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ORIGINAL RESEARCH

Pre-apneic capnography waveform abnormalities during procedural sedation and analgesia

Aaron Conway[1,2,6] · Peter Collins[2] · Kristina Chang[2] · Sebastian Mafeld[3] · Joanna Sutherland[4] · James Fingleton[5] · Matteo Parotto[3,7]

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Abstract
Capnography monitoring is recommended for use during procedural sedation. This study examined associations between capnography waveform abnormalities and the onset of apnea. Capnography waveforms from a sample of 102 participants undergoing moderate procedural sedation with bolus doses of midazolam and fentanyl were analyzed using a mixed effects Cox model. Patients were at increased risk of apnea (classified as end-tidal carbon dioxide concentration of zero) while demonstrating a capnography waveform abnormality classified as hypopnea (more than 10% increase or decrease from baseline end-tidal carbon dioxide concentration) (Hazard Ratio 2.14; 95% CI 1.75 to 2.62). Risk of apnea was not increased during capnography waveform abnormalities classified as bradypnea (capnography-derived respiratory rate less than 8 breaths/min) (Hazard Ratio 0.64; 95% CI 0.33 to 1.25). These estimates were similar when apneic episodes were defined as only those that lasted more than 20 s duration. Deciphering which capnography waveform abnormalities should promote intervention (and therefore alarms to signal the event to clinicians) from those that do not is an essential step towards successful implementation of this technology into practice. Our results indicate that using information about the history of previous capnography waveform abnormalities may be a promising solution to assist prediction of apneic episodes.

Keywords Conscious sedation · Capnography · Respiratory depression

1 Introduction

The use of capnography for respiratory monitoring during procedural sedation and analgesia is recommended in guidance produced by anesthesiologist professional organisations for anesthesia in Canada, the United States and Europe [1–3]. Capnography waveforms display carbon dioxide (CO_2) concentrations in expired breath over time to show changes throughout the respiratory cycle. Abnormal capnography waveforms assist in the detection and diagnosis of specific conditions, such as partial airway obstruction and apnea. For example, significantly decreased capnography waveform amplitude (i.e. the height of the waveform) would indicate hypoventilation. An absent capnography waveform would signal that the patient is apneic, which could be either due to complete airway obstruction or central respiratory depression. Immediate investigation of the cause of this particular capnography waveform abnormality with subsequent prompt initiation of management strategies is particularly important in the context of procedural sedation. Evidence from multiple randomized controlled trials has shown that

✉ Aaron Conway
aaron.conway@utoronto.ca

1 Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Canada

2 Peter Munk Cardiac Centre, University Health Network, Toronto, Canada

3 Toronto General Hospital, University Health Network, Toronto, Canada

4 Department of Anaesthesia, Coffs Harbour Health Campus, Coffs Harbour, Australia

5 Medical Research Institute of New Zealand, Wellington, New Zealand

6 School of Nursing, Queensland University of Technology, Brisbane, Australia

7 Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada

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applying interventions to either stimulate breathing or restore airway patency after detection of short periods of apnea (10–30 s) from capnography monitoring improved patient safety by reducing risk of hypoxemic events (RR 0.71; 95% CI 0.56–0.91) [4].

Deciphering which capnography waveform abnormalities deserve clinicians' attention (and therefore alarms to signal events) from those that do not is an essential step towards successful implementation of this technology into practice. Recently it was shown in a study of emergency department deep sedation that having an abnormal end-tidal carbon dioxide measurement increased risk for an episode of apnea within subsequent 30, 60 and 90 s periods [5]. It should be noted, however, that methods to achieve procedural sedation vary greatly across the large number of clinical contexts in which it is used. For example, medications other than propofol are more commonly used when moderate sedation is the intended target. In this situation, it is more common to use bolus doses of benzodiazepines and opioids [6, 7]. We investigated capnography waveform abnormalities preceding apnea during moderate procedural sedation.

