDEN) and decline in the SpO_2 level of ≥4% from baseline. The apnea episodes for more than 30 seconds occurred in 56 patients (65.8%). As shown in Table S1, there were no significant differences in baseline SpO_2 levels

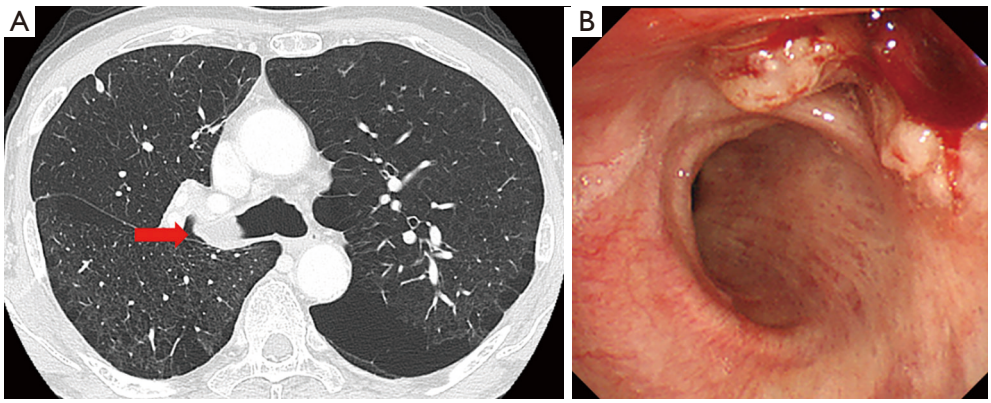

Figure 2 A representative case during bronchoscopy monitored by end-tidal capnography. (A) A 68-year-old man with pulmonary emphysema had a nodule in the right lung. (B) We performed a transbronchial biopsy of the nodule. The red arrow indicates endobronchial tumor.

between the groups with and without prolonged apnea episodes lasting for more than 30 seconds. The total doses of fentanyl and midazolam were higher in the group with prolonged apnea episodes compared to the group without, although the difference was not statistically significant (fentanyl: 51.78 *vs.* 44.82 μg, P=0.12; midazolam: 4.34 *vs.* 3.96 mg, P=0.74, respectively). A representative case is shown in *Figure 2*; a 68-year-old man with chronic respiratory failure managed by noninvasive positive pressure ventilation had a nodule in the right lung (*Figure 2A*). We performed transbronchial biopsy for the nodule safely under fentanyl and midazolam sedation monitored by end-tidal capnography, while a histopathological examination revealed the presence of a squamous cell carcinoma (*Figure 2B*). More than 50% of the cells stained for programmed cell death ligand-1 (PD-L1).

Discussion

Inadvertent oversedation sometimes causes respiratory depression and oxygen desaturation (17), although sedation is necessary and recommended for bronchoscopic procedures (11-13). It has been published that the nadir on SpO_2 decline could be delayed by 45–60 seconds after an apnea episode (18). The capnographic monitoring allows for the earlier detection of apnea episodes in patients undergoing bronchoscopic examinations under midazolam sedation, more real measurement values of carbon dioxide than pulse oximetry (15,16). In our study, cap-ONE YG-227T (NIHON KOHDEN) detected the occurrence of apnea in patients undergoing a bronchoscopic examination under fentanyl and midazolam sedation. Apnea episodes were recorded in 85 patients (100%), although clinical problems did not occur. A previous report showed that a time was 31 (range, 28–42) seconds (16), delayed between the apnea episode and SpO_2 decline of ≥4%. End-tidal capnography using a cap-ONE YG-227T device (NIHON KOHDEN) revealed that the median time delay between the apnea episode and decline in the SpO_2 level of ≥4% from baseline was 32 (range, 5–102) seconds. This device comprises the mainstream capnometer cap-ONE (TG-980P; NIHON KOHDEN), nasal adapter, oxygen cup, and mouthpiece. The nasal adapter collects exhaled nasal flow into a measurement cell, while the oxygen cup delivers oxygen through the patient's nose and has a sponge to scatter oxygen for accurate CO_2 monitoring (19); thus, the device was effective for detecting the occurrence of apnea. Although the difference was not statistically significant, the total doses of fentanyl and midazolam were more than in the group with prolonged apnea episodes compared to the group without. This device might be useful for preventing apnea episodes and oversedation.