2 Methods

This is a secondary analysis of a prospective observational study. The primary aim of the observational study was to identify unique subgroups of patients based on their physiological responses to sedation (i.e. hypoventilation and apneas). Results are reported elsewhere [8]. Written informed consent was obtained prior to participation. The study was approved by human research ethics committees at the participating institutions approved the study (UCH HREC 1614; SVHAC HREC 16/26; QUT 1600000641). It was undertaken in accordance with the Australian National Statement on Ethical Conduct in Human Research [9] and it was registered at the Australia and New Zealand Clinical Trials Registry (ACTRN12616001132437).

2.1 Participants

Consecutive adult patients scheduled to undergo an elective procedure in the cardiac catheterization laboratory with moderate sedation were invited to participate. Exclusion criteria were cognitive impairment (due to inability to provide informed consent) or inability to understand and speak English (if an interpreter was unavailable).

2.2 Sedation

Bolus doses of intravenous midazolam and fentanyl were administered by nurses, and prescribed by a cardiologist. Routine clinical monitoring was applied by nursing staff. This included cardiac rhythm monitoring with 5-lead electrocardiography, non-invasive blood pressure measurements taken every 5–10 min or more frequently as desired by clinical staff as well as continuous pulse oximetry monitoring. Capnography monitoring was undertaken using the Respironics LoFlo sidestream CO_2 sensor. When flow rates higher than 5 L/min were used, a CO_2 sampling cannula was inserted into the sideport of an oxygen face-mask. Otherwise a nasal cannula with separate lines for delivering oxygen and sampling CO_2 was used. The capnography waveform was displayed on the main physiological monitoring screen. The standard algorithm integrated in the LoFlo capnometer was used to trigger a visible alert reading 'No breaths detected' after 10 s of apnea but no other audible or visual alerts were set for capnography waveform abnormalities. This study was observational. No restrictions or specific instructions were provided to clinicians regarding how they should react to detection of any capnography waveform abnormalities as part of the research protocol. Nurses at the data collection sites were trained in advanced life support and also undergo re-certification annually. Airway management training is routinely provided at these courses.

2.3 Data collection

Demographic data and clinical characteristics were collected from medical records and self-report questionnaires prior to procedures. Intra-procedural data were collected in real-time by the researcher who was present in the procedure room. Direct observation of the participant was required to record the timing of sedation administrations and any interventions applied by sedation providers.

2.3.1 Capnography

Respiratory rate and $PetCO_2$ values displayed by the Respironics LoFlo device were used to record the onset and offset times for capnography waveform abnormalities in real-time. Each second of the participant's procedure was classified from these recordings into states termed 'normal breathing', 'apnea' (no waveform or CO_2 concentration of 0), 'bradypnea' (when the capnography-derived respiratory rate was less than 8) or 'hypopnea' (when the $PetCO_2$ concentration was increased or decreased more than 10% from the baseline value). Classifications were based on a definition for capnography waveform abnormalities devised previously [10]. Waveform abnormalities arising from reasons other than respiratory depression (i.e. talking or dislodged sampling cannula) were coded as 'normal breathing'. Baseline measurements of $PetCO_2$ were recorded prior to any sedation administration but after oxygen supplementation was commenced.

2.4 Statistical analysis

Analyses were conducted with `R`, a language and environment for statistical computing [11], using primarily the `coxme` [12] package. Data and statistical code can be accessed in this NextJournal (https://nextjournal.com/aaronconway/pre-apneic-capnography-waveform-abnormalities-during-procedural-sedation-and-analgesia/) notebook.

The Mixed effects Cox model, sometimes called a frailty model, provides a statistical framework to analyze recurrent events data often encountered in a clinical setting [13]. In recurrent events data it is reasonable to assume independence between times to events of different patients, however it is expected that times to events recorded on a single patient are correlated. The mixed effects Cox model can induce dependence among times to events belonging to a single patient by the addition of a random intercept term per patient in the sample.

A mixed-effects Cox model was used to model the onset of apneic episodes in the sample of participants. The model for the (ith) patient at time (t) can be stated mathematically as

$$\lambda_i(t) = \lambda_0(t)e^{\beta' x_i(t)+b' z_i}, \quad (1)$$

$$b \sim N(0, \sigma_b^2), \quad (2)$$

where λ_i is the hazard for the (ith) patient, λ_0 is the unspecified baseline hazard, $x_i(t)$ is the vector of time-dependent covariates, z_i the scalar random effect, β is the vector of fixed effects coefficients, and b is the random effects coefficient. The random effect coefficient b is assumed to be normally distributed with mean zero and fixed variance σ_b^2. The normally distributed random effect across patients is included to induce dependence among recurrent events observed in a single patient as well as to account for unobserved heterogeneity between patients.

Time-varying predictors included in the model were the respiratory state, the total number of apneic episodes experienced, and the total number of sedation doses administered (referred to from now on simply as sedation dose). Respiratory state is a categorical predictor with levels corresponding to normal, hypopneic, bradypneic, and apneic breathing. The respiratory state classification were created by categorizing end-tidal CO_2 ($PetCO_2$) and respiratory rate (RR) waveforms according to the scheme in Table 1. Time-varying predictors are measured on a scale of 1 s/measurement.

2.4.1 Sensitivity analysis

To assess whether results were sensitive to changes in the definition of an apneic episode, we redefined an apneic episode to be 20 consecutive seconds or longer of apneic breathing observed in a patient for sensitivity analysis. An artifact of using this definition is that apnea will be among the respiratory states in the time-varying covariates x_i and will necessarily have a negative coefficient (a patient exhibiting a state of apneic breathing that is not part an apneic episode cannot be at risk for an apneic episode). This phenomenon does not affect the other coefficient estimates so we simply ignore estimates corresponding to the state of apneic breathing in the analysis.

Table 1 Capnography waveform abnormality classifications

Abnormality	Classification
$PetCO_2 = 0$	Apnea
$PetCO_2$ less or more than 10% difference from baseline	Hypopnea
Respiratory rate less than 8 breaths/min	Bradypnea

$PetCO_2$ end-tidal carbon dioxide concentration

3 Results

3.1 Participant characteristics

We recruited 114 of the 129 (88%) patients who were screened over the study period (August 2016 to May 2018). Subsequent exclusions were five participants (4.3%) who did not receive sedation during their procedure, four (4%) participants due to capnography equipment malfunctions and 3 (2.6%) participants due to researcher unavailability for data collection. For 3 of the 4 participants who were not included due to capnography malfunction, capnography was not used at all during the procedure because of the malfunction. The other participant was monitored with capnography for the first 20 min, but at this time the $PetCO_2$ measurements dropped out completely. The malfunction could not be corrected by clinical staff at the time. As the specific cause of this malfunction was not able to be determined, we decided not to include the data that was recorded prior to the malfunction. The final sample comprised 102 participants. Summary statistics of the sample are provided in Table 2. Oxygen flow rate was increased from baseline for 3 (3%) of the participants. For two of these participants, the flow rate was increased from 3 to 5 L/min using the same nasal cannula oxygen administration device. Changes in $PetCO_2$ measurements were observed both prior to and after changing the flow rate. The flow rate for the other participant was changed from 3 L/min via nasal cannula to 6 L/min via face mask.

Table 2 Participant characteristics

Characteristic	Mean (SD) or frequency (%)
Age	72.95 (11.28)
Female	35 (34)
Body mass index	28.74 (5.36)
Diagnosis of obstructive sleep apnea	25 (25)
Charlson comorbidity index	5.61 (2.40)
Procedures	
Permanent pacemaker implant or generator change	62 (61)
Implantable cardioverter defibrillator implant or generator change	10 (10)
Cardiac resynchronisation therapy	5 (5)
Atrial flutter ablation	8 (8)
Other arrhythmia ablation	13 (13)
Diagnostic electrophysiology study	3 (3)
Loop recorder implant	1 (1)
ASA classification status	
Class I	11 (11)
Class II	52 (51)
Class III	32 (31)
Class IV	7 (7)
Sedation	
Midazolam total dose (mg)	2.05 (1.10)
Fetanyl total dose (mcg)	55.40 (24.26)

3.2 Distribution of apneic episodes

Of the 102 patients, 64 participants experienced apnea during the procedure. When considering apneic episodes of any duration, there were 505 events for the analysis, including censored times. There were relatively few episodes of bradypnea in the sample compared to episodes of normal and hypopnea; 52 occurrences versus 792 and 686, respectively. Among patients who had experienced apneic episodes, the median number of episodes was 7 with an interquartile range (IQR) of (4.0, 9.5). The times to apneic events are shown in Fig. 1. The correlation coefficient between the total number of sedation doses administered and the cumulative number of apneic episodes was 0.0626. The low degree of collinearity between these predictors allows us to consider their effects in the models independently from each other.