During bronchoscopy, oxygen desaturation occurs at a higher frequency than during other examinations (e.g., esophagogastroduodenoscopy and colonoscopy) (20-22). Pulse oximetry has become the standard of care in endoscopy units around the world. However, pulse oximetry may not adequately reflect hypoventilation, apnea, impending hemodynamic instability, or vasoconstrictive shock. Capnography has emerged as a noninvasive way of measuring patient ventilation that may be especially useful in patients with comorbidities of lung disease during gastrointestinal endoscopy. It is necessary for safe procedural sedation to detect hypoventilation as early as possible (23,24). In the present study, we performed

transbronchial biopsy safely on a patient with lung squamous cell carcinoma with chronic respiratory failure monitored by end-tidal capnography (*Figure 2*), and more than 50% of the cells stained for PD-L1. Lung cancer is the leading cause of cancer-related mortality worldwide (25). Approximately 85% of cases are non-small cell lung cancer (NSCLC), and tissue analysis is key in the treatment of NSCLC (26,27). Many molecule inhibitors induce rapid and deep responses and confer superior disease control compared with standard platinum doublet chemotherapy (28-31). Indications of capnography for advanced lung cancer patients during endoscopic procedures might be of interest. This study has one limitation. We did not see assessment of all subjects with Richmond Agitation-Sedation Scale. This relatively high midazolam and fentanyl doses might be considered as apnea risk factors.

In previous report, sedation depth was analyzed to reveal noninvasive mechanical ventilation—flexible bronchoscopy risk factor (32). It is necessary to be careful for overdose sedation which could cause severe respiratory depression and oxygen desaturation. The other limitation of our study is that it was a small retrospective analysis. A large-scale study based on clinical practice is needed to confirm these findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1009

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1009). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of the National Hospital Organization, Okayama Medical Center on October 25, 2017 (approval No. H29-RINKEN-ZINSOKU-65), and individual consent for this retrospective analysis was waived.

References

1. Pue CA, Pacht ER. Complications of fiberoptic bronchoscopy at a university hospital. Chest 1995;107:430-2.
2. Maguire GP, Rubinfeld AR, Trembath PW, et al. Patients prefer sedation for fibreoptic bronchoscopy. Respirology 1998;3:81-5.
3. Pereira W Jr, Kovnat DM, Snider GL. A prospective cooperative study of complications following flexible fiberoptic bronchoscopy. Chest 1978;73:813-6.
4. Burgher LW. Complications and results of transbronchoscopic lung biopsy. Nebr Med J 1979;64:247-8.
5. Pastis NJ, Yarmus LB, Schippers F, et al. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. Chest 2019;155:137-46.
6. Herth FJ, Eberhardt R, Vilmann P, et al. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax 2006;61:795-8.