3.3 Mixed effects Cox model

Point-estimates of the hazard ratios (HR) in the mixed effects Cox models along with their 95% Wald confidence intervals are listed in Table 2. The baseline hazard in the model corresponds to a patient who has received an initial dose of sedation, has not yet experienced an apneic episode, and is exhibiting normal breathing.

In the primary model, where we consider apneic episodes of any duration, the HR of hypopnea and bradypnea are 2.14 (95% CI 1.75 to 2.62) and 0.64 (95% CI 0.33 to 1.25), respectively. Each additional sedation dose is associated with an increase in HR of 2.86 (95% CI 2.15 to 3.81) and each additional apneic episode is associated with an increase in HR of 1.05 (95% CI 1.01 to 1.08). The 95% confidence intervals for the random effect term for participants ranged from 0.04 to 23.32. This means there was a large amount of variation not accounted for by the fixed effects included in the model. In the sensitivity analysis, parameter estimates were largely unaffected by changing the definition of apnea to consider only episodes of at least 20 s duration (Table 3).

Figure 2 provides a visualization of how the risk of an apneic episode dynamically changed during the procedure for an illustrative patient in the sample. Predictions from the first model were used. The HR at the beginning of the procedure was 5.6 [4.2, 7.5] due to the random effect, indicating that this patient was innately at a higher risk for apnea when compared to others in the sample. Upon administration of additional sedative, the HR increases to 12.0 [7.3, 19.5] and the overall HR remains elevated throughout the rest of the procedure. There is a greater extent of uncertainty in HR during states of bradypnea due to the small number of occurrences in the sample. Model predictions for risk of apnea during procedures for all participants in the study can be viewed at this webpage (https://aconway.dev/pre-apneic).

4 Discussion

We found that risk of apnea was increased when $PetCO_2$ concentration deviated from the baseline value by more than 10% (termed a state of hypopnea). In addition, the risk of apnea increased with each additional sedation dose and, to a smaller extent, each episode of apnea. These results could be interpreted that clinicians need to be aware of the potential increased likelihood of an impending apneic event when the $PetCO_2$ concentration deviates from the baseline value. How this information can best be communicated to, and then used by, clinicians are important considerations. Incorporating alerts about changes in $PetCO_2$ concentrations into capnography monitoring devices would be one potential course of action. In fact, some monitor alarms already take such information into account. For example, the Integrated Pulmonary Index (IPI), which is a mathematically-derived index of physiological parameters related to the assessment of respiratory function, assigns lower scores (indicating worse respiratory function) in situations where the $PetCO_2$ concentration is reduced [14]. As such, our results do provide some additional justification for existing situations where clinicians are already receiving alerts when $PetCO_2$

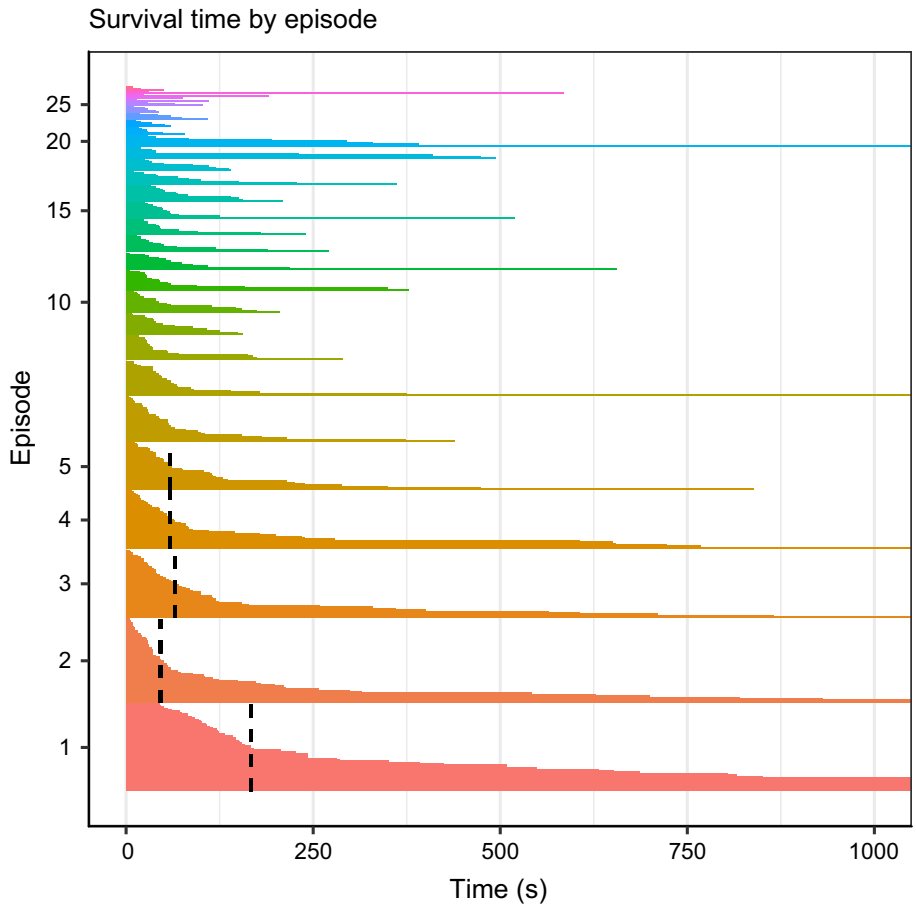

Fig. 1 Times to apneic episodes, omitting censored times. Dashed vertical lines indicate the median time to apneic event (i.e. time before the next episode of apnea) in each group

Table 3 Hazard ratio (HR) estimates and their 95% confidence intervals

	Model 1			Model 2		
	HR	95% CI		HR	95% CI	
		Lower	Upper		Lower	Upper
Hypopnea	2.14	1.75	2.62	2.14	1.75	2.61
Bradypnea	0.64	0.33	1.25	0.64	0.33	1.24
Apnea	NA	NA	NA	0.17	0.04	0.70
Sedation dose	2.86	2.15	3.81	2.75	2.07	3.67
Number of apneic episodes	1.05	1.01	1.08	1.05	1.01	1.08

Model 1 is the model considering apneic episodes of any duration. Model 2 is the model considering only apneic episodes of at least 20 s in length

CI confidence interval

concentration is higher or lower than the baseline value instead of only when apnea has already occurred.

However, it is essential that the potential negative consequences of introducing additional alerts into physiological monitoring systems, such as alarm fatigue, are taken into account. It is common for capnography waveform abnormalities indicative of hypopnea to be present frequently and for long periods during procedural sedation. In our sample, there were nearly than 700 distinct episodes of hypopnea. Clearly, providing alerts once low or high $PetCO_2$ thresholds are crossed would significantly increase alarm frequency, with alarm fatigue certain to become a concern in such circumstances [15]. In this regard, a more appropriate course of action may be to first undertake additional research with larger samples to determine how well using information about the history of previous capnography waveform abnormalities can predict the onset of apnea during procedural sedation. This research should probably utilize