7. Yasufuku K, Pierre A, Darling G, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg 2011;142:1393-400.e1.
8. Kinsey CM, Arenberg DA. Endobronchial ultrasound-guided transbronchial needle aspiration for non-small cell lung cancer staging. Am J Respir Crit Care Med 2014;189:640-9.
9. Wahidi MM, Jain P, Jantz M, et al. American College of Chest Physicians consensus statement on the use of topical anesthesia, analgesia, and sedation during flexible bronchoscopy in adult patients. Chest 2011;140:1342-50.
10. Du Rand IA, Blaikley J, Booton R, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax 2013;68 Suppl 1:i1-i44.
11. Minami D, Takigawa N, Watanabe H, et al. Safety and discomfort during bronchoscopy performed under sedation with fentanyl and midazolam: a prospective study. Jpn J Clin Oncol 2016;46:871-4.
12. Minami D, Takigawa N, Kano H, et al. Discomfort during bronchoscopy performed after endobronchial intubation with fentanyl and midazolam: a prospective study. Jpn J Clin Oncol 2017;47:434-7.
13. Minami D, Nakasuka T, Ando C, et al. Bronchoscopic diagnosis of peripheral pulmonary lung cancer employing sedation with fentanyl and midazolam. Respir Investig 2017;55:314-7.
14. Forster A, Gardaz JP, Suter PM, et al. Respiratory depression by midazolam and diazepam. Anesthesiology 1980;53:494-7.
15. Ishiwata T, Tsushima K, Terada J, et al. Efficacy of End-Tidal Capnography Monitoring during Flexible Bronchoscopy in Nonintubated Patients under Sedation: A Randomized Controlled Study. Respiration 2018;96:355-62.
16. Ishiwata T, Tsushima K, Fujie M, et al. End-tidal capnographic monitoring to detect apnea episodes during flexible bronchoscopy under sedation. BMC Pulm Med 2017;17:7.
17. Franzen D, Bratton DJ, Clarenbach CF, et al. Target-controlled versus fractionated propofol sedation in flexible bronchoscopy: A randomized noninferiority trial. Respirology 2016;21:1445-51.
18. Netzer N, Eliasson AH, Netzer C, et al. Overnight pulse oximetry for sleep-disordered breathing in adults: a review. Chest 2001;120:625-33.
19. Chang AC, Solinger MA, Yang DT, et al. Impact of flumazenil on recovery after outpatient endoscopy: a placebo-controlled trial. Gastrointest Endosc 1999;49:573-9.
20. Takimoto Y, Iwasaki E, Masaoka T, et al. Novel mainstream capnometer system is safe and feasible even under CO2 insufflation during ERCP-related procedure: a pilot study. BMJ Open Gastroenterol 2019;6:e000266.
21. Classen DC, Pestotnik SL, Evans RS, et al. Intensive surveillance of midazolam use in hospitalized patients and the occurrence of cardiorespiratory arrest. Pharmacotherapy 1992;12:213-6.
22. Cohen J, Haber GB, Dorais JA, et al. A randomized, double-blind study of the use of droperidol for conscious sedation during therapeutic endoscopy in difficult to sedate patients. Gastrointest Endosc 2000;51:546-51.
23. Stolz D, Kurer G, Meyer A, et al. Propofol versus combined sedation in flexible bronchoscopy: a randomised non-inferiority trial. Eur Respir J 2009;34:1024-30.
24. Lo YL, Lin TY, Fang YF, et al. Feasibility of bispectral index-guided propofol infusion for flexible bronchoscopy sedation: a randomized controlled trial. PLoS One 2011;6:e27769.
25. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
26. Tian S, Wang C, An MW. Test on existence of histology subtype-specific prognostic signatures among early stage lung adenocarcinoma and squamous cell carcinoma patients using a Cox-model based filter. Biol Direct 2015;10:15.
27. Oezkan F, Herold T, Darwiche K, et al. Rapid and Highly Sensitive Detection of Therapeutically Relevant Oncogenic Driver Mutations in EBUS-TBNA Specimens From Patients With Lung Adenocarcinoma. Clin Lung Cancer 2018;19:e879-84.
28. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.
29. Wang Y, Schmid-Bindert G, Zhou C. Erlotinib in the treatment of advanced non-small cell lung cancer: an update for clinicians. Ther Adv Med Oncol 2012;4:19-29.
30. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
31. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in

lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
32. Skoczyński S, Ogonowski M, Tobiczyk E, et al. Risk factors of complications during noninvasive mechanical ventilation -assisted flexible bronchoscopy. Adv Med Sci 2021;66:246-53.

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Supplementary

Table S1 Characteristics of patients with and without more than 30-second apnea episodes

Variable	With apnea episodes	Without apnea episodes	P value
Number of patients	56	29	–
Male/female, n	37/19	15/14	–
Median age [range], years	72 [42–88]	70 [31–84]	–
BMI, mean ± SD, kg/m^2	21.38±4.76	23.02±6.51	–
Comorbidities and diagnosis, n (%)	–	–	–
Lung cancer	25 (44.6)	11 (37.9)	–
Infectious disease	14 (25.0)	5 (17.2)	–
ILD	4 (7.14)	1 (3.8)	–
Other	13 (23.2)	12 (41.3)	–
Procedures, %	–	–	–
TBB	66.0	58.6	–
Brushing	46.4	37.9	–
Washing	21.4	10.3	–
EBUS-TBNA	14.2	6.8	–
Baseline SpO_2, mean ± SD, %	97.0±1.36	96.8±1.73	0.54
Total dose of fentanyl, mean ± SD, μg	51.78±21.41	44.82±18.4	0.12
Total dose of midazolam, mean ± SD, mg	4.34±1.97	3.96±1.48	0.74

Apnea, cessation of airflow for more than 30 seconds; BMI, body mass index; SD, standard deviation; ILD, interstitial lung disease; TBB, transbronchial biopsy; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

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