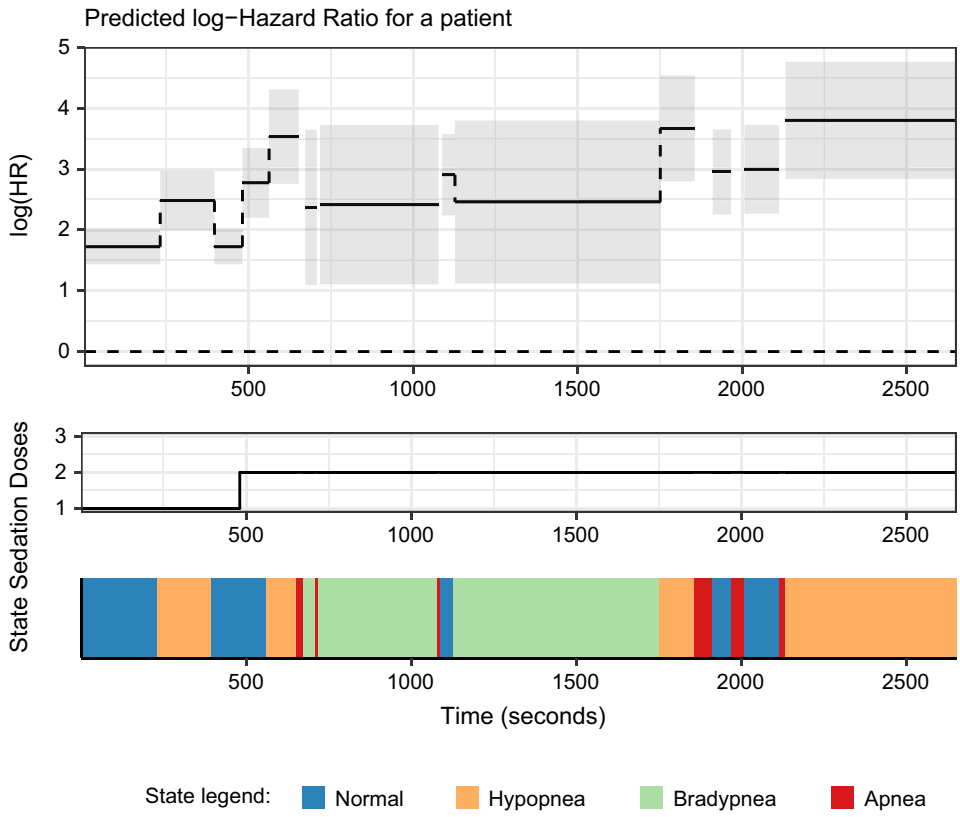

Fig. 2 The first model, considering apneic episodes of any duration, is used to predict the natural logarithm of the hazard ratio for a selected patient over the duration of their procedure. Model predictions for risk of apnea during procedures for all participants in the study can be viewed at this webpage (https://aconway.dev/pre-apneic)

state-of-the-art machine learning algorithms to maximize accuracy of the predictive modelling task. Such an approach responds to a call from The Society for Critical Care Medicine Alarm and Alert Fatigue Task Force, that machine learning techniques should be used to advance the quality of alerts that clinicians receive and to individualise alert delivery based on clinician response characteristics, such as alert frequency and severity [16].

Only one previous study investigated associations between the onset of apneic episodes with preceding capnography waveform abnormalities [5]. There were very marked differences between ours and the previous study, which was focused on emergency department sedation [5]. For example, participants in our sample were mostly older (average age 73) than participants in the emergency department study (average age 48). The medications used for sedation were also different (combinations of midazolam and fentanyl in our study versus propofol or ketamine in the emergency department study). Although in the emergency department study many patients received opioid analgesia in the lead up to their procedure, it was not administered concomitantly with the sedative as was the case in our study. Despite these differences, results were remarkably similar. The median time to first apnea in our sample was consistent with the prior study [5]. The hazard ratios for abnormal $PetCO_2$ were in the same range (within 2–3) in both studies and there was no statistically significant association between the abnormal respiratory rate variable with apnea in either study. The reproducibilty of such results in quite different populations should increase confidence in our estimates about the associations between high or low $PetCO_2$ concentrations and the subsequent increased risk for onset of apneic episodes.

That abnormal respiratory rate was not associated with apnea in our study is interesting. Krauss et al. [5] observed a similar result in their emergency department study. It should be noted that bradypnea occurred fewer times in our sample in comparison to the state of hypopnea. This may be in part due to the combination of medications used for sedation. A recent study of midazolam identified that reduction in tidal volume after drug administration is commonly coupled with increased respiratory rate to support minute ventilation within near normal parameters in some populations [17]. Yet, in a small proportion of the sample (20%) lacked the compensatory respiratory rate increase [17]. Replication of our study in larger samples would provide more accurate estimates of the incidence of the bradypneic respiratory pattern and whether or not there is a tendency for a subsequent risk of apnea.

We did not measure arterial CO_2 concentration in our study, as this is not a routine measurement in clinical practice during moderate sedation. As such, it was not possible

to determine how accurately absolute changes from baseline $PetCO_2$ concentrations (in either direction) represented the severity of hypoventilation. In simple terms, this means that we can not know if a person with an $PetCO_2$ concentration of 15 mmHg experienced more severe hypoventilation than a person with a $PetCO_2$ concentration of 25 mmHg. For this reason and also for consistency with prior research, we used pre-specified cut-offs to classify different types of capnography waveform abnormalities. Numeric thresholds were used for $PetCO_2$ (30 mmHg and 50mmHg) by Krauss et al. [17] in their emergency department study instead of change from baseline. In the majority of circumstances, the $PetCO_2$ of patients in our study classified to be in a state of 'hypopnea' based on the change in concentration from baseline values did have an $PetCO_2$ below 30 mmHg. This may have been one reason why the results of our analyses were similar.

Results of the sensitivity analysis we conducted with apneic events defined as episodes of more than 20 s duration was consistent with the primary analysis. This demonstrates the insensitivity of the model to the definition of apnea. The mixed effects Cox model we used is superior to models for survival analysis in which certain lag-times for events preceding apnea must be explicitly chosen, which is ultimately an arbitrary decision. In the previous study, hazard ratios for apnea did not change substantially between the different lag-times that were chosen (30, 60 and 90 s).

4.1 Limitations

Although 102 participants were included in the study, the effective sample size for this analysis was smaller because only 64 participants experienced at least one episode of apnea. The only other previous study that investigated the association between capnography waveform abnormalities with the onset of apnea had more than 300 participants and 161 of those experienced an apneic event. [5] However, an advantage of our study is that we were able to include each apneic event that occurred during procedures. Thus, over 500 apneic events were included in our model. Due to sample size considerations, we chose not to include a larger list of other variables in the model that may also have been associated with the onset of apnea. However, incorporation of the random effect for each patient in the mixed effect Cox model takes unmeasured heterogeneity that was not explained by the fixed effects included in the model into account [18]. This approach reduces the potential that the associations we observed between apnea and hypopnea were due to residual confounding. In this regard, it should also be noted that the fixed effects included in our model did not explain a large proportion of the variation in apneic episodes. We used direct observation to code capnography waveform abnormalities in real-time in an effort to ensure abnormal capnography waveforms due to dislodged CO_2 sampling cannula or intentional breath holding were coded as 'normal breathing'. This mimics how clinicians monitor ventilation in practice but it should nevertheless be noted that there may be advantages to undertaking off-line coding of recorded waveform data as an alternative. It is also possible that different results may have been observed if different classifications for capnography waveform abnormalities were used. The potential that classifications for hypoventilations and apneas were influenced by changes in oxygen flow rates should be considered. Due to the small number of participants in which the flow rates of oxygen were altered (n = 3, 3%), it is unlikely that this would have made a substantial impact on the results.

4.2 Conclusions

This study has identified that a specific type of capnography waveform abnormality (change in the $PetCO_2$ concentration of more than 10%) may signal increased risk of apneic events during procedural sedation performed with bolus doses of midazolam and fentanyl where moderate sedation is targeted. This finding was consistent with prior research undertaken in emergency department patients undergoing deep sedation with propofol or ketamine. Importantly, results from our primary analysis were robust to changing the definition of apneic episodes to those that lasted more than 20 s duration. As such, the totality of evidence at hand suggests that using information about the history of previous capnography waveform abnormalities may be a promising solution to assist prediction of apneic episodes. If sufficiently accurate predictions about impending apneic episodes can be achieved, such predictions could be operationalized in capnography monitoring systems as alerts to guide treatment of sedation-induced respiratory depression.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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